US 20230011726A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2023/0011726 A1**

LI et al. (43) **Pub. Date: Jan. 12, 2023**

(54) **KRAS MUTANT PROTEIN INHIBITORS**

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(21) Appl. No.: **17/407,418**

(22) Filed: **Aug. 20, 2021**

Related U.S. Application Data

(63) Continuation of application No. 17/197,095, filed on Mar. 10, 2021, which is a continuation of application No. PCT/CN2020/137497, filed on Dec. 18, 2020.

(30) **Foreign Application Priority Data**

Dec. 19, 2019	(CN)	PCT/CN2019/126687
Jan. 8, 2020	(CN)	PCT/CN2020/070885
Jan. 22, 2020	(CN)	PCT/CN2020/073723
Mar. 10, 2020	(CN)	PCT/CN2020/078565

Publication Classification

(51) **Int. Cl.**

C07D 487/04	(2006.01)
A61P 35/00	(2006.01)
A61K 9/00	(2006.01)

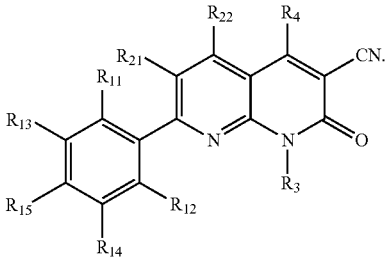
(52) **U.S. Cl.**

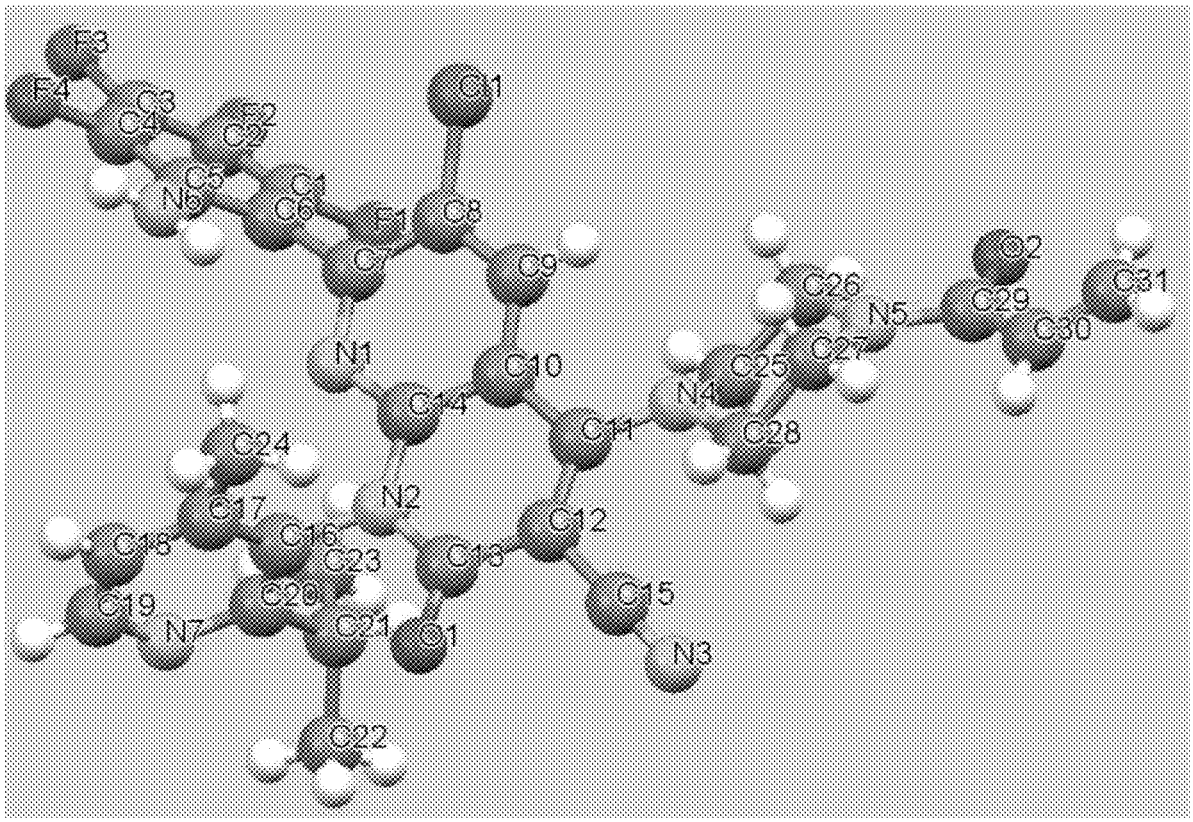
CPC ***C07D 487/04*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61P 35/00*** (2018.01)

(57) **ABSTRACT**

The invention relates to a KRAS mutant protein inhibitor shown as formula (I), a composition containing the inhibitor and the use thereof.

(I)





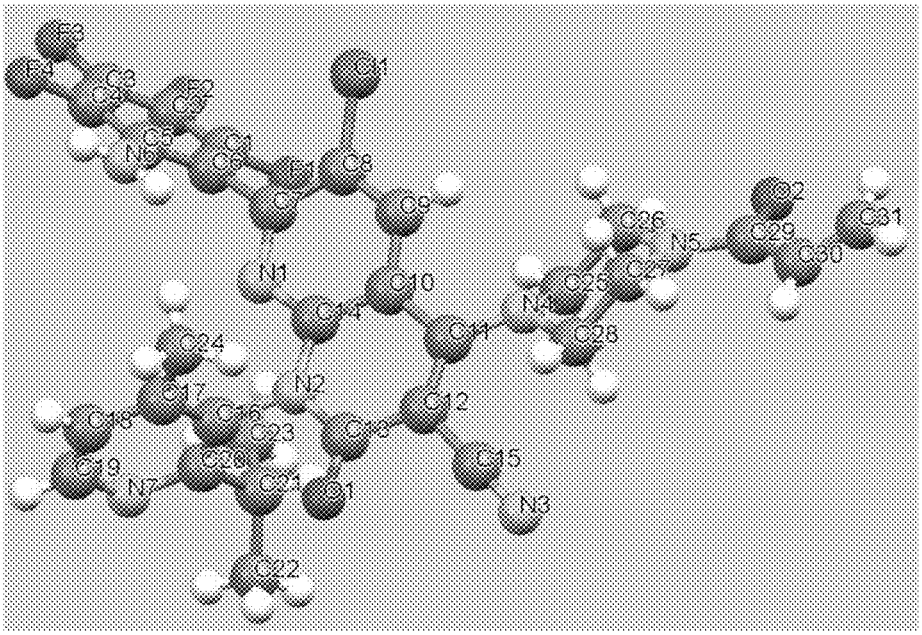


Figure 1

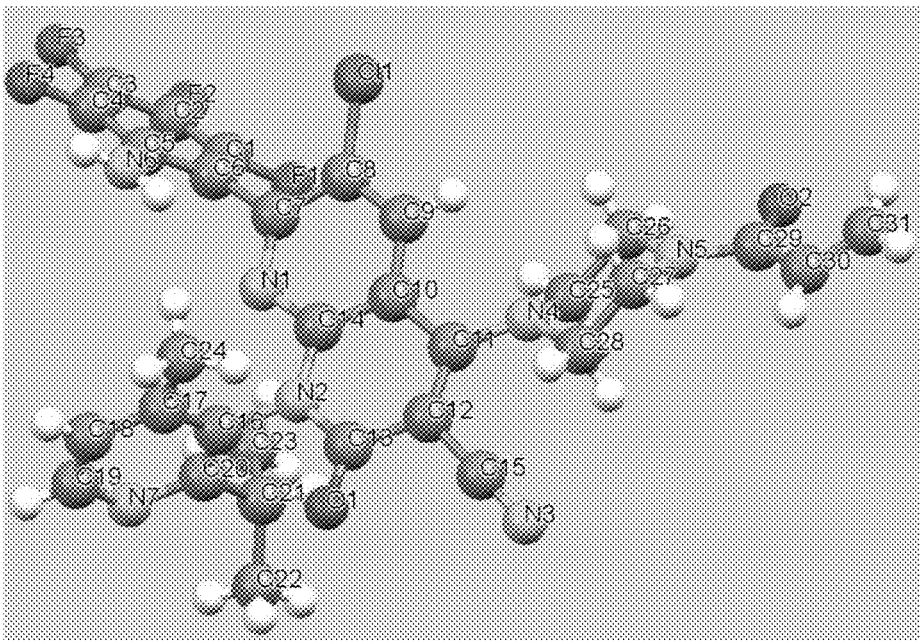


Figure 2

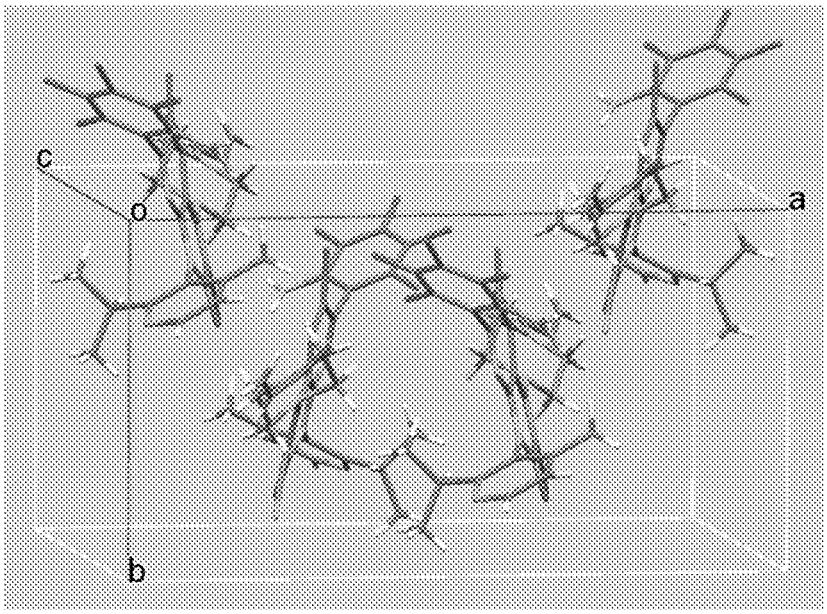
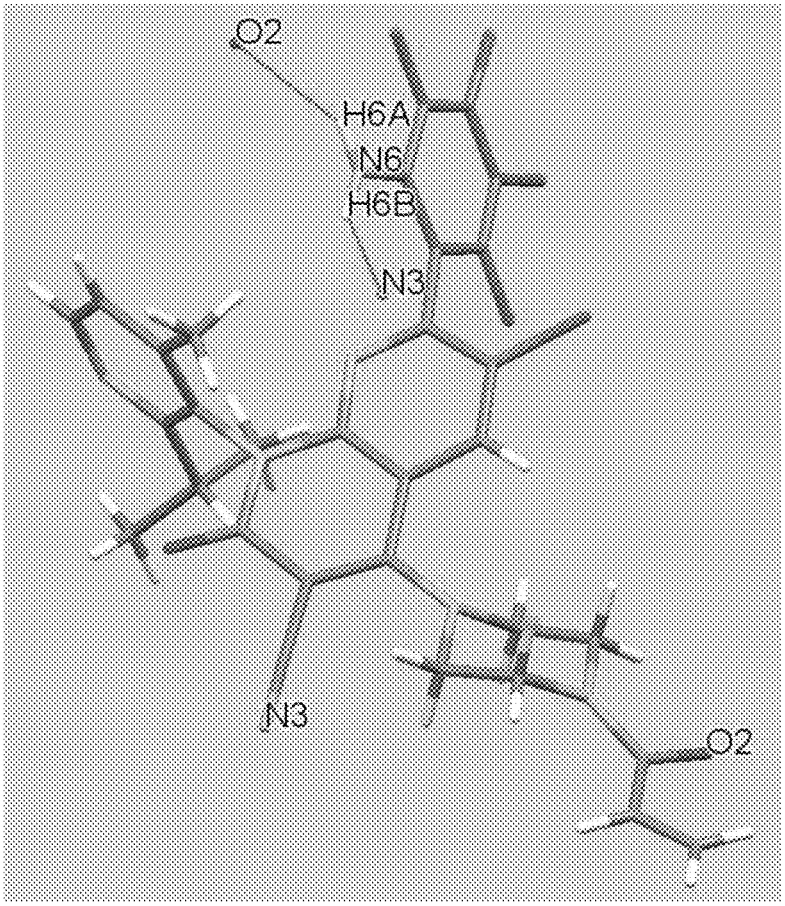


Figure 3



O2---H6A-N6; N3---H6B-N6

Figure 4

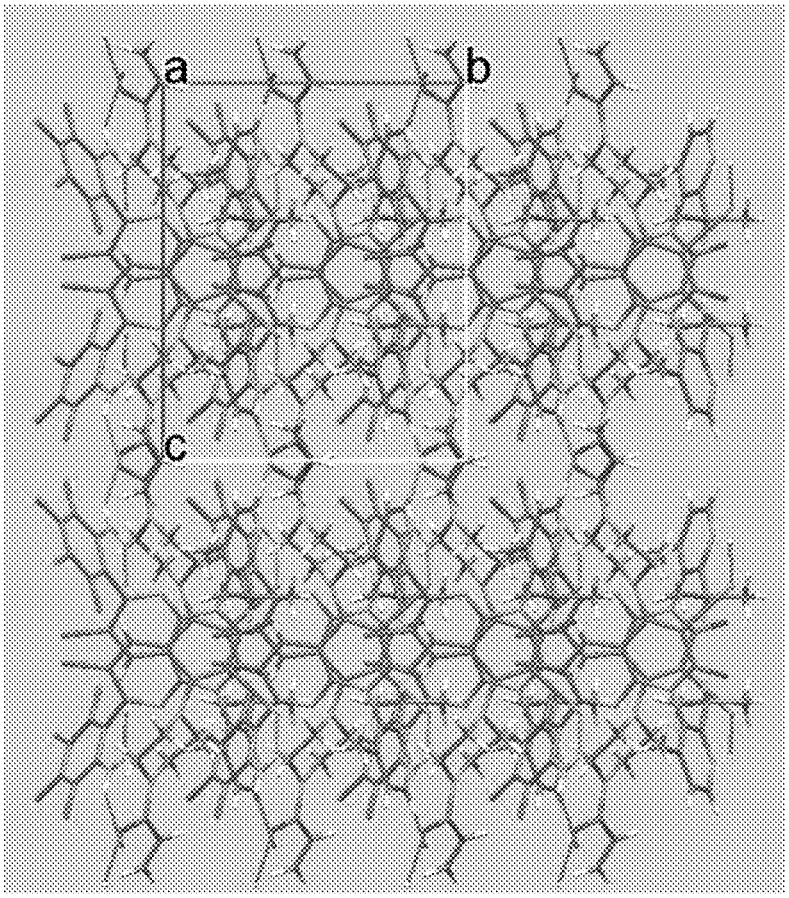


Figure 5

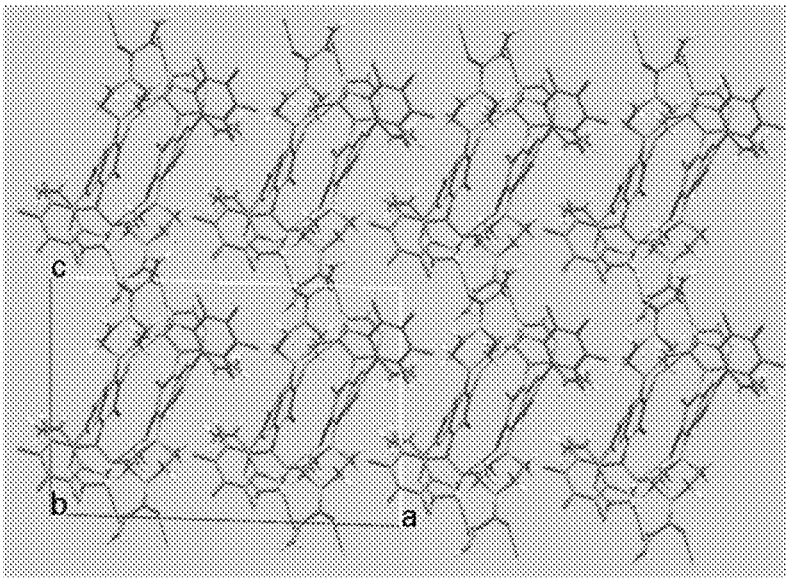


Figure 6

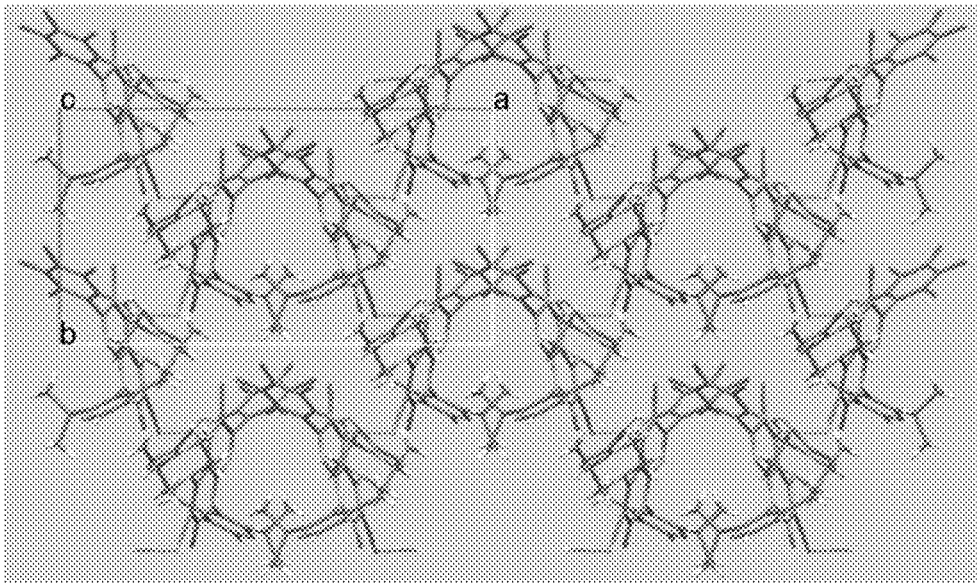


Figure 7

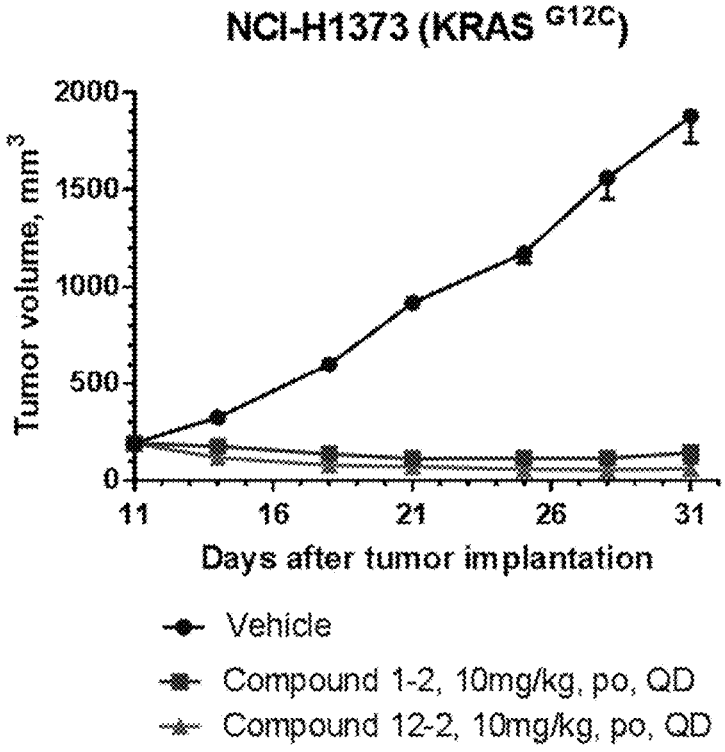


Figure 8

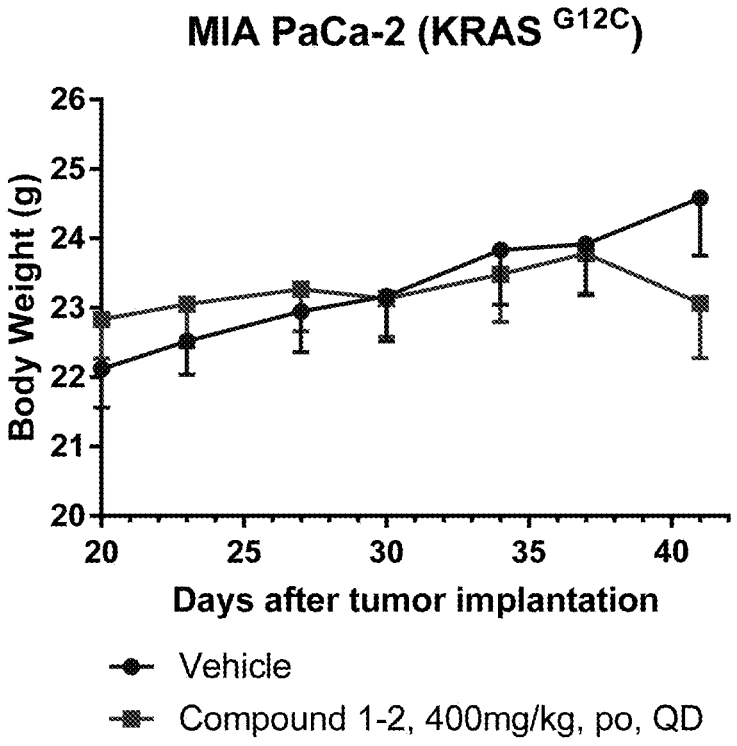

MIA PaCa-2 (KRAS G12C)
Body Weight (g)
26
25
24
23
22
21
20
20
25
30
35
40
Days after tumor implantation
Vehicle
Compound 1-2, 400mg/kg, po, QD

Figure 9

KRAS MUTANT PROTEIN INHIBITORS

TECHNICAL FIELD

[0001] The invention relates to a KRAS mutant protein inhibitors, a composition containing the inhibitors and the use thereof.

BACKGROUND ART

[0002] RAS represents a population of 189 amino acid monomeric globular proteins (21 kDa molecular weight) that are associated with the plasma membrane and bind to GDP or GTP, and RAS acts as a molecular switch. When the RAS contains bound GDP, it is in a stationary or closed position and is "inactive". When cells are exposed to certain growth-promoting stimuli, RAS is induced to exchange their bound GDP for GTP. In the case of binding to GTP, RAS is "opened" and is capable of interacting with other proteins (its "downstream targets") and activating the proteins. The RAS protein itself has an inherently low ability to hydrolyze GTP back to GDP, thereby turning itself into a closed state. Closing RAS requires an exogenous protein called GTPase activating protein (GAP) that interacts with RAS and greatly accelerates the conversion of GTP to GDP. Any mutation in RAS that affects its ability to interact with GAP or convert GTP back to GDP will result in prolonged protein activation, and thus conduction to the cell to inform its signaling of continued growth and division. Since these signals cause cell growth and division, over-activated RAS signaling can ultimately lead to cancer.

[0003] Structurally, the RAS protein contains a G domain responsible for the enzymatic activity of RAS, guanine nucleotide binding and hydrolysis (GTPase reaction). It also contains a C-terminal extension called the CAAX cassette, which can be post-translationally modified and responsible for targeting the protein to the membrane. The G domain contains a phosphate binding ring (P-ring). The P-loop represents a pocket of a binding nucleotide in a protein, and this is a rigid portion of a domain with conserved amino acid residues necessary for nucleotide binding and hydrolysis (glycine 12 and lysine 16). The G domain also contains a so-called switch I region (residues 30-40) and a switch II region (residues 60-76), both of which are dynamic parts of the protein, since the dynamic portion is converted between stationary and loaded states. The ability is often expressed as a "spring loaded" mechanism. The primary interaction is the hydrogen bond formed by threonine-35 and glycine-60 with the gamma-phosphate of GTP, which maintains the active conformation of the switch 1 region and the switch 2 region, respectively. After hydrolysis of GTP and release of phosphate, the two relax into an inactive GDP conformation.

[0004] The most notable members of the RAS subfamily are HRAS, KRAS and NRAS, which are primarily involved in many types of cancer. Mutation of any of the three major isoforms of the RAS gene (HRAS, NRAS or KRAS) is one of the most common events in human tumor formation. Approximately 30% of all tumors in human tumors were found to carry some mutations in the RAS gene. It is worth noting that KRAS mutations were detected in 25%-30% of tumors. In contrast, the rate of carcinogenic mutations in NRAS and HRAS family members was much lower (8% and 3%, respectively). The most common KRAS mutations were found at residues G12 and G13 in the P-loop as well as at residue Q61.

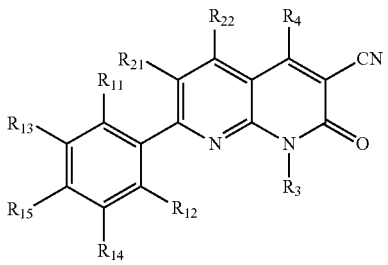
[0005] G12C is a frequently occurring KRAS gene mutation (glycine-12 is mutated to cysteine). This mutation has been found in about 13% of cancers, about 43% in lung cancer, and almost 100% in MYH-associated polyposis (familial colon cancer syndrome). However, targeting this gene with small molecules is a challenge.

[0006] Thus, despite advances in this field, there remains a need in the art for improved compounds and methods for treating cancer, such as by inhibiting KRAS, HRAS or NRAS. The present invention fulfills this need and provides other related advantages.

SUMMARY OF INVENTION

[0007] In one aspect, provided herein is A compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof:

(I)



[0008] Wherein:

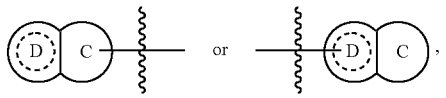
[0009] R_{11}, R_{12}, R_{13}, R_{14} or R_{15} is independently selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6}carbocyclic, 3- 6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{11}, R_{12}, R_{13}, R_{14} or

[0010] R_{15} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituent(s) selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S=O or $S(=O)_2$;

[0011] R_{21} or R_{22} is independently selected from hydrogen, halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6}carbocyclic, 3- 6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{21} or R_{22} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituent(s) selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo,

—OC_{1-6}alkyl, —SC_{1-6}alkyl, —NR_5R_6, —C(—O)R_5, —C(═O)OR_5, —OC(═O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6}carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(═O)_2$;

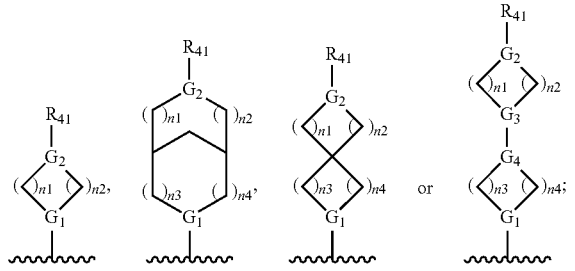
[0012] R_3 is selected from —C_{1-14} alkyl, —C_{2-14} alkenyl, —C_{2-14} alkynyl, —C_{6-10} aryl, 5-10 membered heteroaryl, 3-14 membered heterocyclic, —C_{3-14}carbocyclic,



each ring C at each occurrence is independently selected from a C_{3-14} carbocyclic or 3-14 membered heterocyclic ring, each ring D at each occurrence is independently selected from a C_{6-10} aryl or 5-10 membered heteroaryl ring, each hydrogen in R_3 is independently optionally substituted with 1, 2, 3, 4, 5 or 6 R_{31}; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, S═O or $S(═O)_2$;

[0013] Each R_{31} at each occurrence is independently selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —C(—O)R_5, —C(—O)OR_5, —OC(—O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$NR_5SO_2R_6$, —SO_2R_5, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6}carbocyclic, 3- 6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{31} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituent(s) selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, heteroC_{2-6}alkyl, —CN, oxo, —OC_{1-6}alkyl, —SC_{1-6}alkyl, —NR_5R_6, —C(═O)R_5, —C(═O)OR_5, —OC(═O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(═O)_2$;

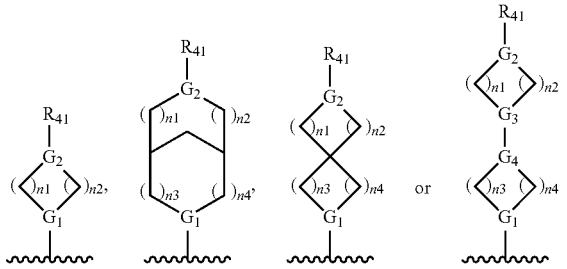
[0014] R_4 is selected from



[0015] Each G_1, G_2, G_3 or G_4 at each occurrence is independently selected from N or CH;

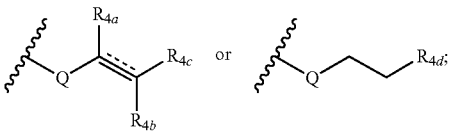
[0016] Each n1, n2, n3, n4 or n5 at each occurrence is independently selected from 0, 1, 2, 3, 4, 5 or 6, provided that n1 and n2 is not 0 at the same time, n3 and n4 is not 0 at the same time;

[0017] Each hydrogen in



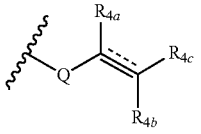
is independently optionally substituted with $1R_{42}$, $2R_{42}$, $3R_{42}$, $4R_{42}$, $5R_{42}$ or $6R_{42}$;

[0018] Each R_{41} at each occurrence is independently selected from



[0019] Each of Q at each occurrence is independently selected from C(═O), NR_5C(═O), $S(═O)_2$ or NR_5S(═O)$_2$;

[0020] ═══ in



is selected from ═══ or ═══;

[0021] when ═══ is ═══, R_{4a}, R_{4b} or R_{4c} is independently selected from hydrogen, halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —C(═O)R_5, —C(═O)OR_5, —OC(═O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$NR_5SO_2R_6$, —SO_2R_5, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{4a}, R_{4b} or R_{4c} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —C(═O)R_5, —C(═O)OR_5, —OC(═O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$NR_5SO_2R_6$, —SO_2R_5, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(═O)_2$; or

[0022] when ═══ is ═══, R_{4a} is selected from hydrogen, halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —C(═O)R_5, —C(═O)OR_5, —OC(═O)R_5, —C(═O)NR_5R_6, —NR_5C(═O)R_6, —$NR_5SO_2R_6$, —SO_2R_5, —$S(═O)_2NR_5R_6$, —POR_5R_6, —C_{3-6}carbocyclic, 3- 6 membered heterocyclic, —C_{6-10} aryl, or 5-10

membered heteroaryl, each hydrogen in R_{4a} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6}alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; and R_{4b} and R_{4c} together with the carbon which they both attach to form a C_{3-10} carbocyclic ring or a 3-10 membered heterocyclic ring, each hydrogen in the C_3-10 carbocyclic ring or the 3-10 membered heterocyclic ring is optionally substituted by 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6}alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(=O)_2$; or

[0023] when ⋯ is ═, R_{4a} and R_{4c} with the carbon they respectively attach to form a C_3-10 carbocyclic ring or a 3-10 membered heterocyclic ring, each hydrogen in the C_{3-10} carbocyclic ring or the 3-10 membered heterocyclic ring is optionally substituted by 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; and R_{4b} is selected from hydrogen, halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{ob} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(=O)_2$;

[0024] when ⋯ is ═, R_{4a} is absent, R_{4b} is absent, R_{4c} is selected from hydrogen, halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{4c} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocyclic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(=O)_2$;

[0025] R_{4d} is halogen;

[0026] Each R_{42} at each occurrence is independently selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6}alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{42} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_6$, —$NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —POR_5R_6, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; or

[0027] Two R_{42} together with the atom which they both or respectively attach to form a C_{3-6} carbocyclic or 3-6 membered heterocyclic ring, each hydrogen in the C_{3-6} carbocyclic or 3-6 membered heterocyclic ring is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6}alkyl, —SC_{1-6}alkyl, —NR_5R_6, —$C(=O)R_5$, —$C(=O)OR_5$, —$OC(=O)R_5$, —$C(=O)NR_5R_6$, —$NR_5C(=O)R_5$, —$C(=O)NR_5SO_2R_6$, —SO_2R_5, —$S(=O)_2NR_5R_6$, —$PO(R_5)_2$, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{1-6}aryl, or 5-10 membered heteroaryl; each heterocyclic and heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(=O)_2$;

[0028] Each R_5 and R_6 at each occurrence is independently selected from hydrogen or —C_{1-6} alkyl; or

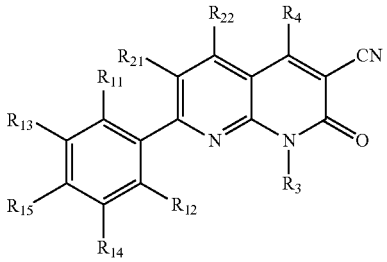
[0029] R_5 and R_6 together with the atom which they both or respectively attach to form a 3-10 membered heterocyclic ring, the 3-10 membered heterocyclic ring is optionally further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, S(═O) or $S(=O)_2$, and each hydrogen in the 3-10 membered heterocyclic ring is independently optionally substituted with $1R_{51}$, $2R_{51}$, $3R_{51}$, $4R_{51}$, $5R_{51}$ or $6R_{51}$;

[0030] Each R_{51} is selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_7R_8, —$C(=O)R_7$, —$C(=O)OR_7$, —$OC(=O)R_7$, —$C(=O)NR_7R_8$, —$NR_7C(=O)R_8$, —$NR_7SO_2R_8$, —SO_2R_7, —$S(=O)_2NR_7R_8$, —POR_7R_8, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl, each hydrogen in R_{51} is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituent(s) selected from halogen, —C_{1-6} alkyl, —C_{2-6} alkenyl, —C_{2-6} alkynyl, heteroC_{2-6} alkyl, —CN, oxo, —OC_{1-6} alkyl, —SC_{1-6} alkyl, —NR_7R_8, —$C(=O)R_7$, —$C(=O)OR_7$, —$OC(=O)R_7$, —$C(=O)NR_7R_8$, —$NR_7C(=O)R_8$, —$NR_7SO_2R_8$, —SO_2R_7, —$S(=O)_2NR_7R_8$, —POR_7R_8, —C_{3-6} carbocyclic, 3-6 membered heterocyclic, —C_{6-10} aryl, or 5-10 membered heteroaryl; each heterocy-

clic or heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatom(s) selected from N, O, S, S═O or $S(═O)_2$;

[0031] Each R_7 and R_8 at each occurrence is independently selected from hydrogen or —C_{1-6} alkyl.

[0032] In some embodiments, there is provided a compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof:



(I)

[0033] Wherein:

[0034] R_{11}, R_{12}, R_{13}, R_{14} or R_{15} is independently selected from —OH; halogen; —NR_aR_b; —C_{1-6} alkyl; —OC_{1-6} alkyl; —C_{1-6} alkylene-OH; —C_{1-6} alkylene-O—C_{1-6} alkyl; —C_{1-6}alkyl substituted with halogen, —NH_2, —CN or —OH; —O—C_{1-6} alkyl substituted with halogen, —NH_2, —CN or —OH; —O—C_{1-6} alkyl; —SO_2R_a; —CN; —C(═O)NR_aR_b; —C(═O)R_a; —OC(═O)R_a; —C(═O)OR_a; or —C_{3-6} carbocyclic;

[0035] R_a or R_b is independently selected from hydrogen or —C_{1-6} alkyl;

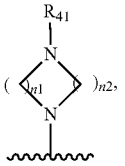
[0036] R_{21} is selected from hydrogen; halogen; —C_{1-6} alkyl; —C_{1-6} alkyl substituted with halogen, —NH_2, —CN or —OH; —C_{2-6} alkenyl; or —C_{3-6} carbocyclic;

[0037] R_{22} is selected from hydrogen; halogen; —C_{1-6} alkyl; —C_{1-6} alkyl substituted with halogen, —NH_2, —CN or —OH; —C_{2-6} alkenyl; or —C_{3-6} carbocyclic;

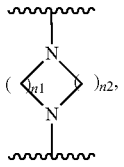
[0038] R_3 is selected from —C_{6-10} aryl or 5-10 membered heteroaryl, each of 5-10 membered heteroaryl at each occurrence independently contains 1, 2, 3 or 4 heteroatoms selected from N, O or S, each hydrogen in the —C_{6-10} aryl or 5-10 membered heteroaryl at each occurrence is independently optionally substituted with $1R_{31}$, $2R_{31}$, $3R_{31}$, $4R_{31}$, $5R_{31}$ or 6 R_{31};

[0039] Each R_{31} at each occurrence is independently selected from halogen, —C_{1-6} alkyl, —CN, —OH, —O—C_{1-6} alkyl, —NH_2, —NH(C_{1-6} alkyl), —N(C_{1-6} alkyl)$_2$ or —C_{3-6} carbocyclic;

[0040] R_4 is



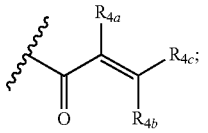
each hydrogen in the



is independently optionally substituted with $1R_{42}$, $2R_{42}$, $3R_{42}$, $4R_{42}$, $5R_{42}$ or 6 R_{42};

[0041] n1 or n2 is independently selected from 1, 2, 3, 4, 5 or 6;

[0042] R_{41} is



[0043] R_{4a}, R_{4b} or R_{4c} is independently selected from hydrogen, halogen, —C_{1-6} alkyl or —C_{1-6} alkylene-N(C_{1-6}alkyl)$_2$;

[0044] Each R_{42} at each occurrence is independently selected from —C_{1-6} alkyl; —C_{1-6} alkylene-CN or —C_{1-6} alkyl substituted with halogen.

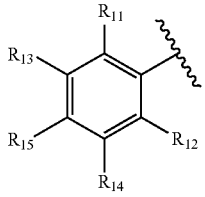
[0045] In some embodiments, R_{11}, R_{12}, R_{13}, R_{14} or R_{15} is independently selected from —OH; —F; —C_1; —Br; —NR_aR_b; —C_{1-3} alkyl; —OC_{1-3} alkyl; —C_{1-3}alkylene-OH; —C_{1-3} alkylene-O—C_{1-3} alkyl; —C_{1-3}alkyl substituted with —F or —Cl; —O—C_{1-3} alkyl substituted with —F or —Cl; —SO_2R_a; —CN; —C(═O)NR_aR_b; —C(═O)R_a; —OC(═O)R_a; —C(═O)OR_a; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic or 6-membered carbocyclic;

[0046] R_a or R_b is independently selected from hydrogen or —C_{1-3} alkyl.

[0047] In some embodiments, R_{11}, R_{12}, R_{13}, R_{14} or R_{15} is independently selected from —OH, —F, —Cl, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —CH_3, —CH_2CH_3, —$CH_2CH_2CH_3$, —$CH(CH_3)_2$, —OCH_3, —OCH_2CH_3, —$OCH_2CH_2CH_3$, —$OCH(CH_3)_2$, —CH_2OH, —CH_2CH_2OH, —CH_2OCH_3, —CHF_2, —CH_2F, —CF_3, —OCH_2F, —$OCHF_2$, —OCF_3, —SO_2CH_3, —CN, —C(═O)NH_2, —C(═O)CH_3, —OC(═O)CH_3, —C(═O)OCH_3 or 3-membered carbocyclic.

[0048] In some embodiments, R_{11}, R_{12}, R_{13}, R_{14} or R_{15} is independently selected from —OH, —F, —Cl, —NH_2, —CH_3 or —CF_3.

[0049] In some embodiments, the



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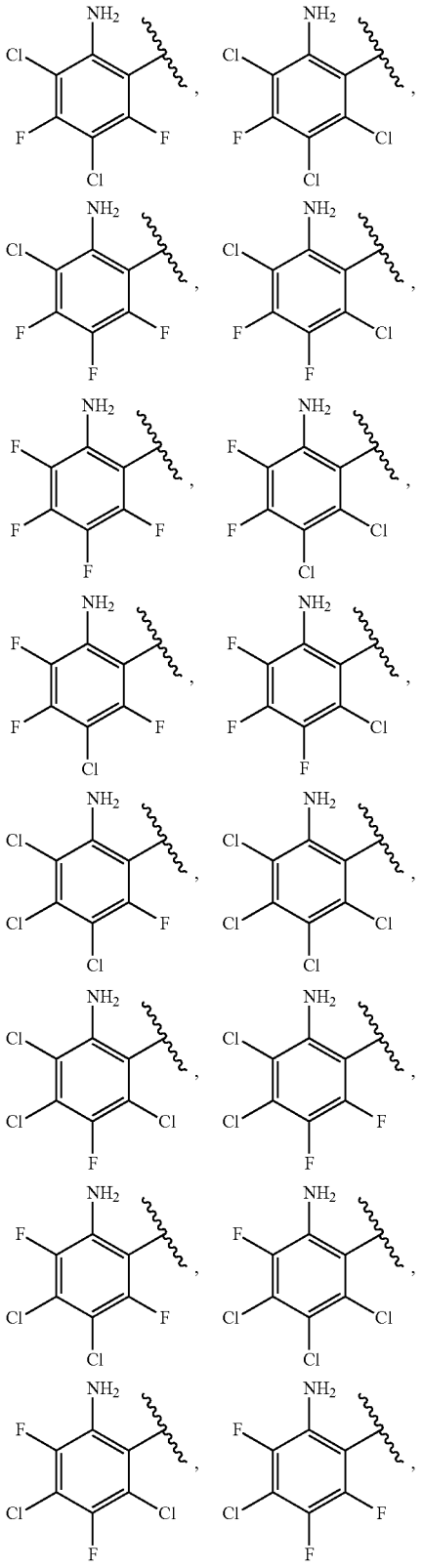

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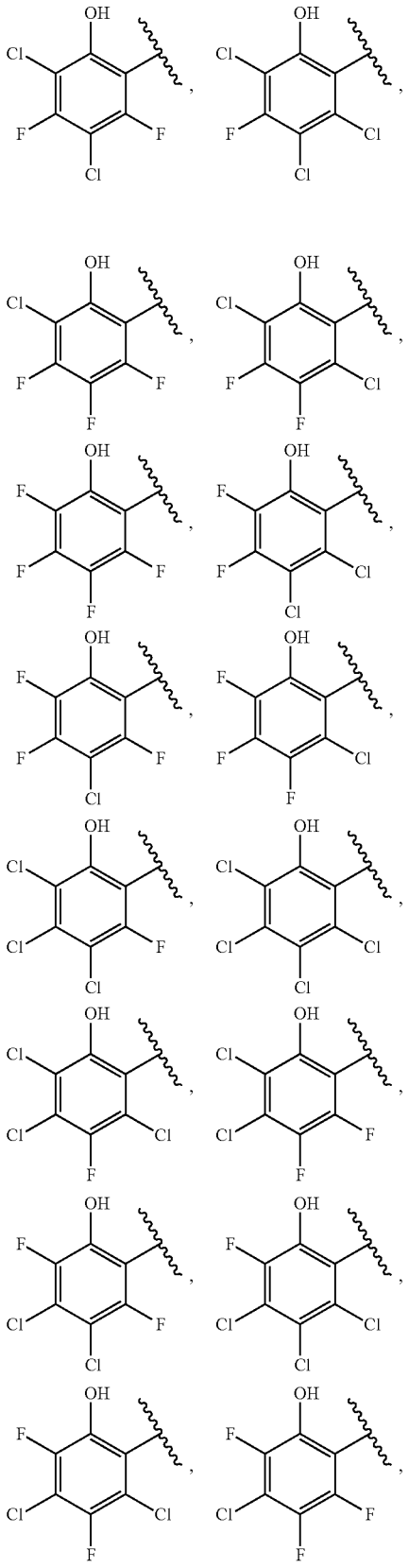

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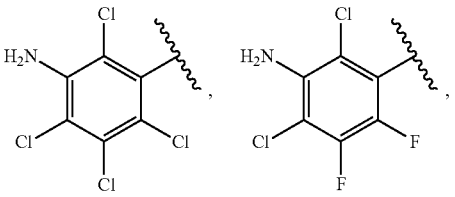

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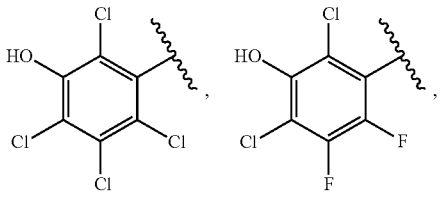

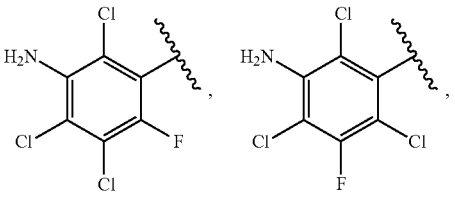

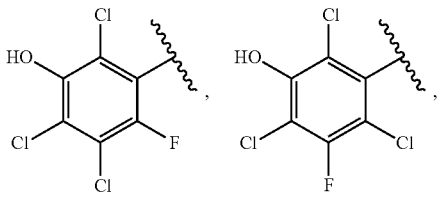

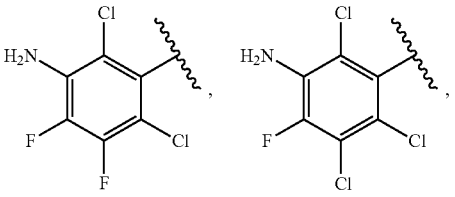

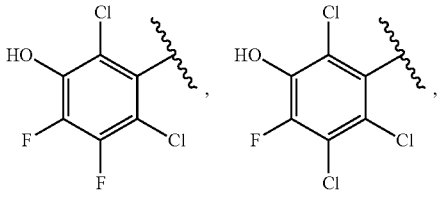

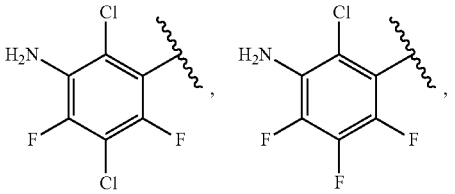

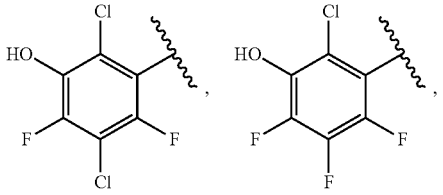

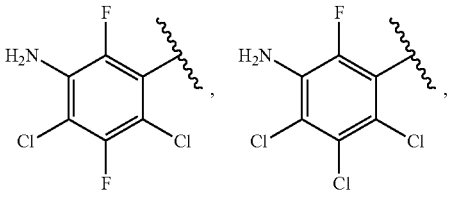

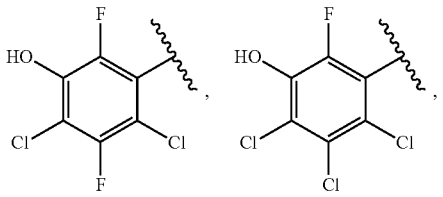

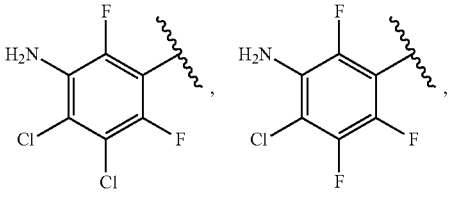

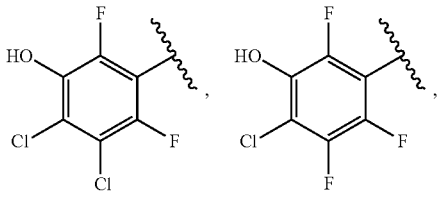

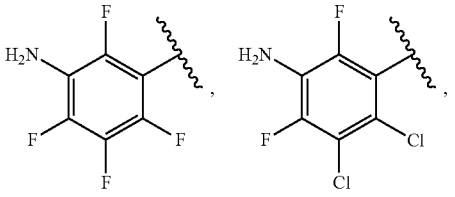

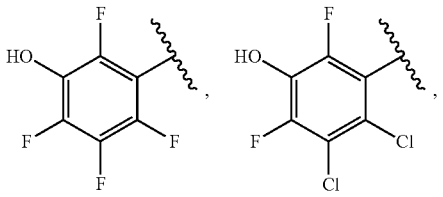

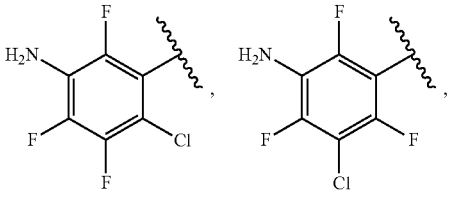

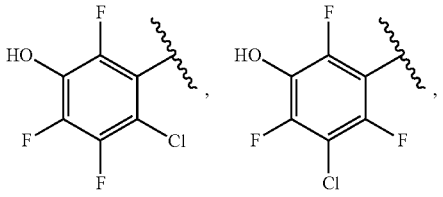

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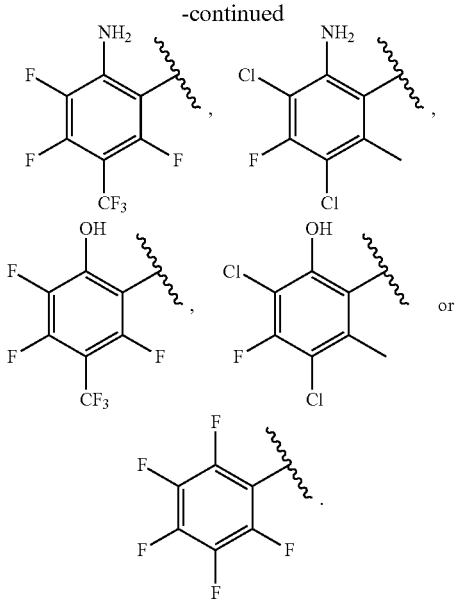


[0050] In some embodiments, R_{21} is selected from hydrogen; —F; —Cl; —Br; —C_{1-3} alkyl; —C_{1-3} alkyl substituted with —F or —Cl; —C_{2-3} alkenyl; or —C_{3-6} carbocyclic.

[0051] In some embodiments, R_{21} is selected from hydrogen; —F; —Cl; methyl; ethyl; propyl; isopropyl; methyl substituted with —F; ethyl substituted with —F; propyl substituted with —F; isopropyl substituted with —F; ethenyl; propenyl; 3 membered carbocyclic; 4 membered carbocyclic; 5 membered carbocyclic; or 6 membered carbocyclic.

[0052] In some embodiments, R_{21} is —Cl.

[0053] In some embodiments, R_{22} is selected from hydrogen; —F; —Cl; —Br; —C_{1-3} alkyl; —C_{1-3} alkyl substituted with —F or —Cl; —C_{2-3} alkenyl; or —C_{3-6} carbocyclic.

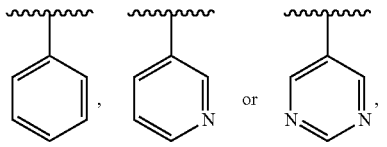
[0054] In some embodiments, R_{22} is selected from hydrogen; —F; —Cl; methyl; ethyl; propyl; isopropyl; methyl substituted with —F; ethyl substituted with —F; propyl substituted with —F; isopropyl substituted with —F; ethenyl; propenyl; 3 membered carbocyclic; 4 membered carbocyclic; 5 membered carbocyclic; or 6 membered carbocyclic.

[0055] In some embodiments, R_{22} is hydrogen.

[0056] In some embodiments, R_3 is selected from phenyl, naphthyl, 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, each heteroaryl at each occurrence independently contains 1, 2 or 3 heteroatoms selected from N or O, each hydrogen in R_3 at each occurrence is independently optionally substituted with $1R_{31}$, $2R_{31}$, $3R_{31}$, $4R_{31}$ or $5R_{31}$.

[0057] In some embodiments, R_3 is selected from phenyl or 6 membered heteroaryl, the heteroaryl contains 1 or 2 heteroatoms selected from N, each hydrogen in the phenyl or 6 membered heteroaryl at each occurrence is independently optionally substituted by $1R_{31}$, $2R_{31}$, $3R_{31}$ or $4R_{31}$.

[0058] In some embodiments, R_3 is selected from



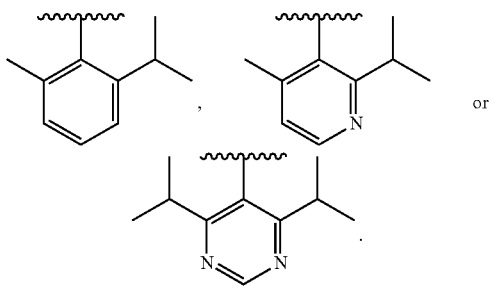
each hydrogen in the R_3 at each occurrence is independently optionally substituted by $1R_{31}$, $2R_{31}$, $3R_{31}$ or $4R_{31}$.

[0059] In some embodiments, each R_{31} at each occurrence is independently selected from —F, —Cl, —Br, —C_{1-3} alkyl, —CN, —OH, —O—C_{1-3} alkyl, —NH_2, —NH(C_{1-3} alkyl), —N(C_{1-3} alkyl)$_2$ or —C_{3-6} carbocyclic.

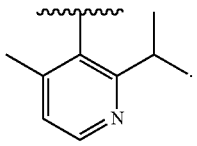
[0060] In some embodiments, each R_{31} at each occurrence is independently selected from —F, —Cl, methyl, ethyl, propyl, isopropyl, —CN, —OH, methoxy, ethoxy, propoxy, isopropoxy, —NH_2, —$NHCH_3$, —$NHCH_2CH_3$, —NH($CH_2CH_2CH_3$), —NH($CH(CH_3)_2$), —$N(CH_3)_2$, —$N(CH_2CH_3)_2$, —$N(CH_3)(CH_2CH_3)$, 3 membered carbocyclic, 4 membered carbocyclic, 5 membered carbocyclic or 6 membered carbocyclic.

[0061] In some embodiments, each R_{31} at each occurrence is independently selected from methyl or isopropyl.

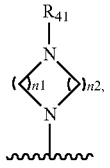
[0062] In some embodiments, R_3 is selected from



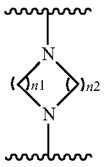
[0063] In some embodiments, R_3 is



[0064] In some embodiments, R_4 is



each hydrogen in the

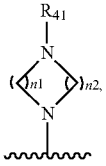


is independently optionally substituted with $1R_{42}$, $2R_{42}$, $3R_{42}$ or $4R_{42}$;

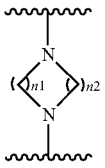
[0065] n1 is selected from 1, 2 or 3;

[0066] n2 is selected from 1, 2 or 3.

[0067] In some embodiments, R_4 is selected from



each hydrogen in the

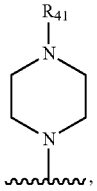


is independently optionally substituted with $1R_{42}$ or $2R_{42}$;

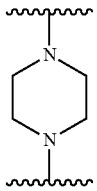
[0068] n1 is selected from 1 or 2;

[0069] n2 is selected from 1 or 2.

[0070] In some embodiments, R_4 is

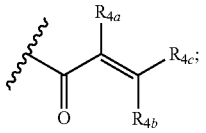


each hydrogen in the



is independently optionally substituted with $1R_{42}$ or $2R_{42}$.

[0071] In some embodiments, R_{41} is



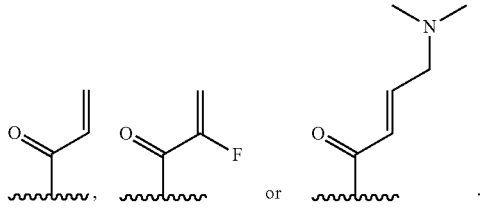
[0072] R_{4a}, R_{4b}, or R_{4c} is independently selected from hydrogen, —F, —Cl, —Br, —C_{1-3} alkyl or —C_{1-3} alkylene-$N(C_{1-3}$ alkyl$)_2$.

[0073] In some embodiments, R_{4a}, R_{4b} or R_{4c} is independently selected from hydrogen, —F, —C_1, methyl, ethyl, propyl, isopropyl, —CH_2—$N(CH_3)_2$, —CH_2—$N(CH_2CH_3)_2$ or —CH_2—$N(CH_3)(CH_2CH_3)$.

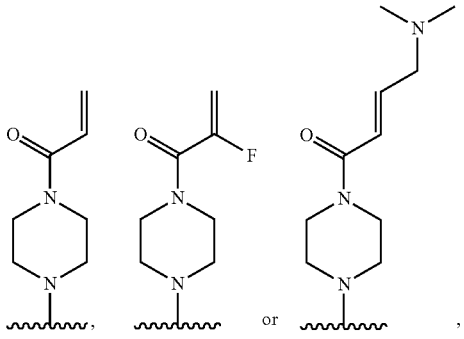
[0074] In some embodiments, R_{4a}, R_{4b} or R_{4c} is independently selected from hydrogen, —F, methyl or —CH_2—$N(CH_3)_2$.

[0075] In some embodiments, R_{4a} is selected from hydrogen or —F; R_{4b} is hydrogen; R_{4c} is selected from hydrogen or —CH_2—$N(CH_3)_2$.

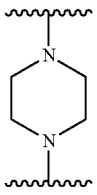
[0076] In some embodiments, R_{41} is selected from:



[0077] In some embodiments, R_4 is selected from



each hydrogen in the



at each occurrence is independently optionally substituted with $1R_{42}$ or $2R_{42}$.

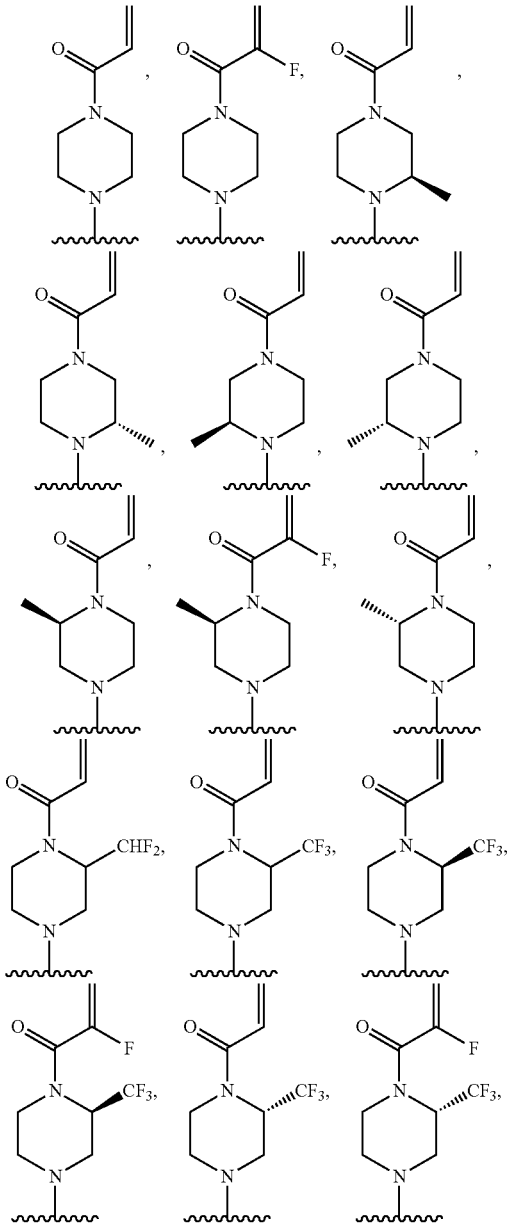
[0078] In some embodiments, each R_{42} at each occurrence is independently selected from —C_{1-3} alkyl; —C_{1-3} alkylene-CN; or —C_{1-3} alkyl substituted with —F or —Cl.

[0079] In some embodiments, each R_{42} at each occurrence is independently selected from methyl; ethyl; propyl; isopropyl; -methylene-CN; -ethylene-CN; -propylene-CN; methyl substituted with —F; ethyl substituted with —F; propyl substituted with —F; or isopropyl substituted with —F.

[0080] In some embodiments, each R_{42} at each occurrence is independently selected from methyl; ethyl; -methylene-CN or methyl substituted with —F.

[0081] In some embodiments, each R_{42} at each occurrence is independently selected from —CH_3, —CH_2CH_3, —CH_2CN, —CHF_2 or —CF_3.

[0082] In some embodiments, R_4 is selected from:



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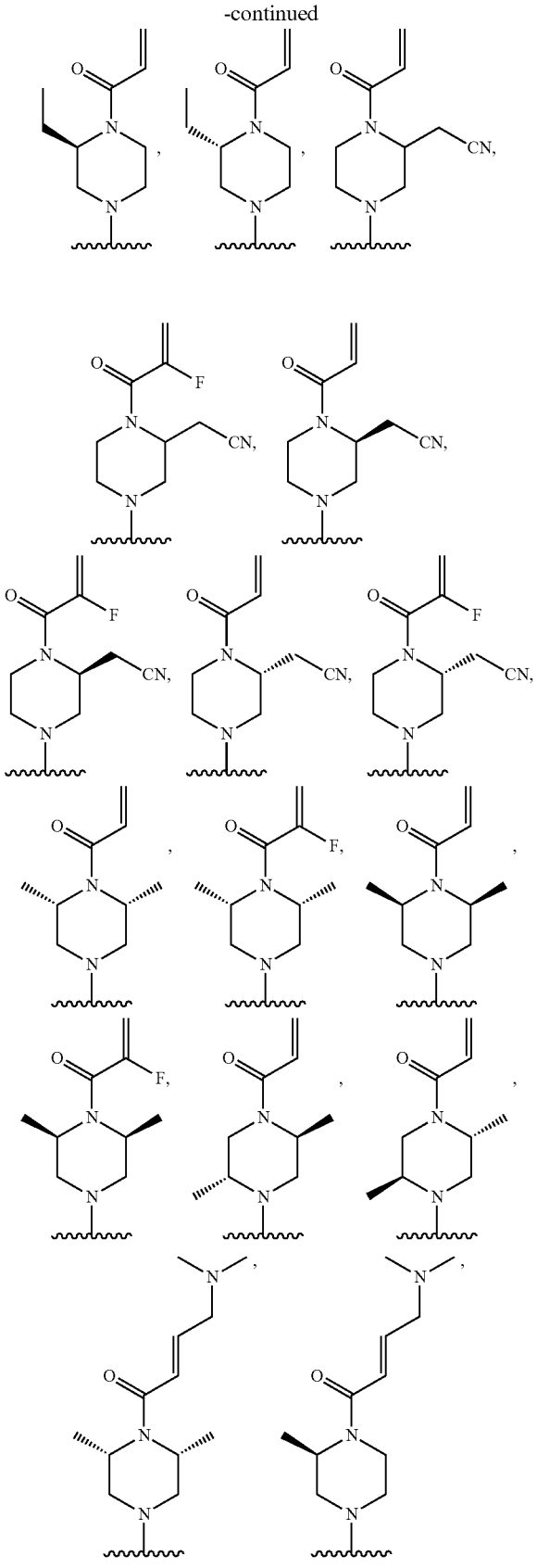

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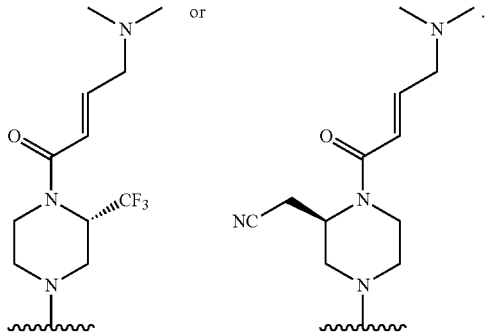
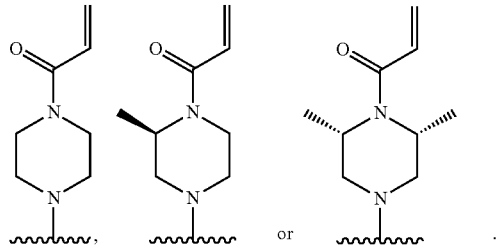
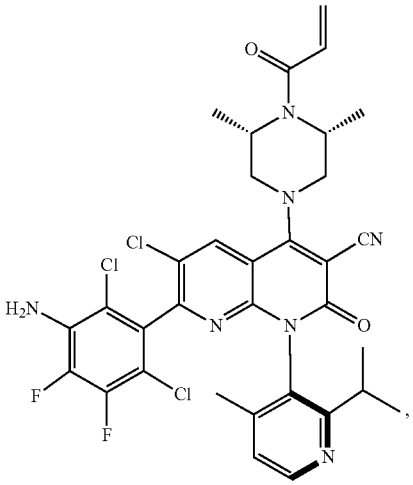
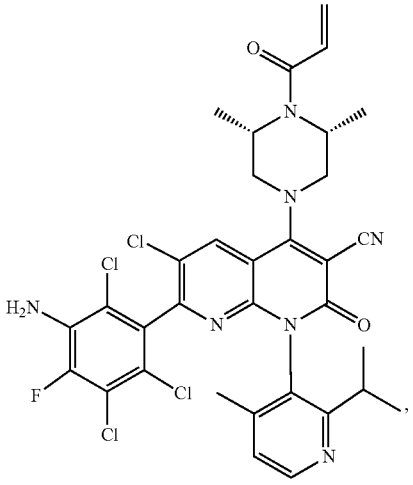


[0083] In some embodiments, R_4 is selected from:



[0084] In some embodiments, the compound is selected from:





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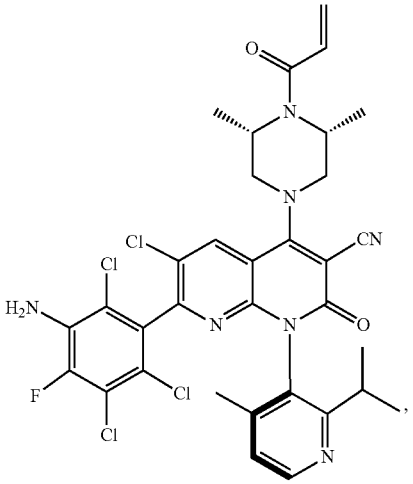

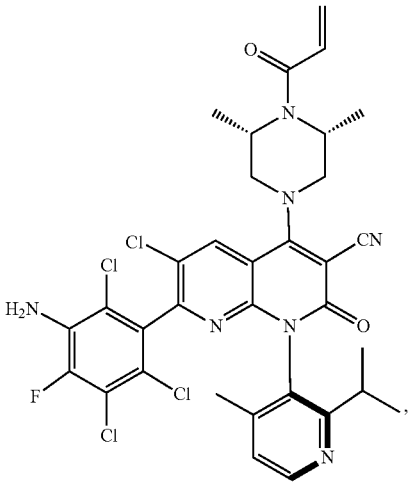

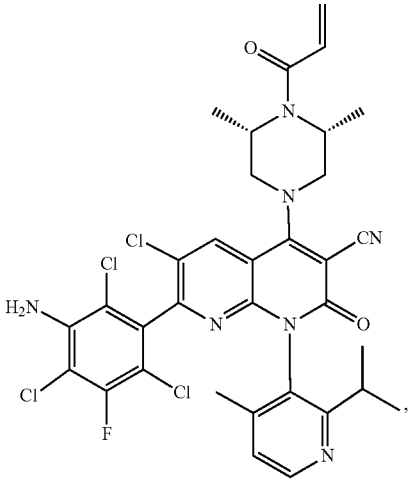

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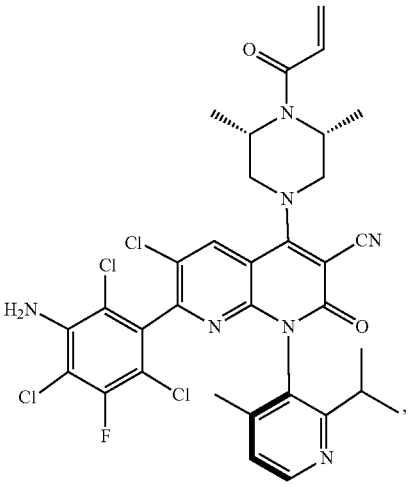

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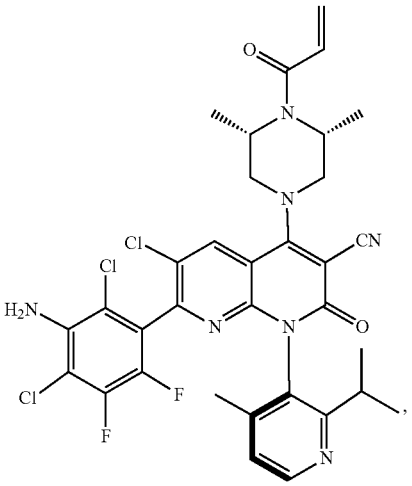

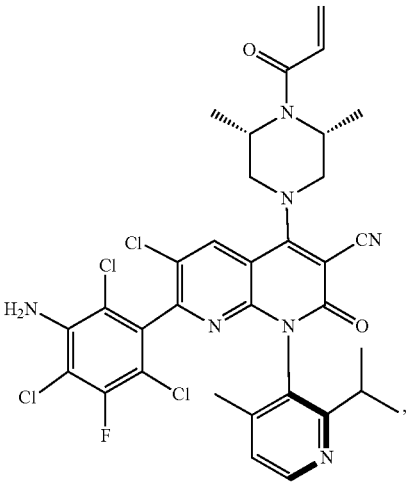

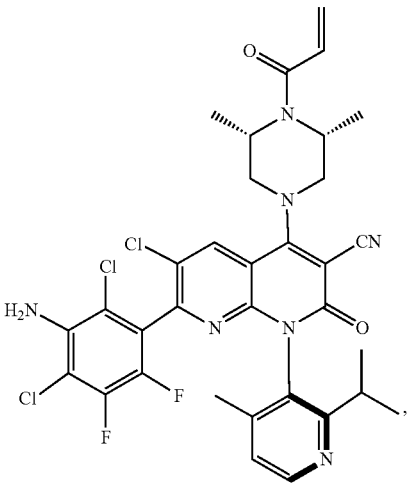

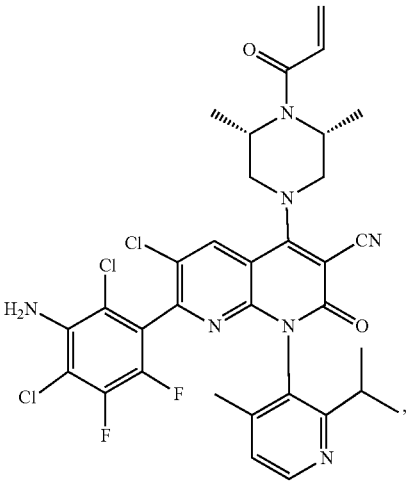

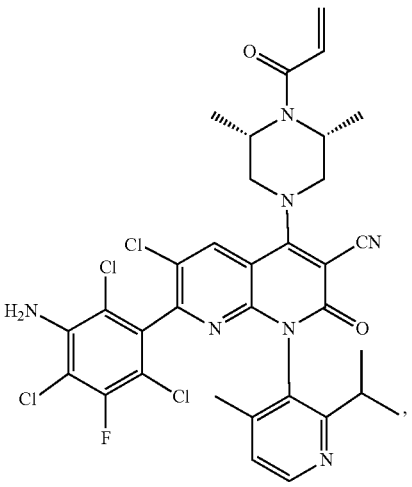

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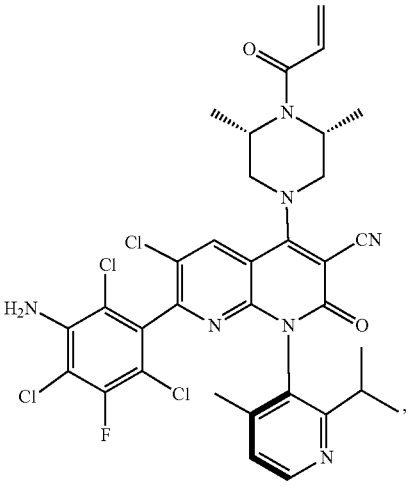

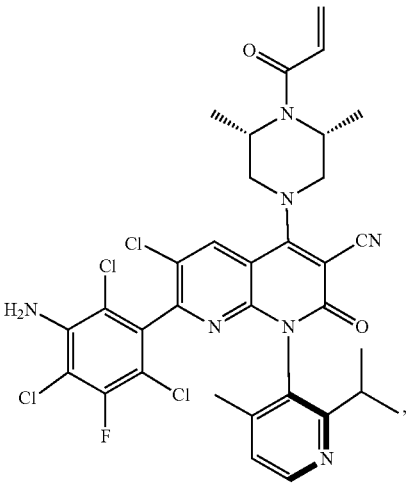

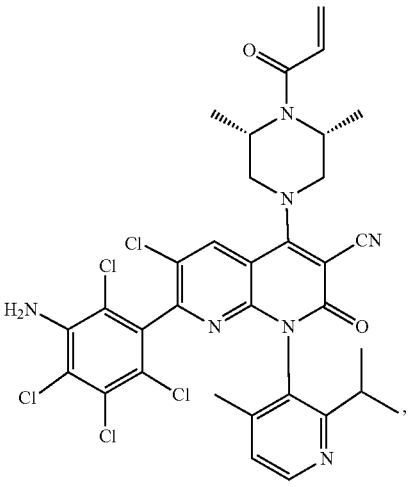

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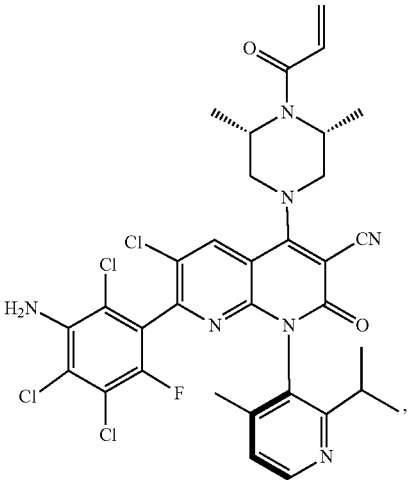

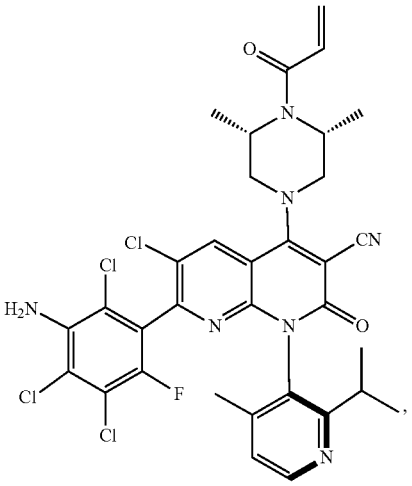

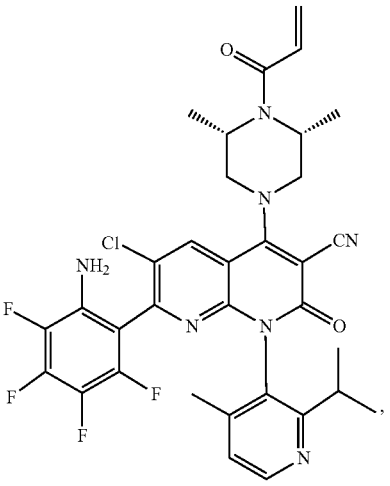

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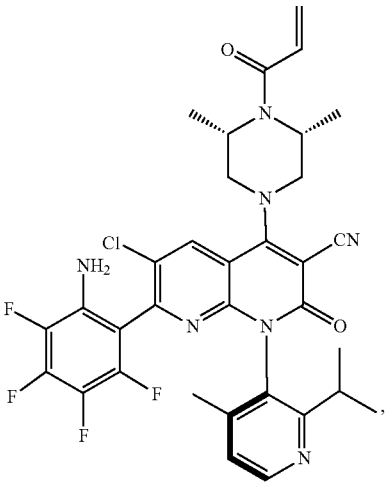

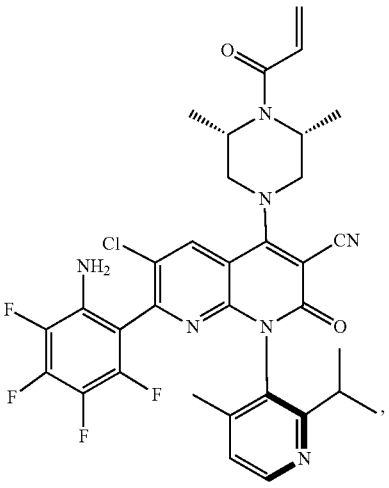

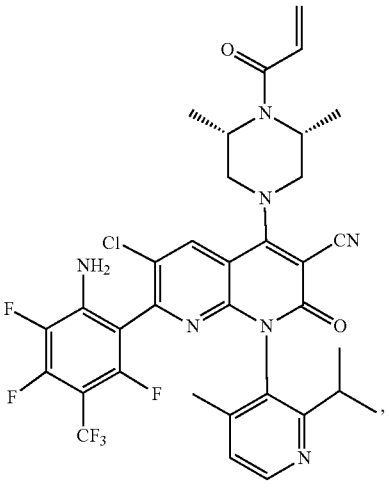

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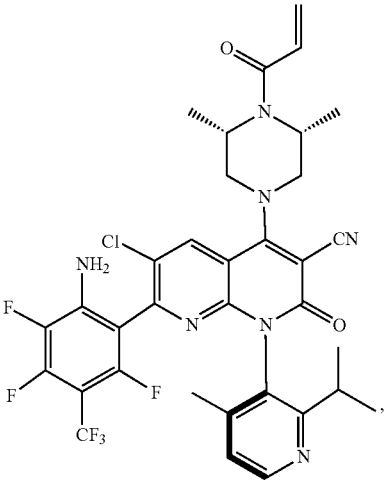

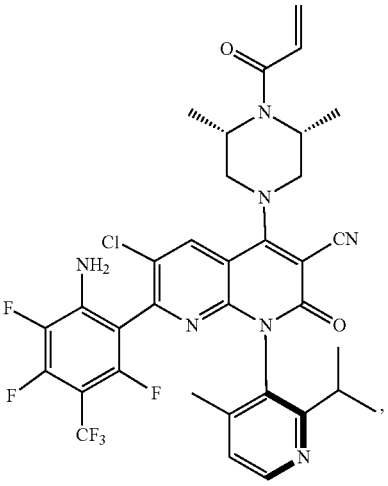

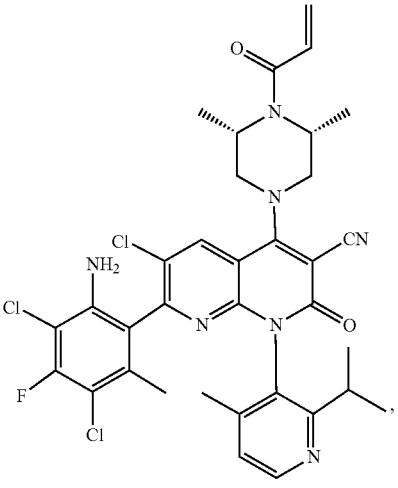

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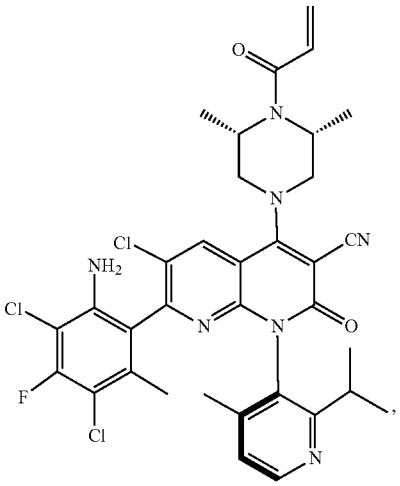

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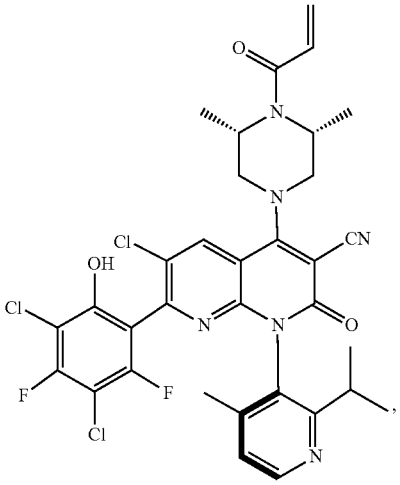

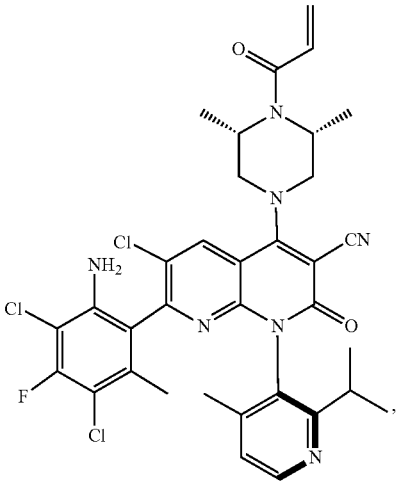

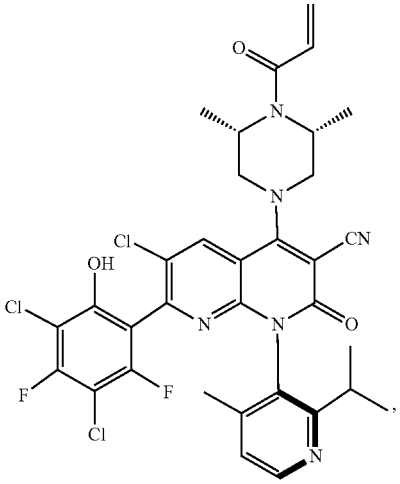

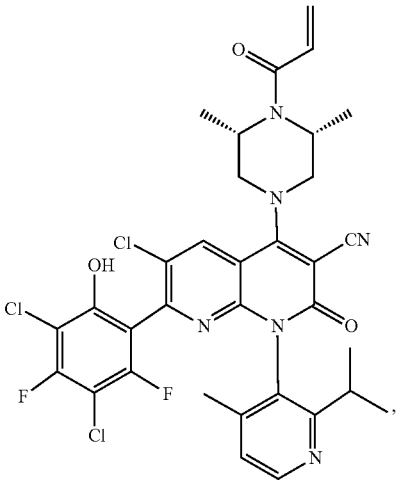

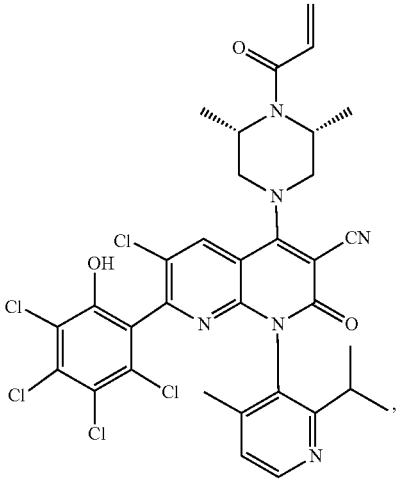

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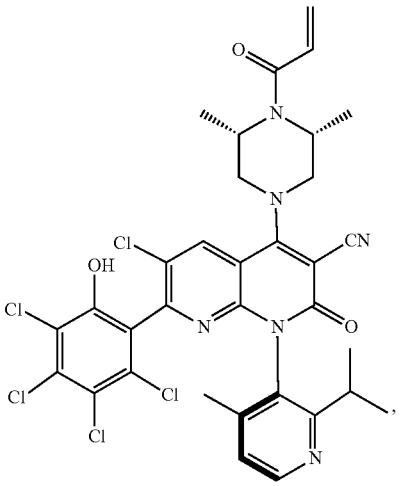

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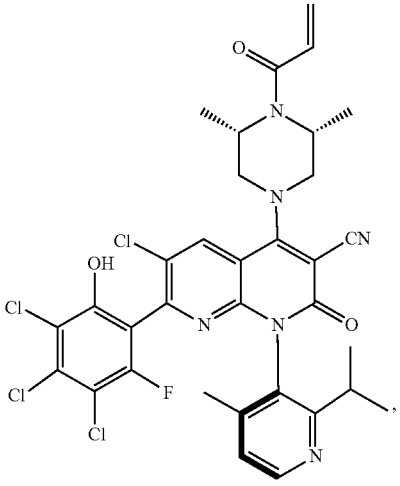

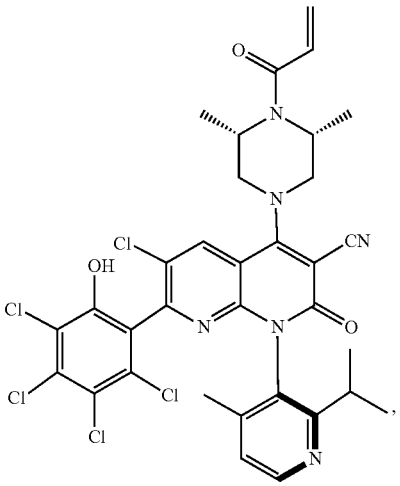

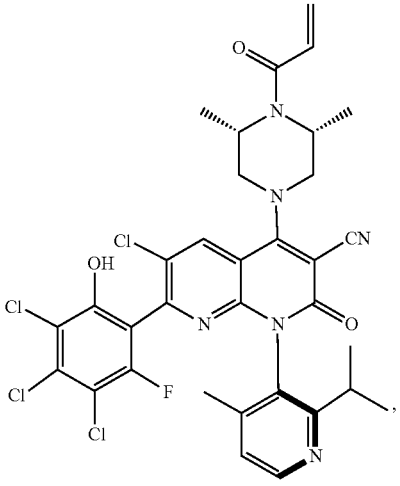

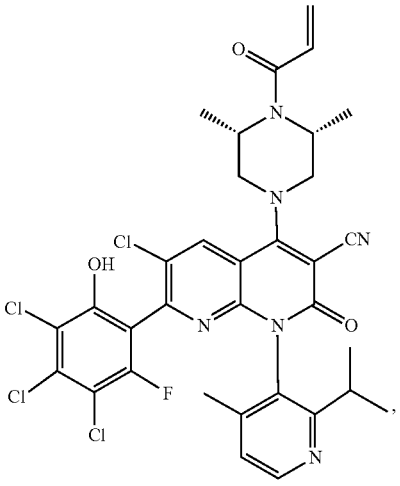

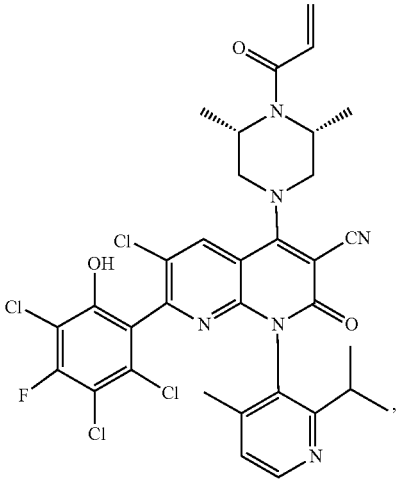

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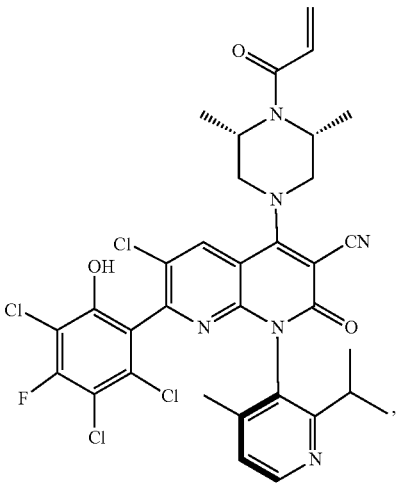

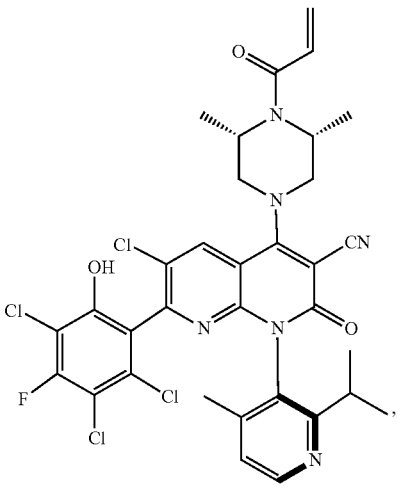

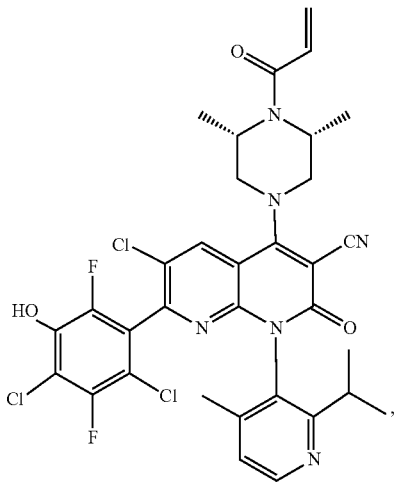

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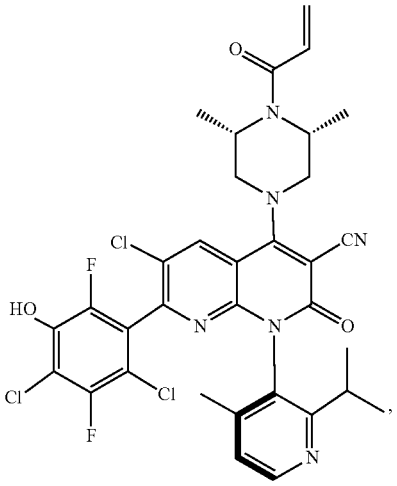

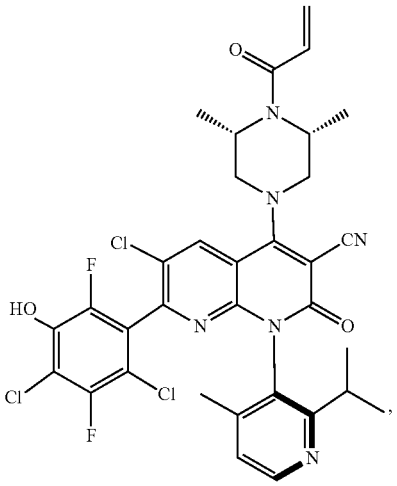

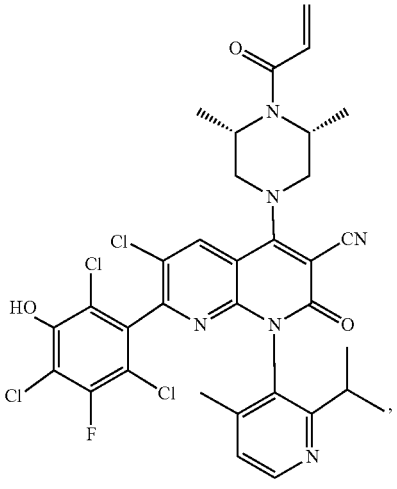

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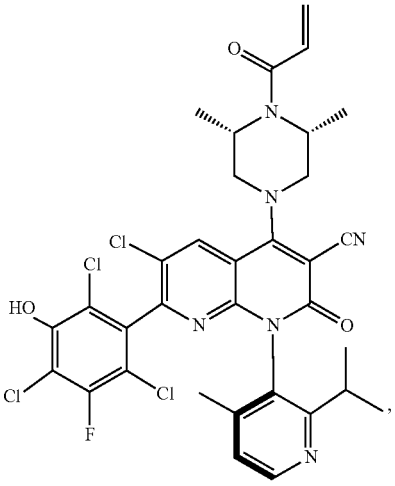

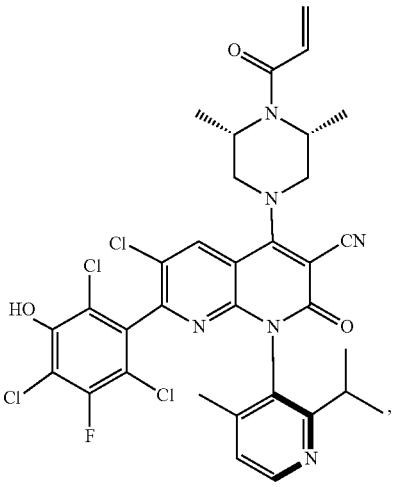

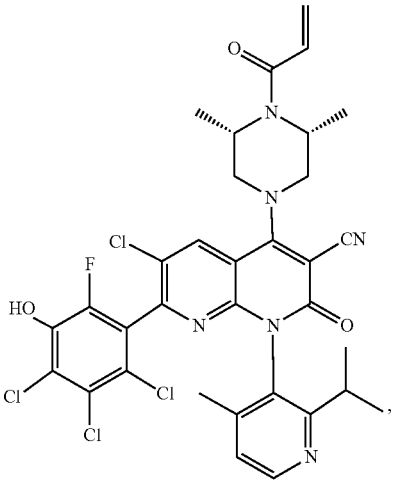

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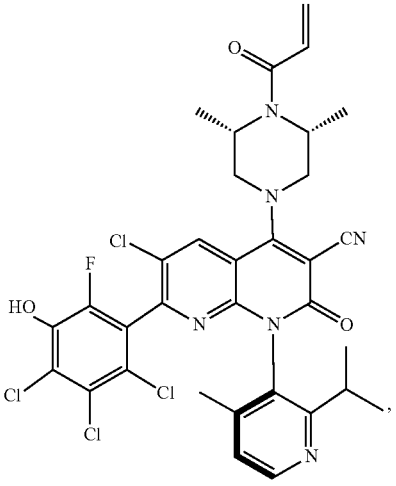

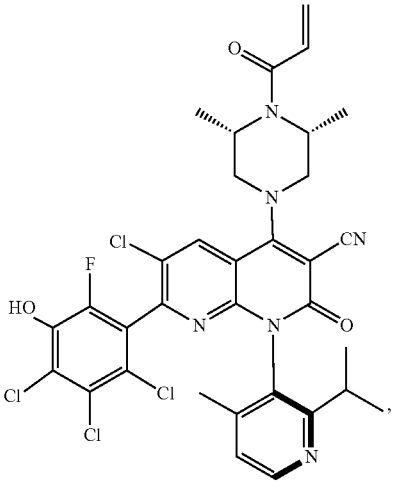

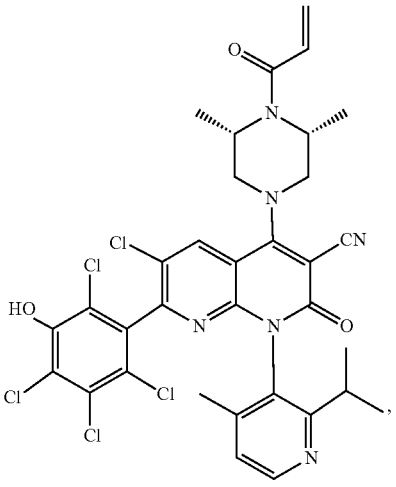

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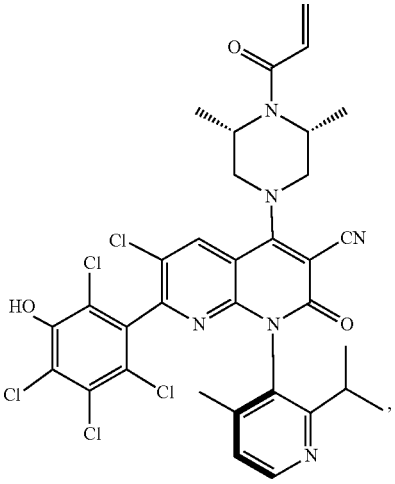

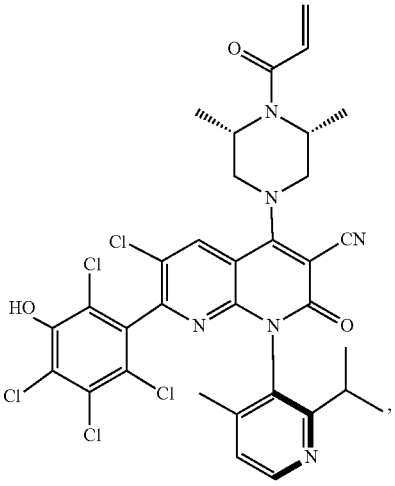

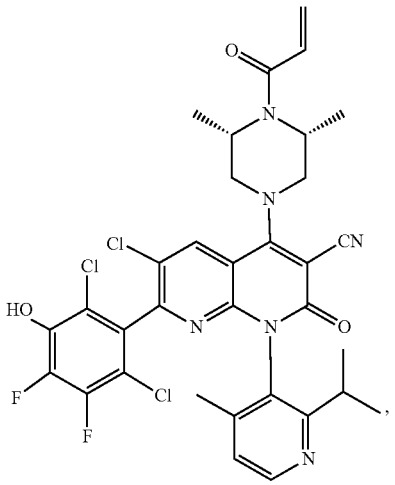

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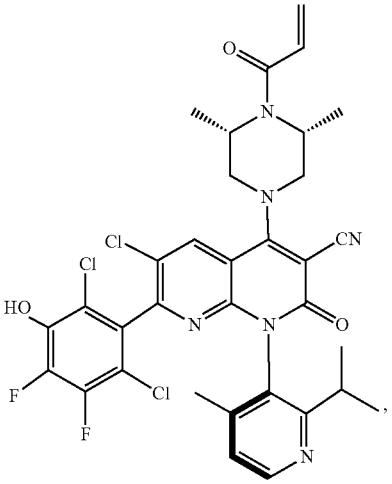

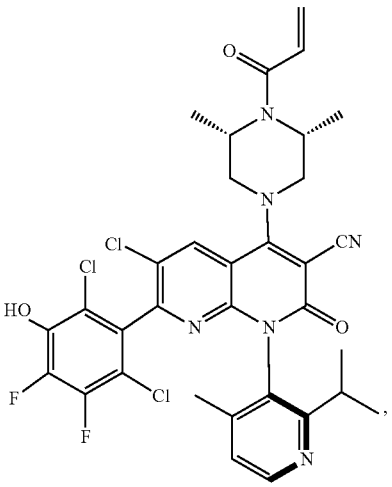

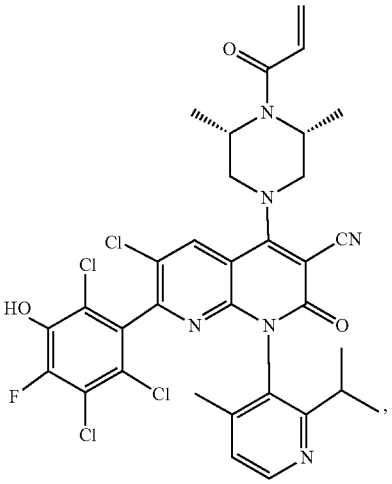

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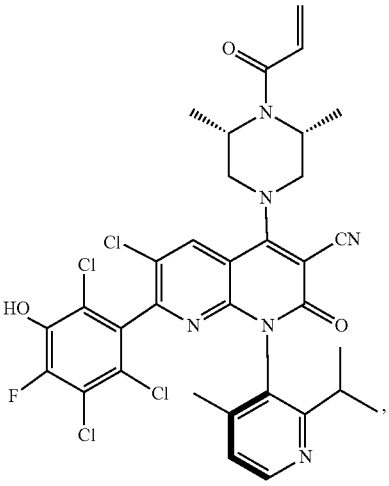

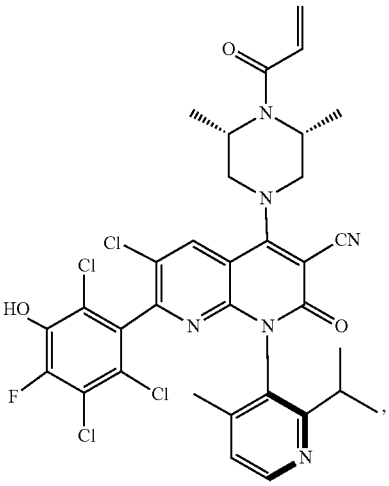

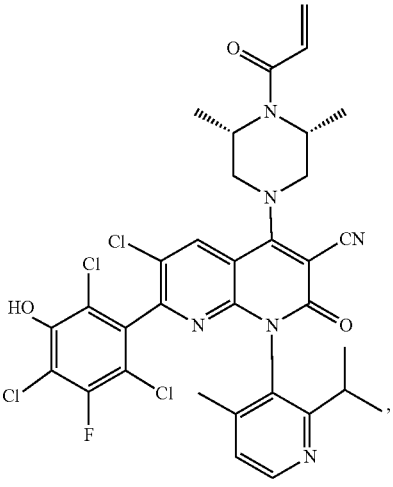

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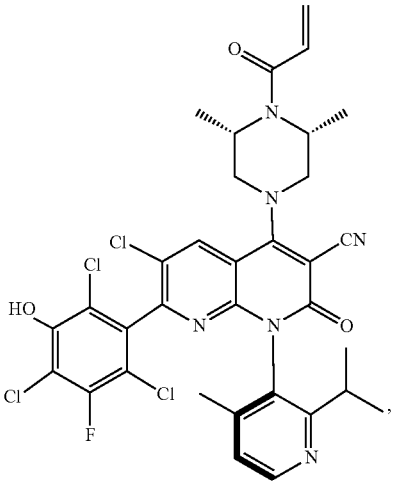

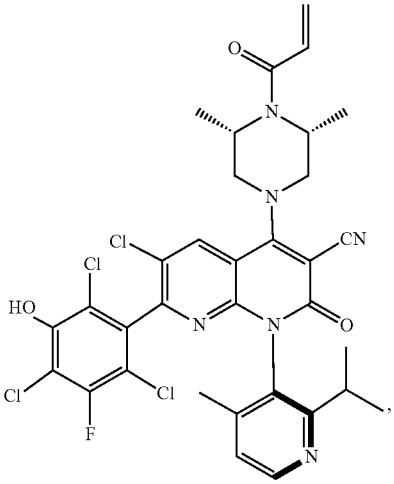

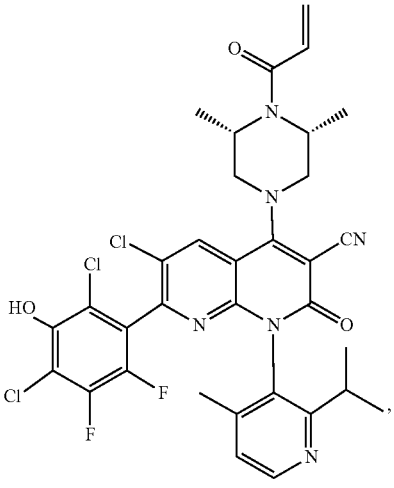

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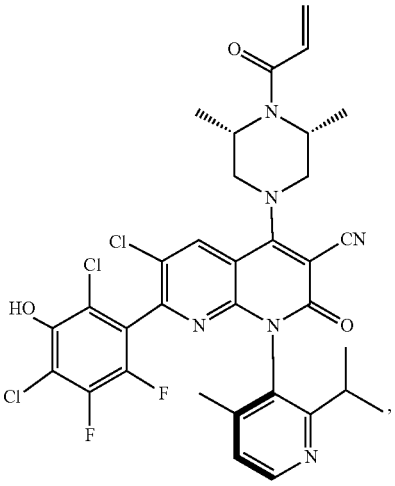

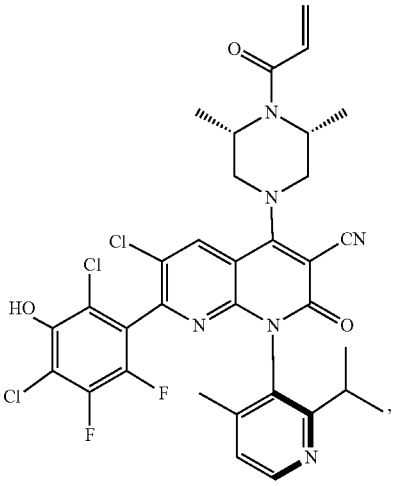

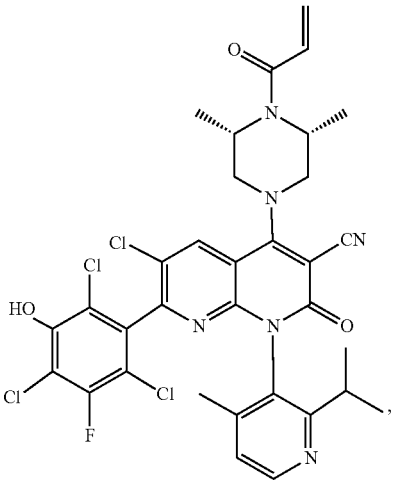

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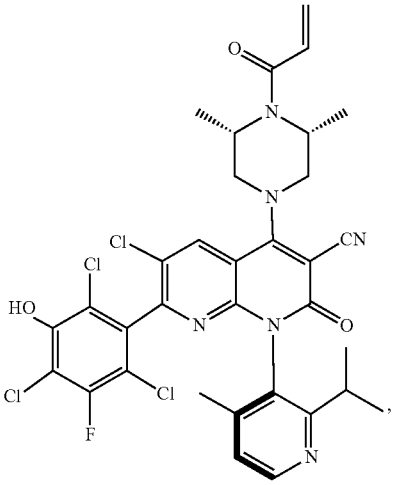

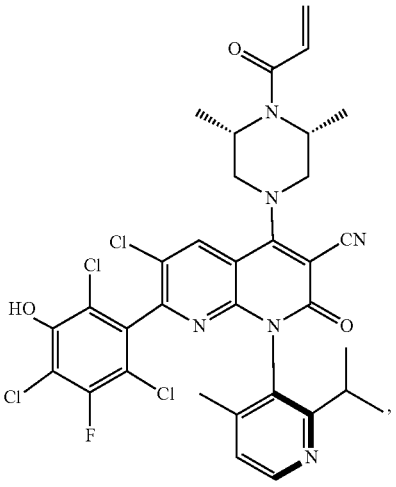

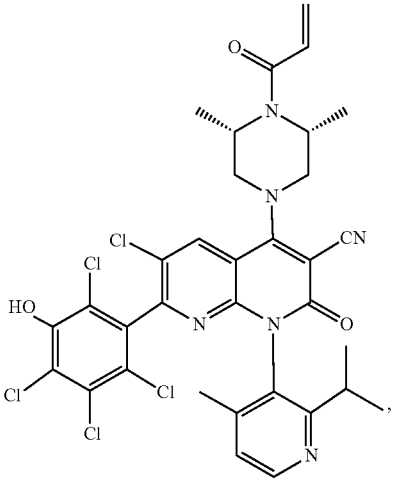

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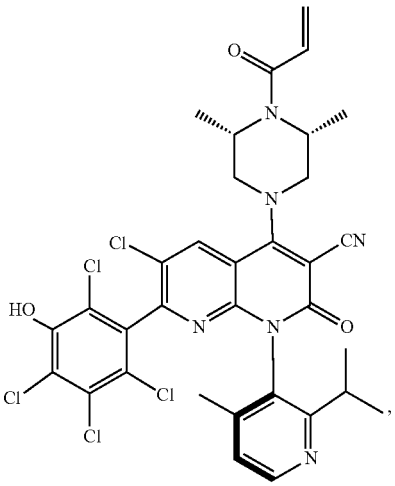

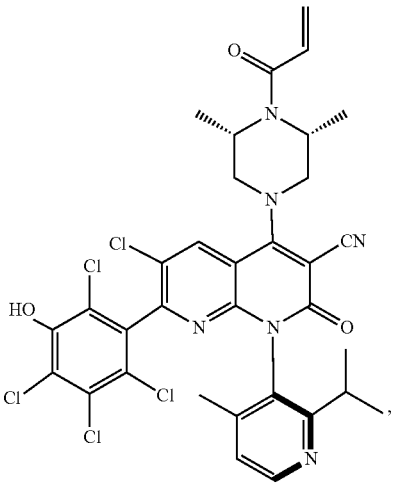

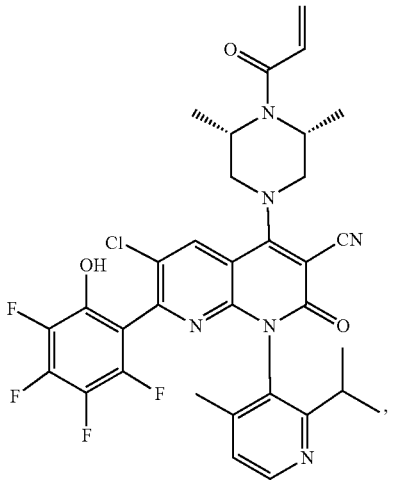

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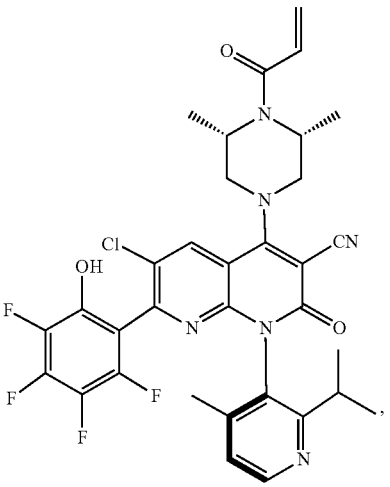

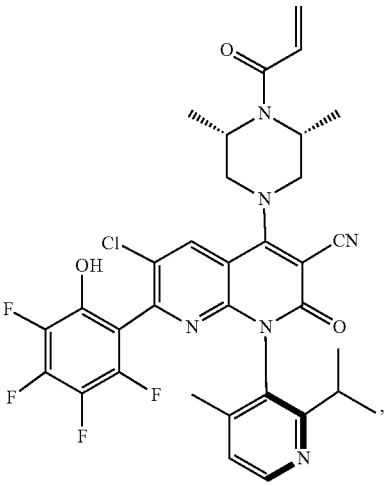

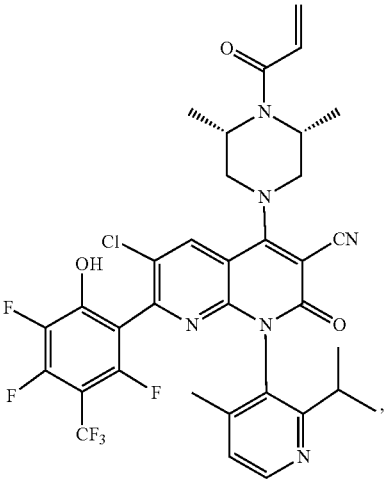

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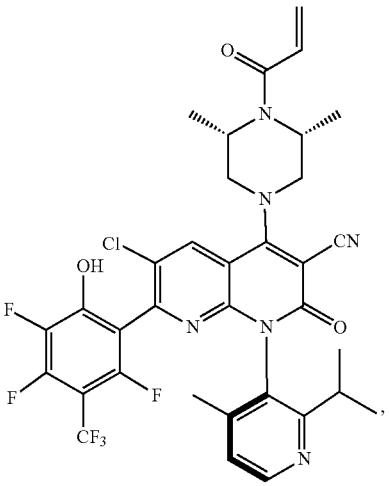

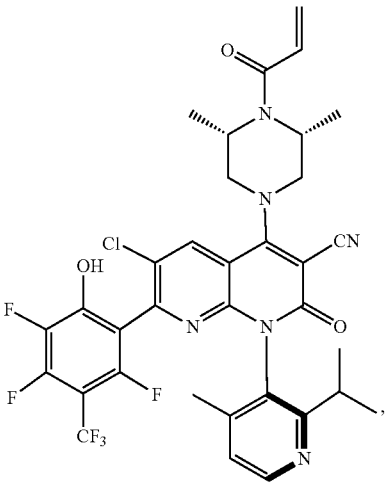

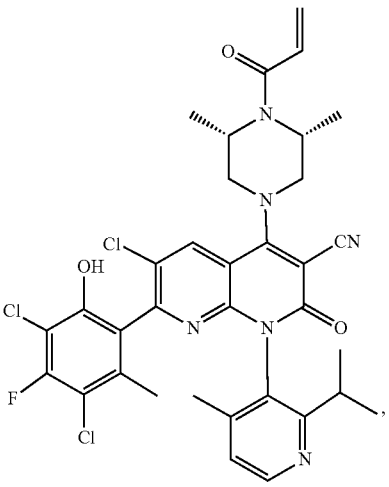

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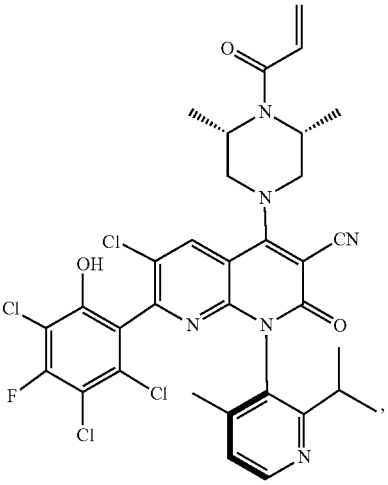

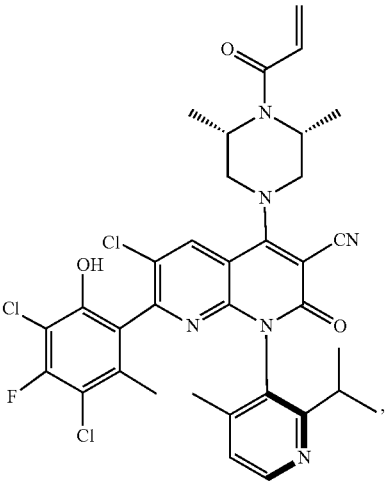

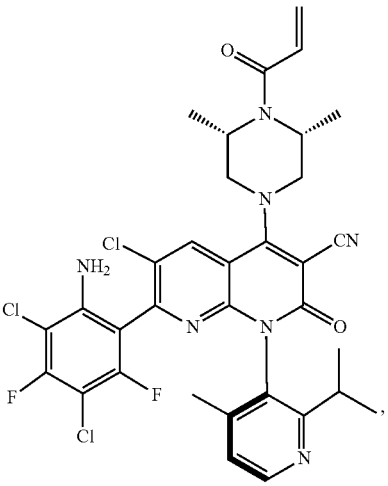

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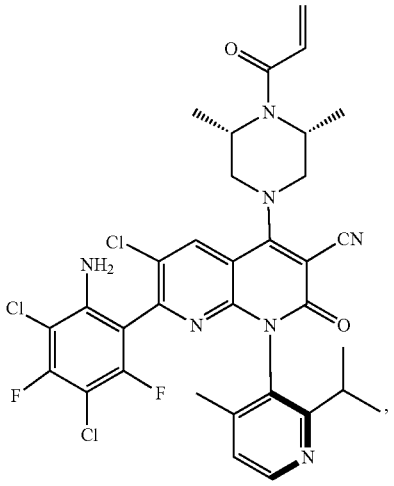

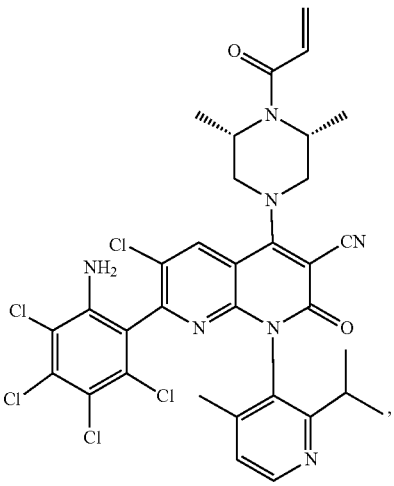

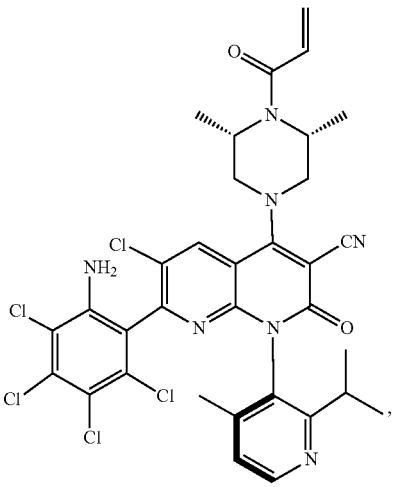

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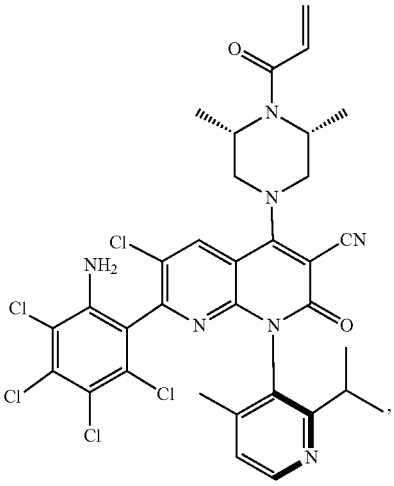

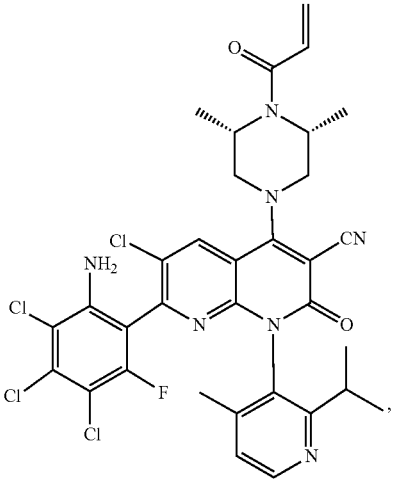

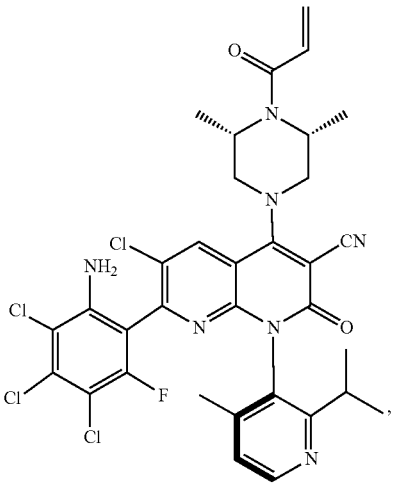

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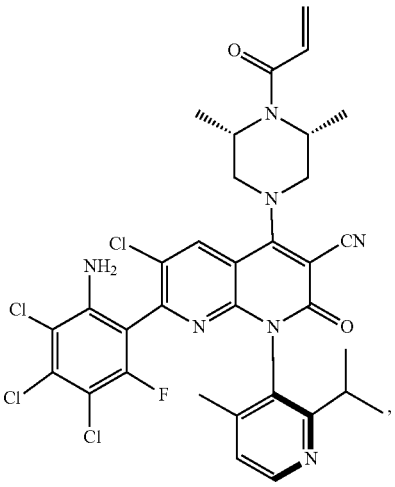

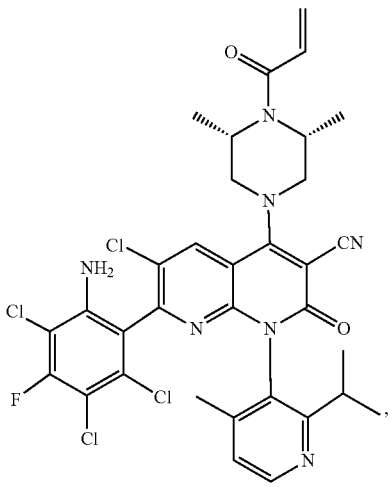

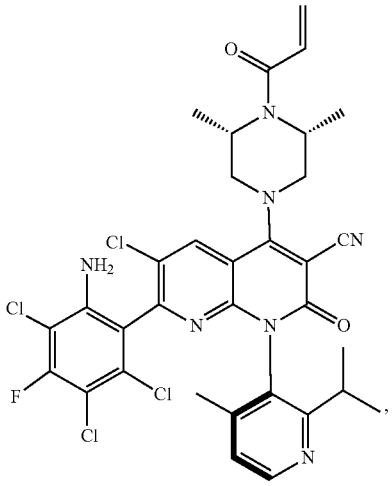

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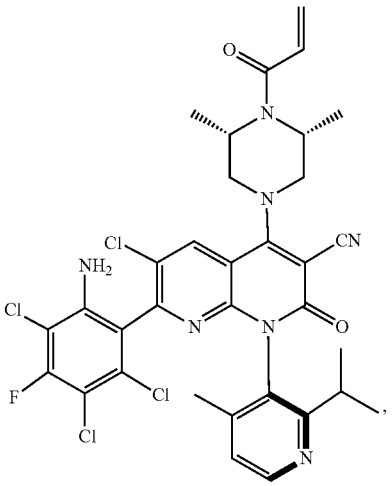

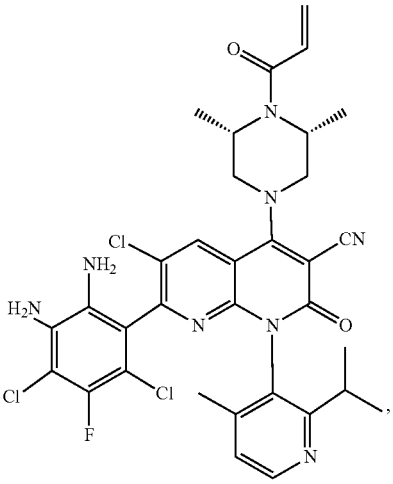

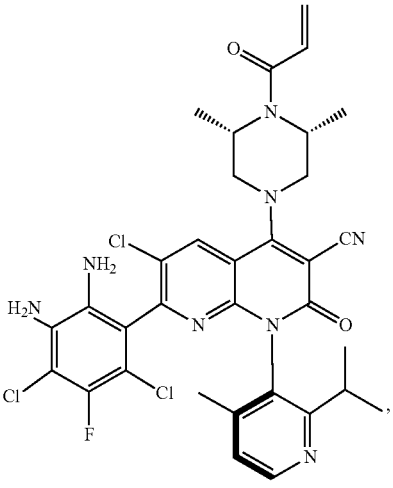

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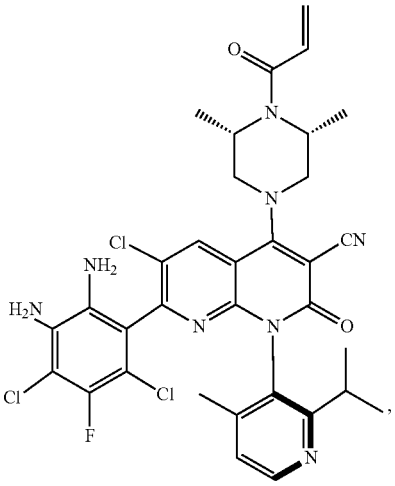

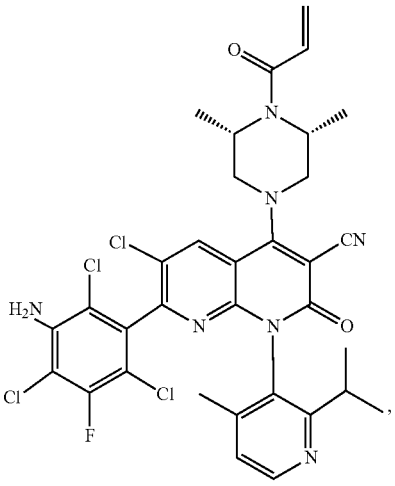

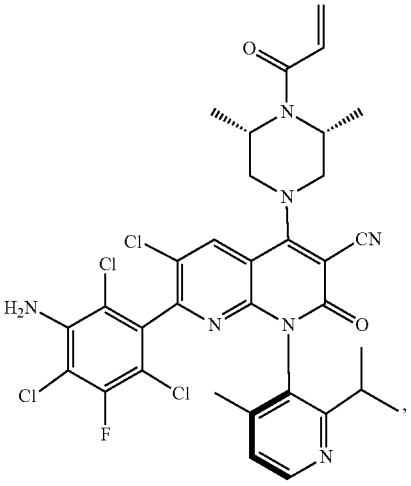

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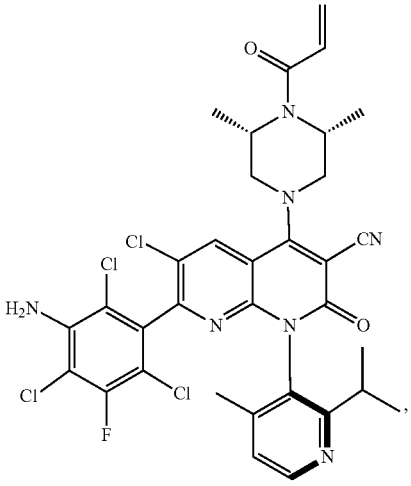

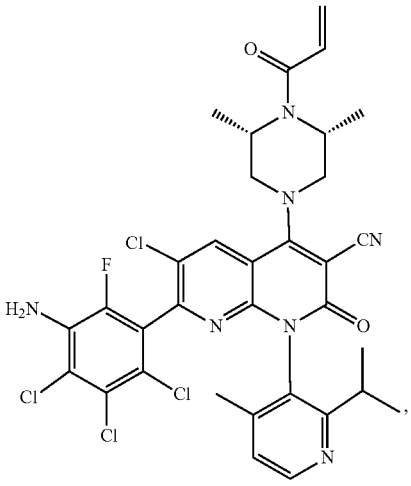

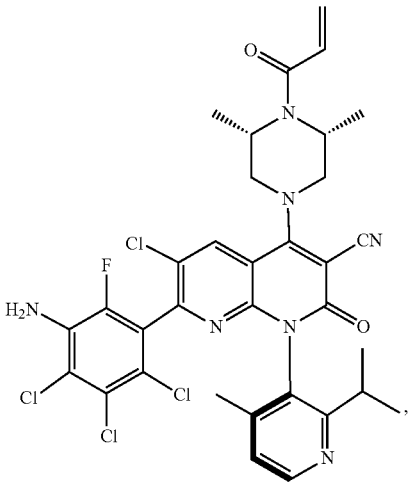

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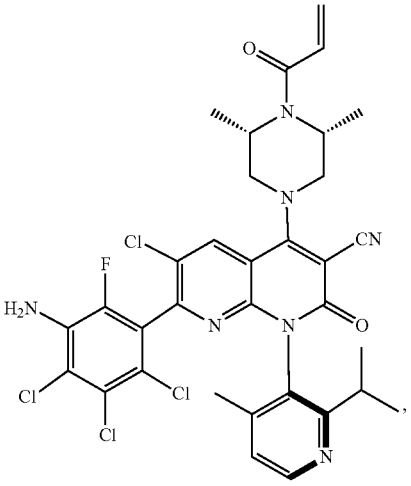

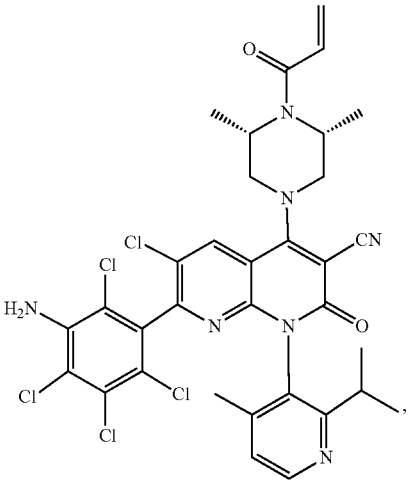

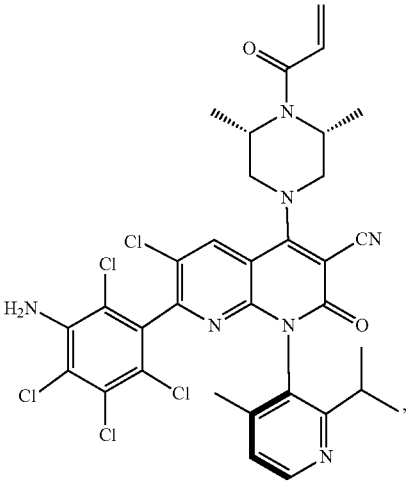

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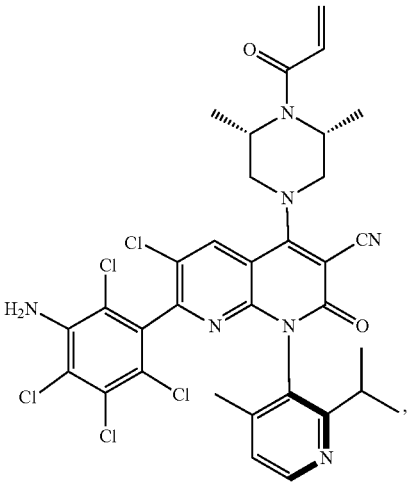

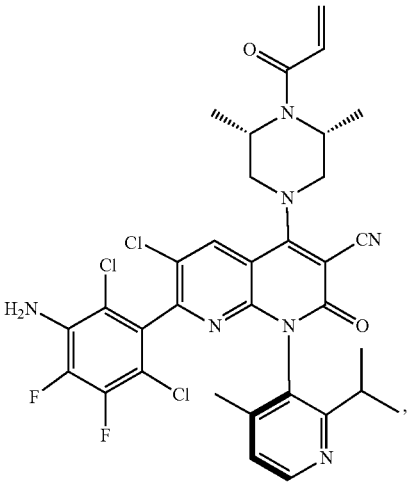

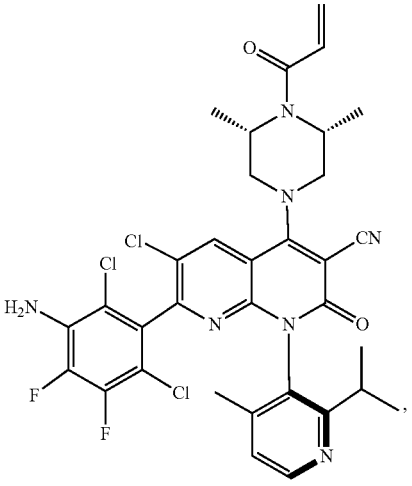

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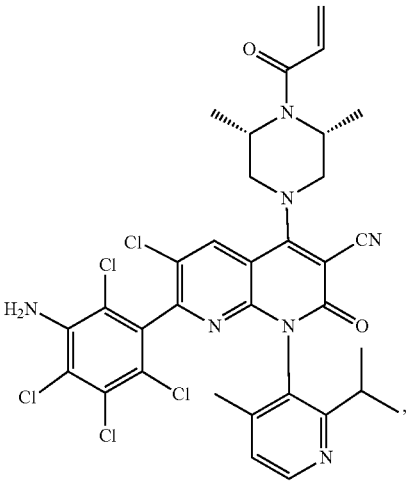

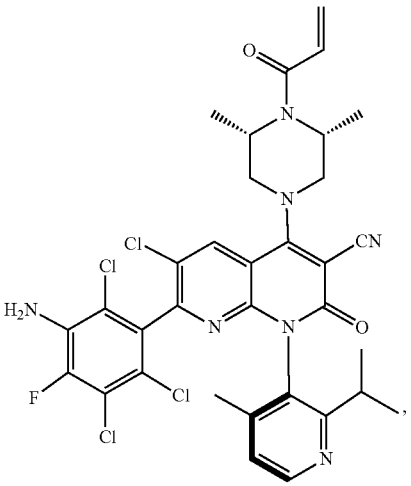

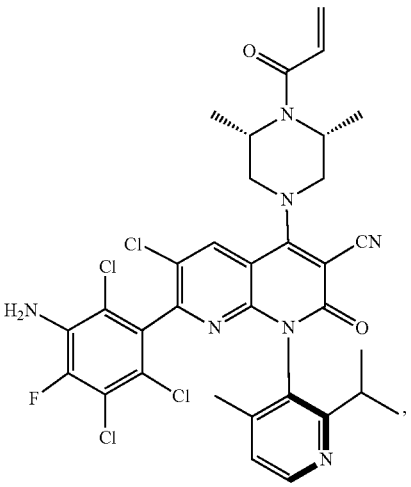

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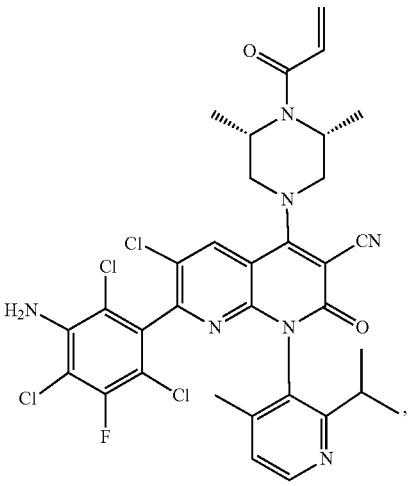

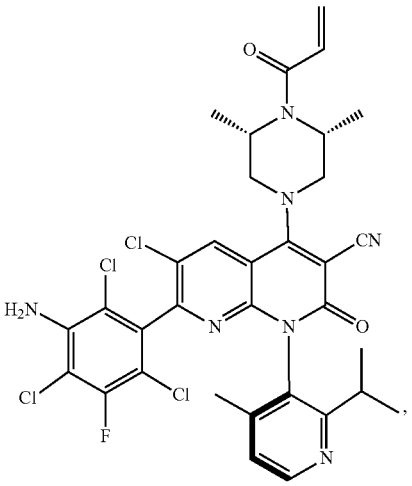

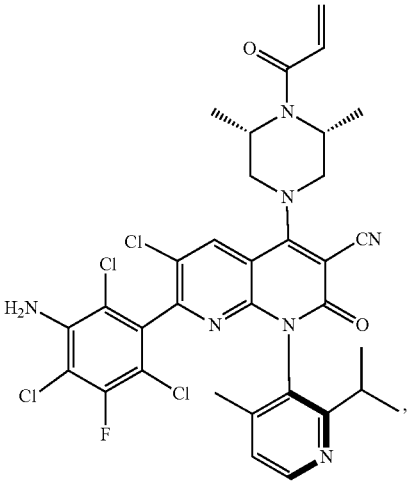

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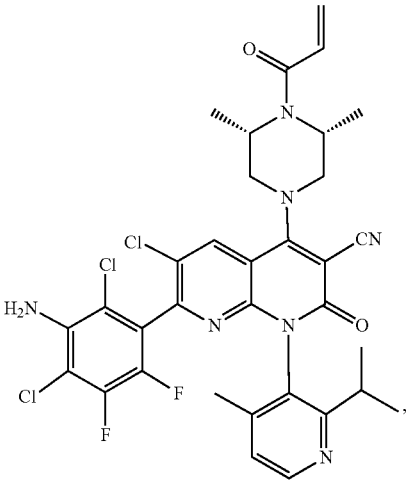

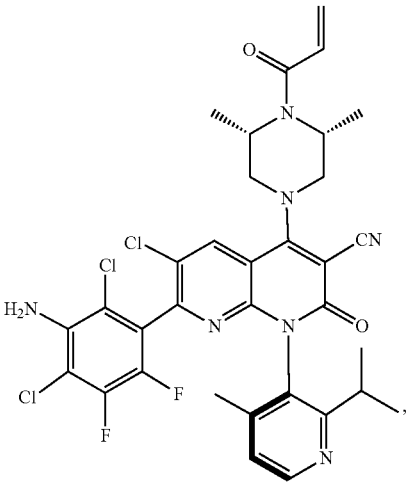

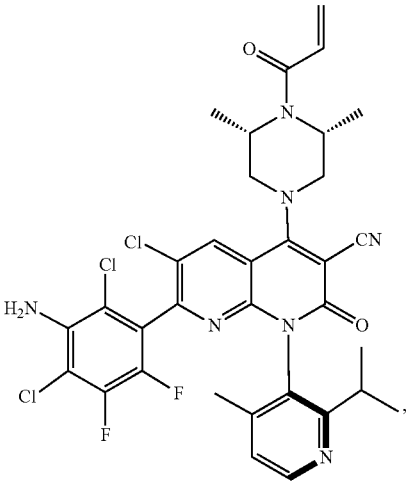

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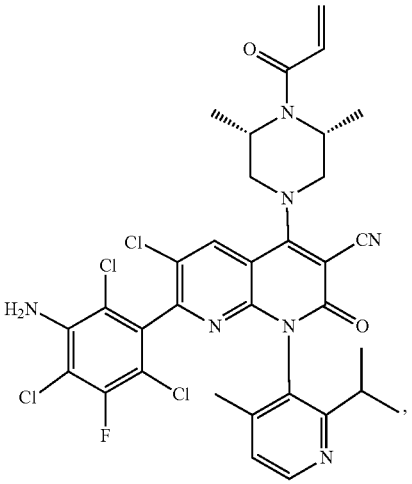

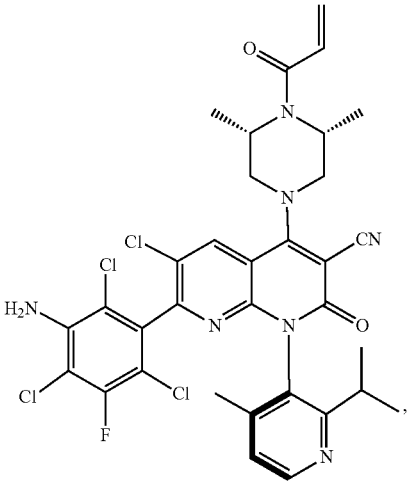

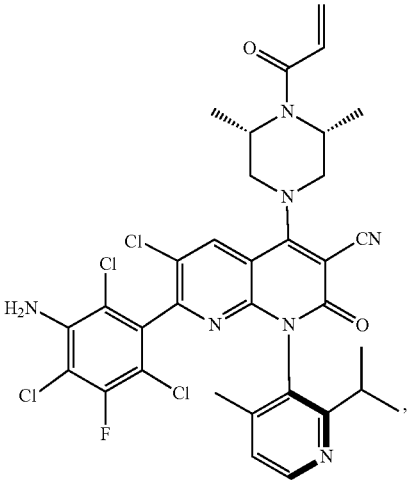

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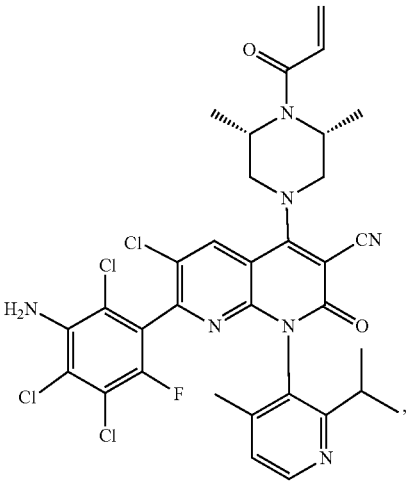

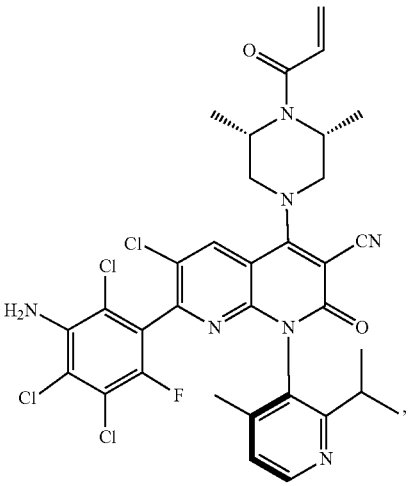

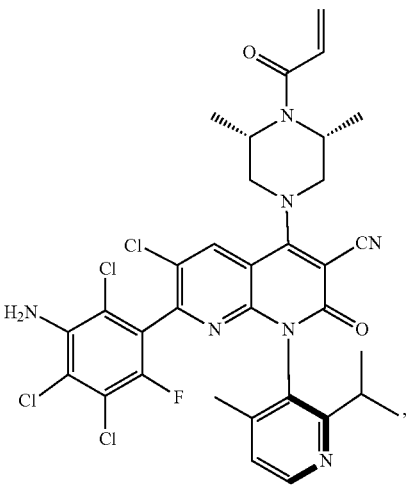

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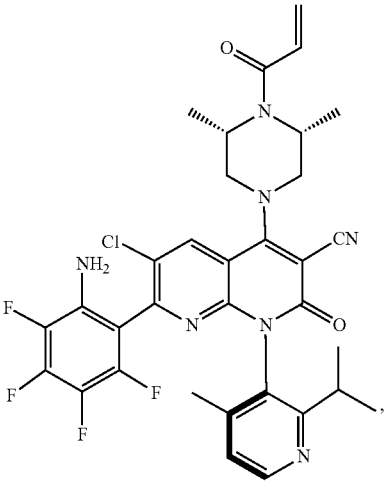

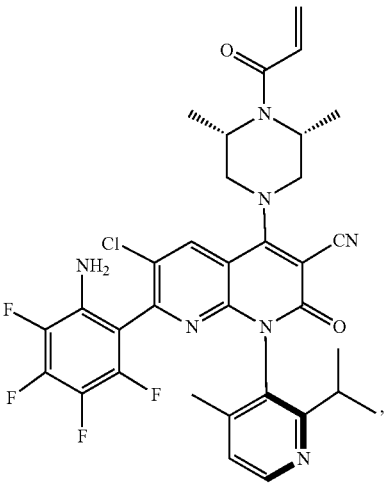

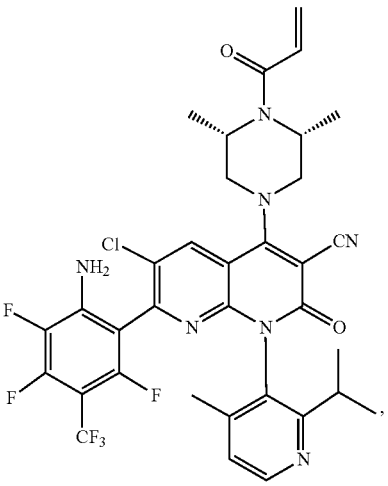

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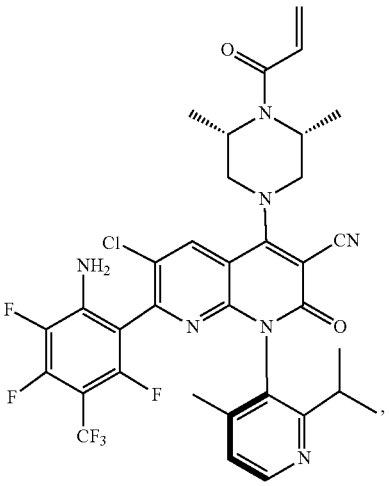

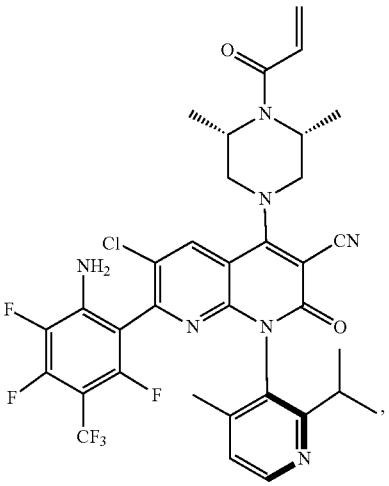

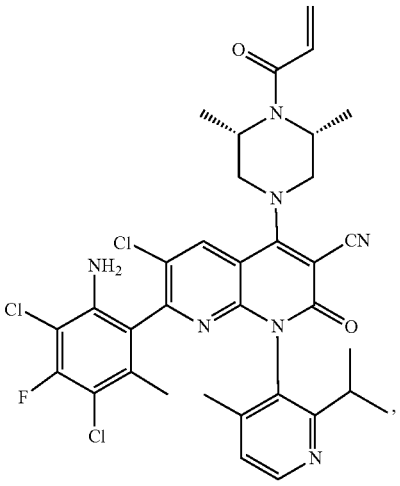

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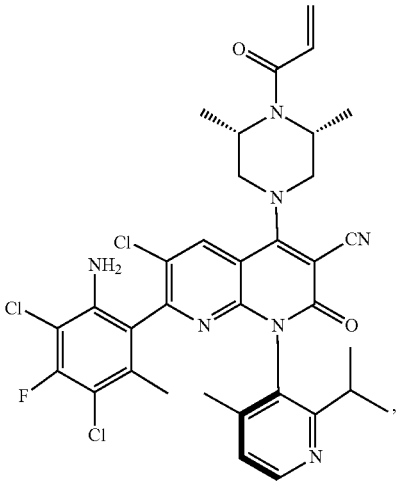

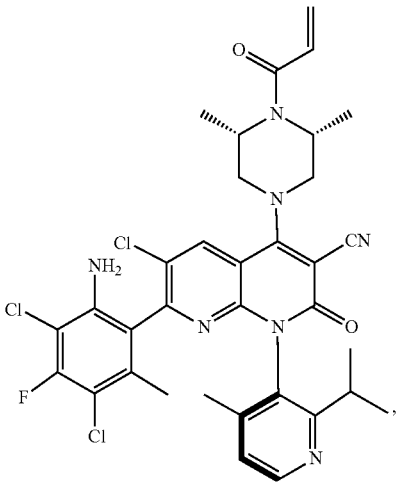

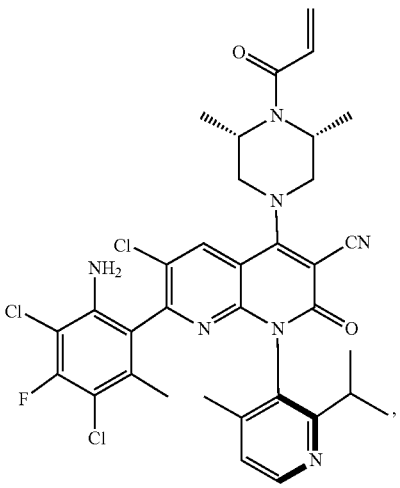

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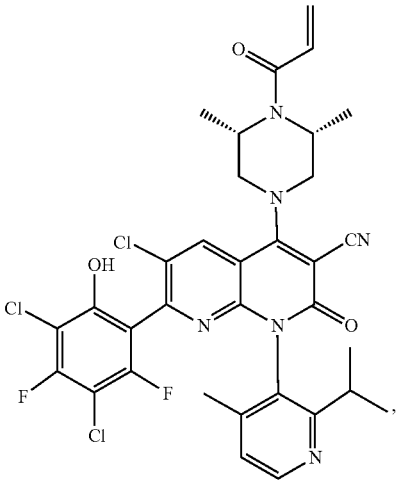

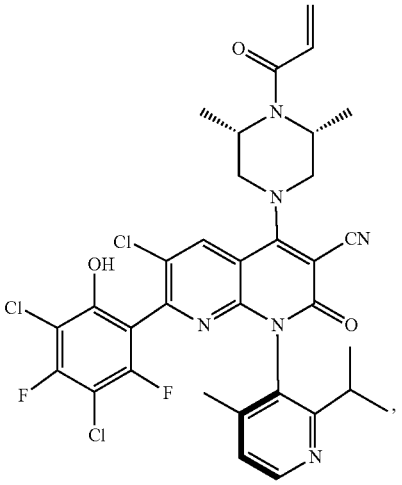

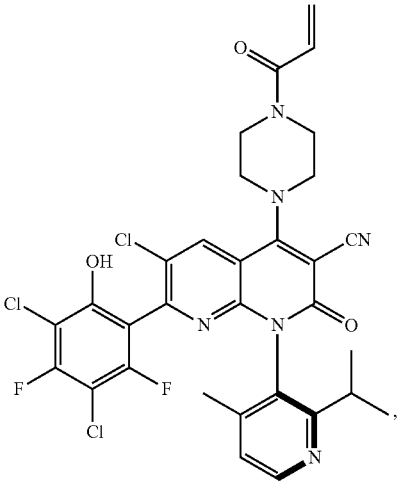

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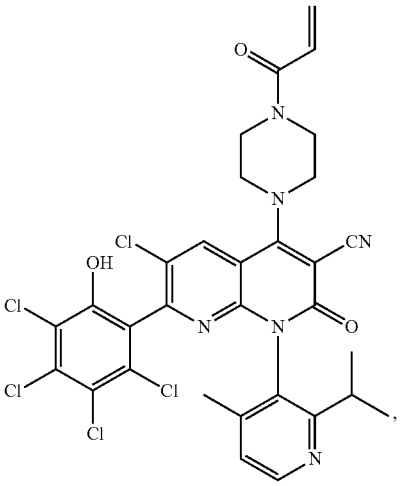

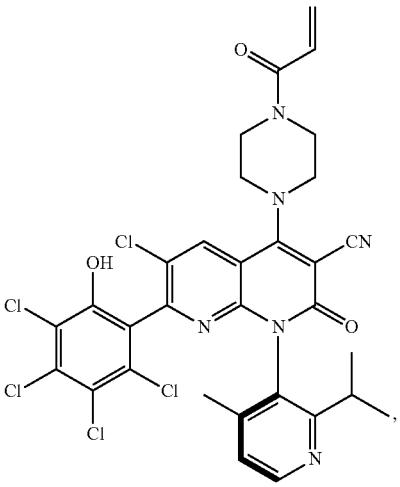

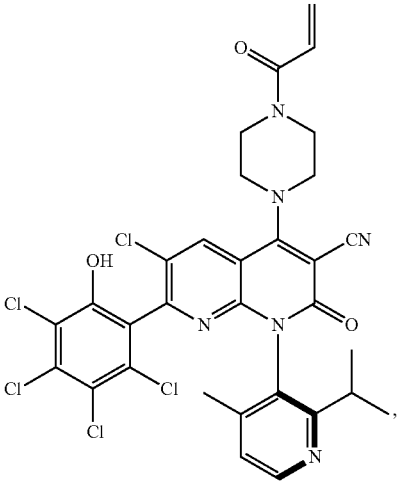

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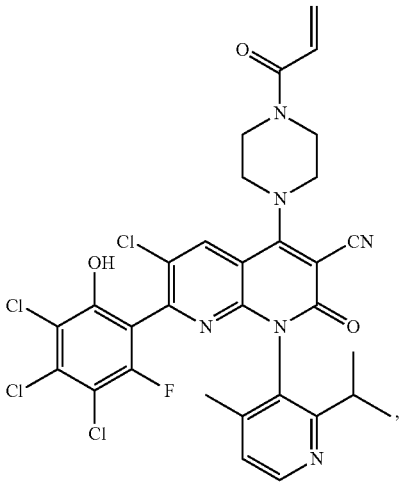

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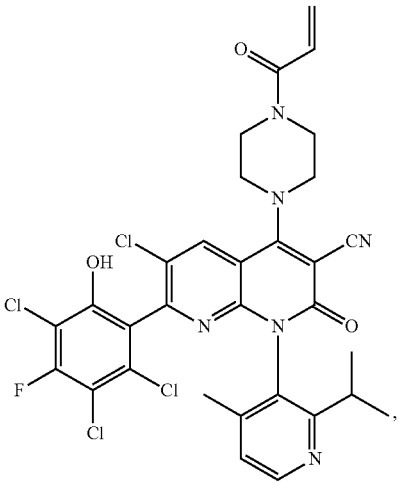

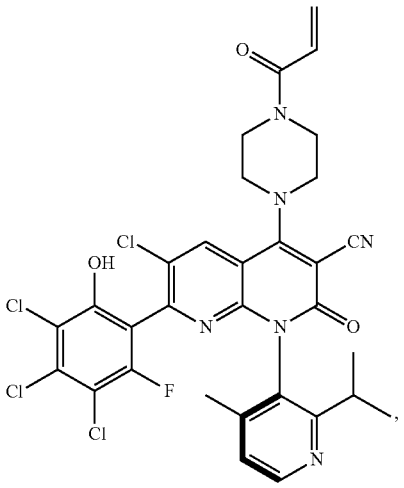

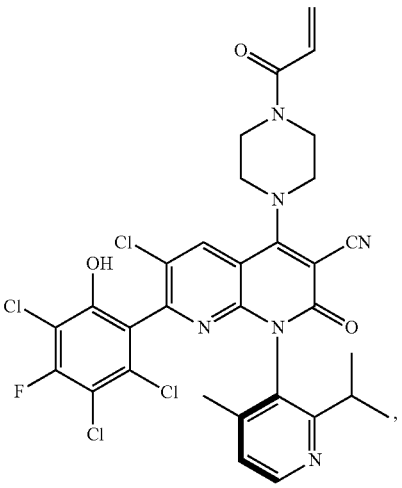

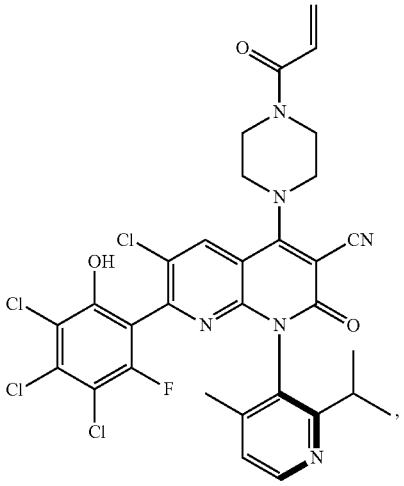

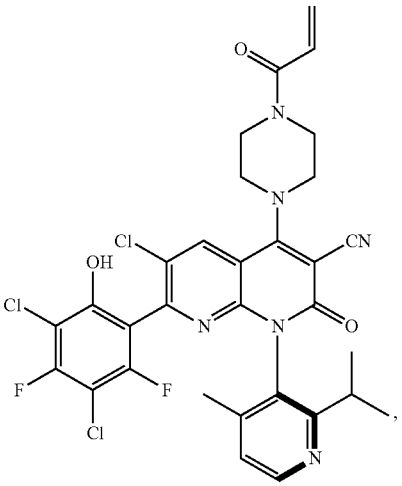

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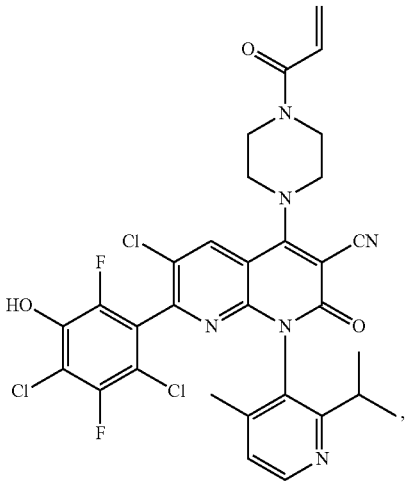

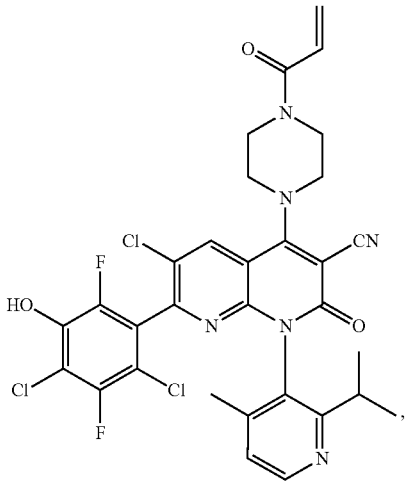

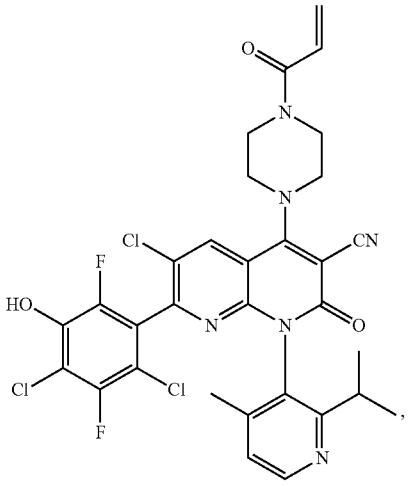

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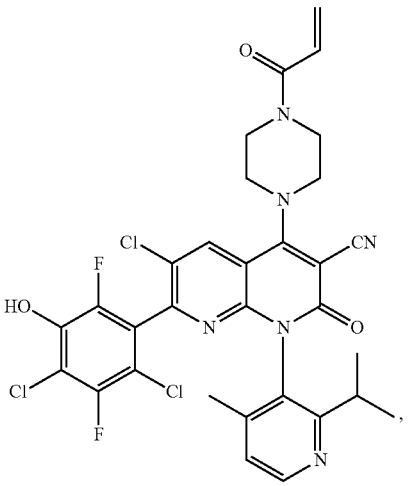

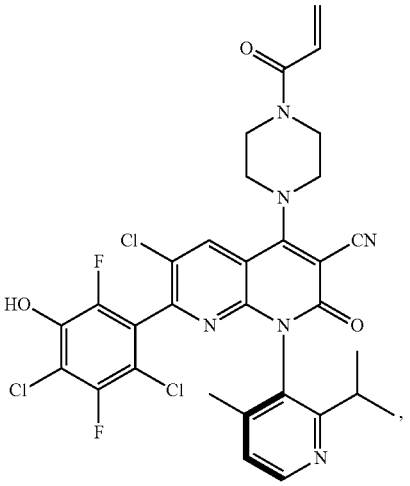

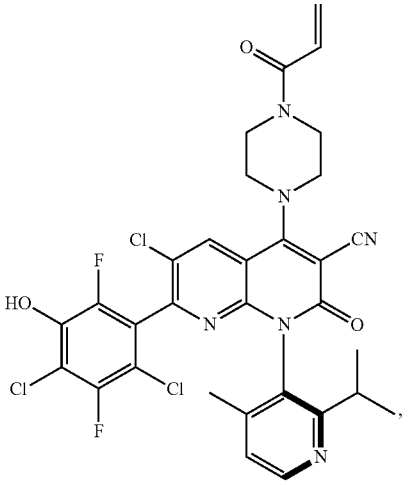

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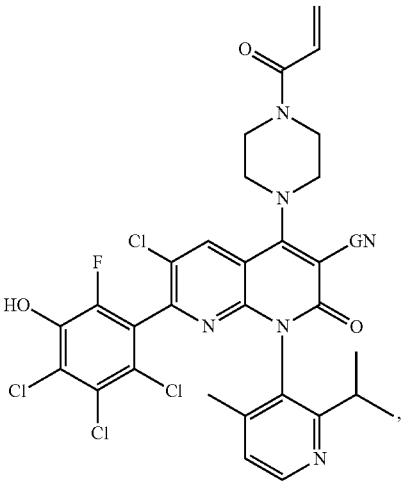

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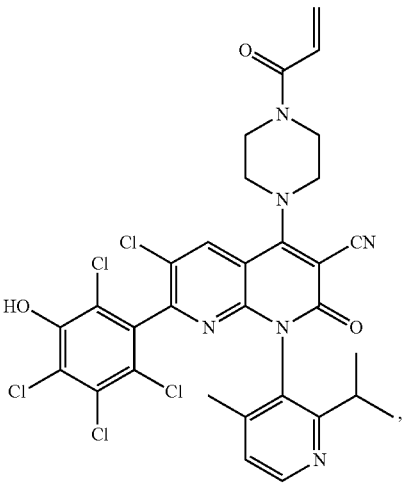

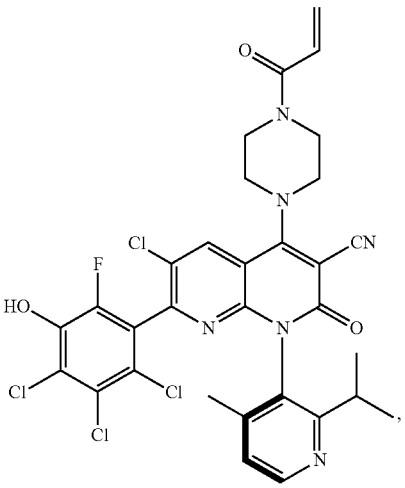

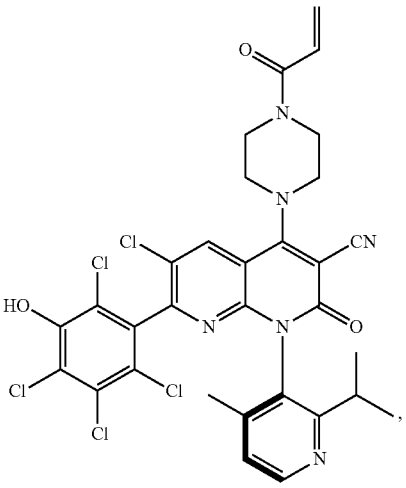

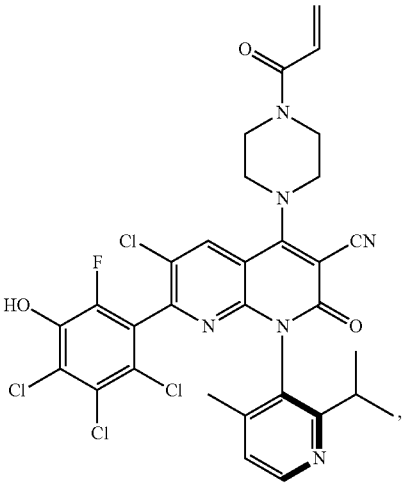

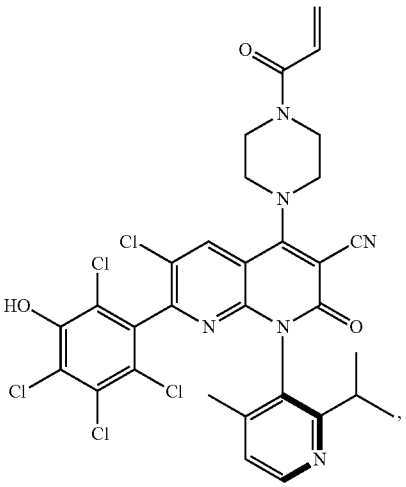

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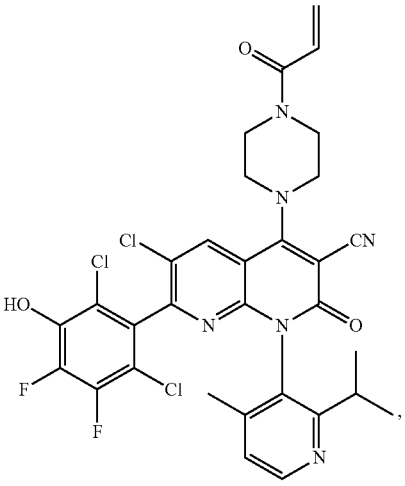

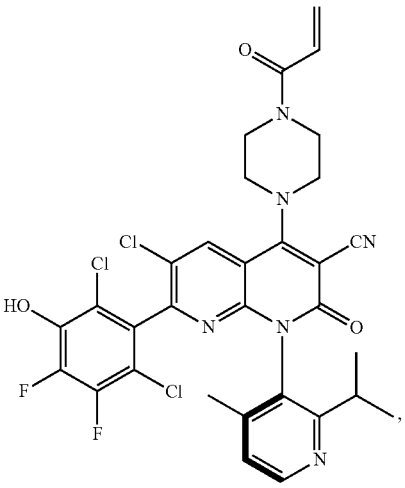

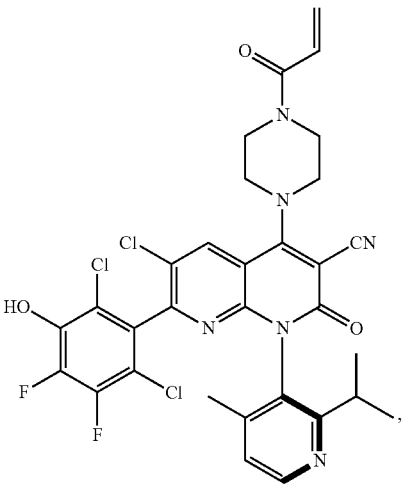

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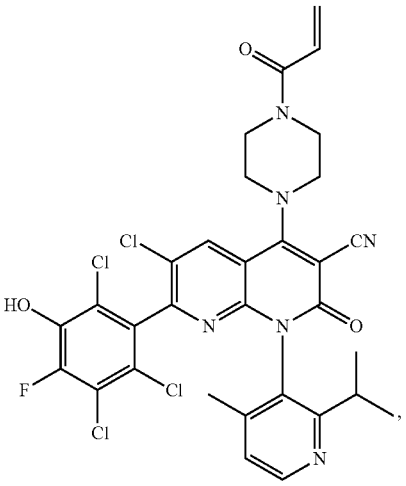

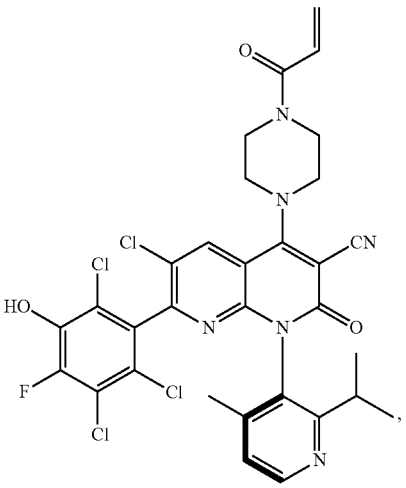

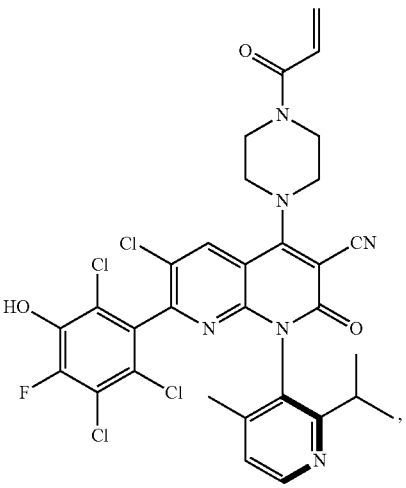

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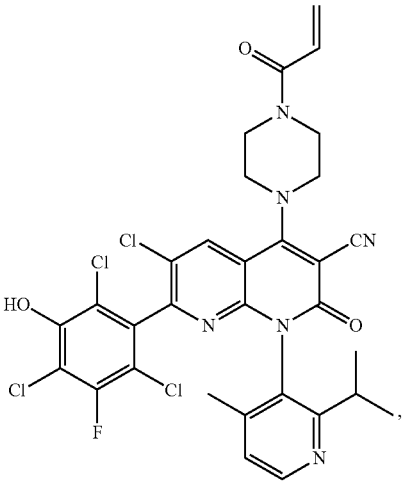

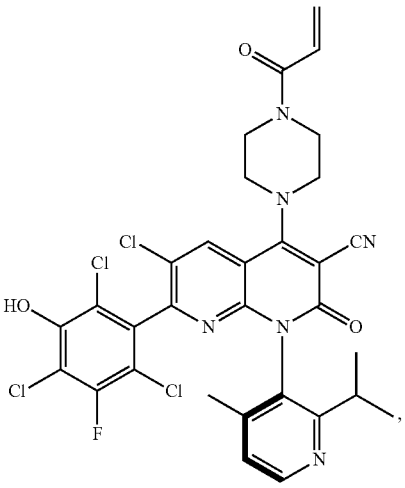

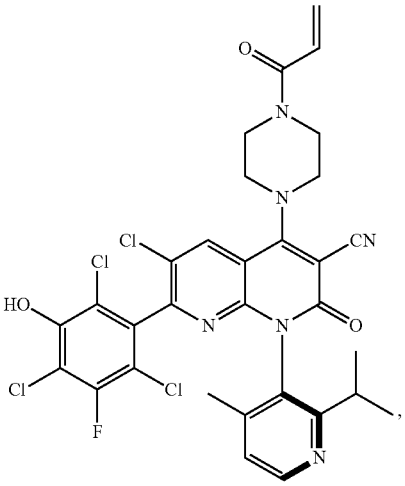

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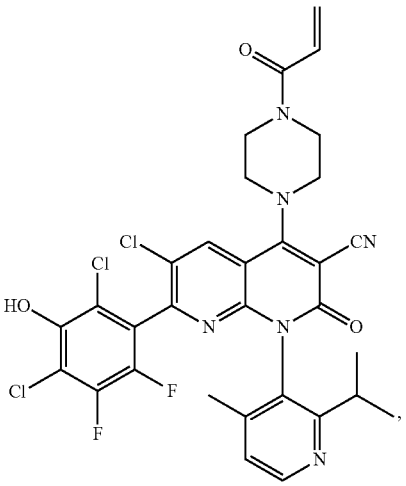

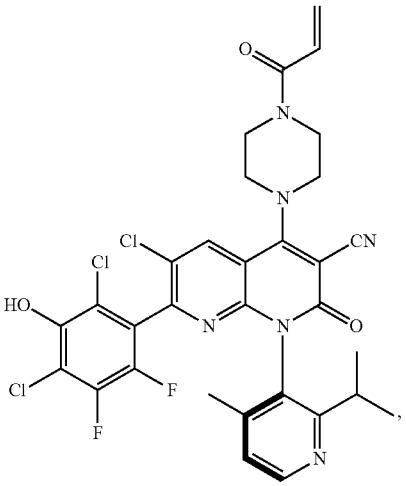

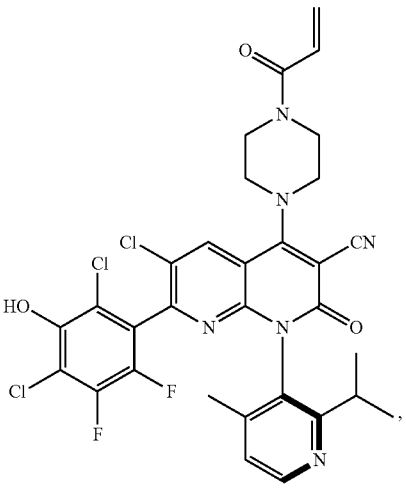

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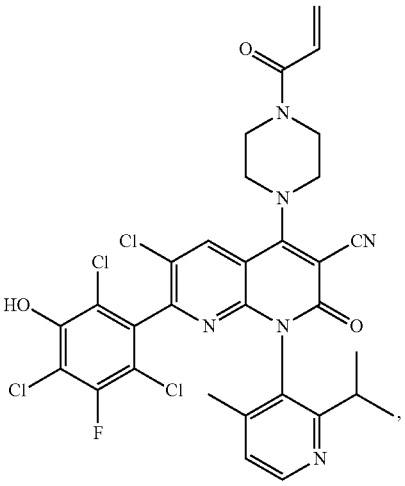

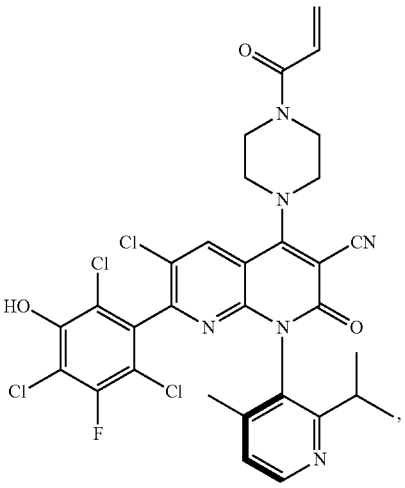

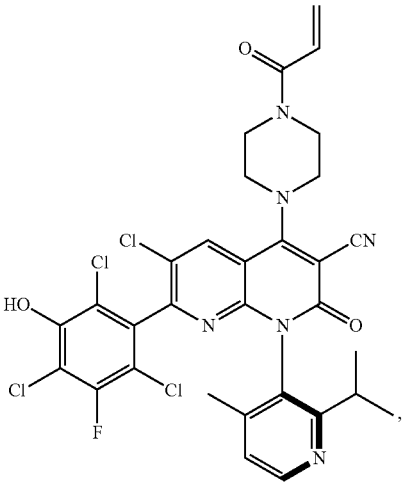

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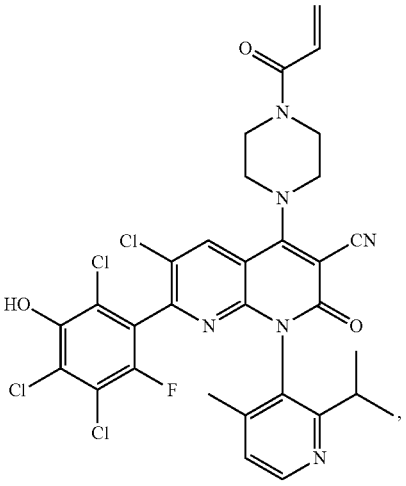

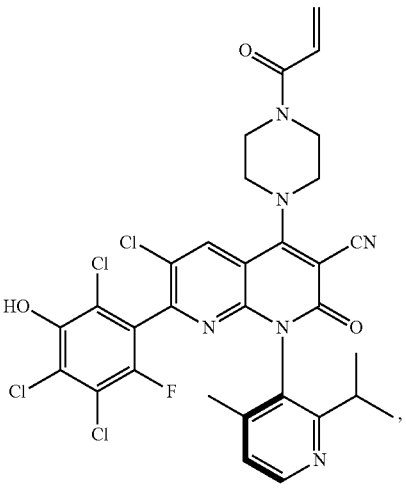

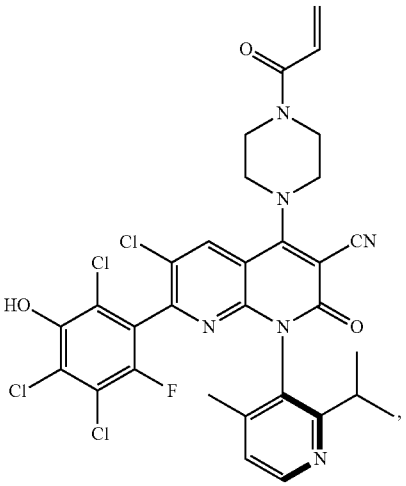

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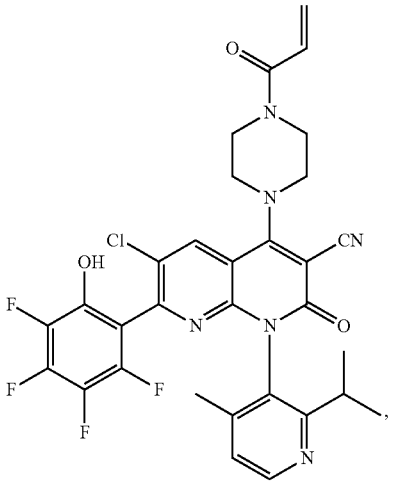

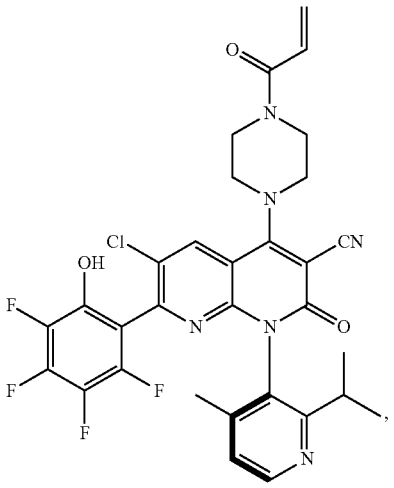

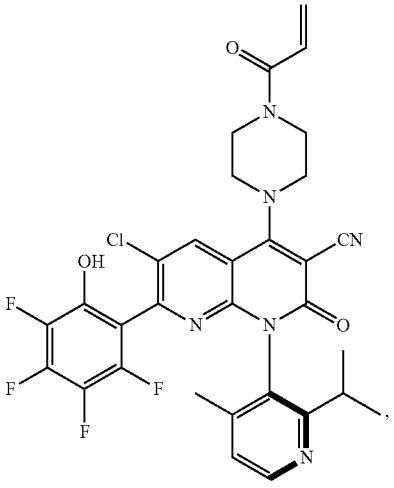

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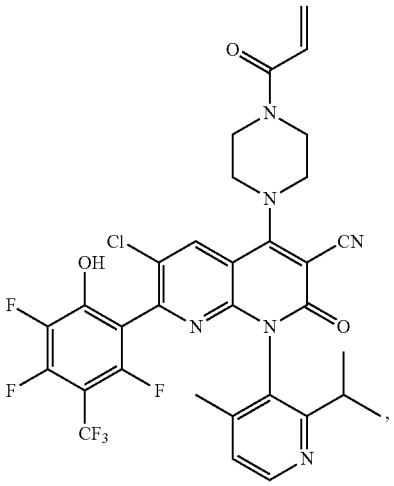

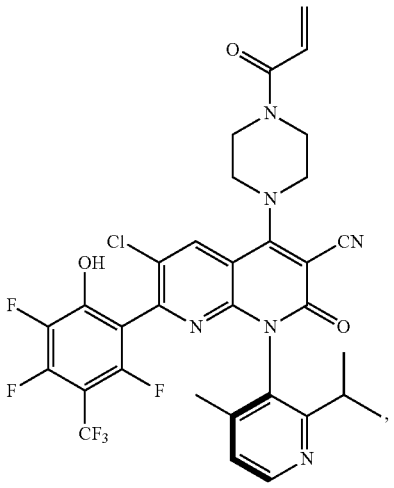

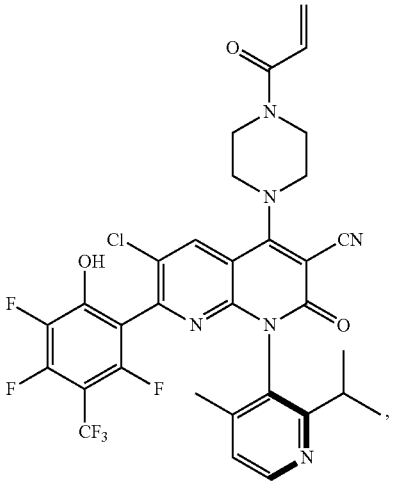

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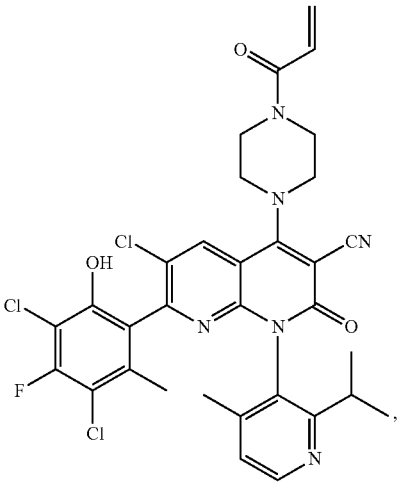

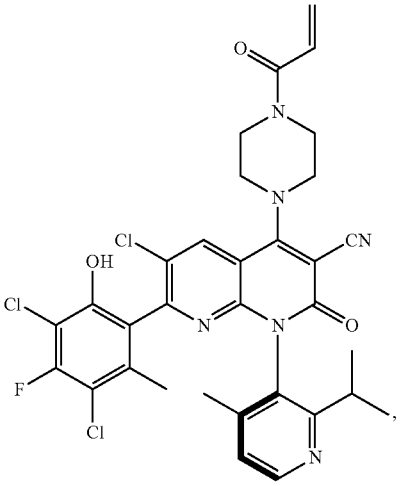

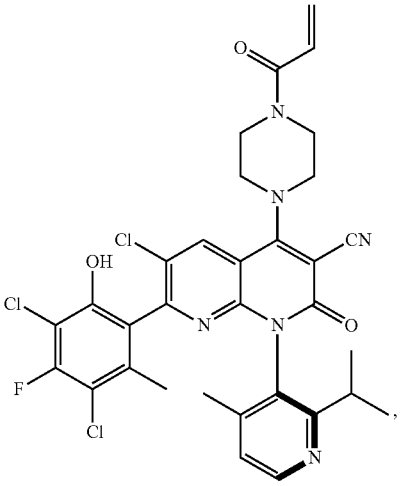

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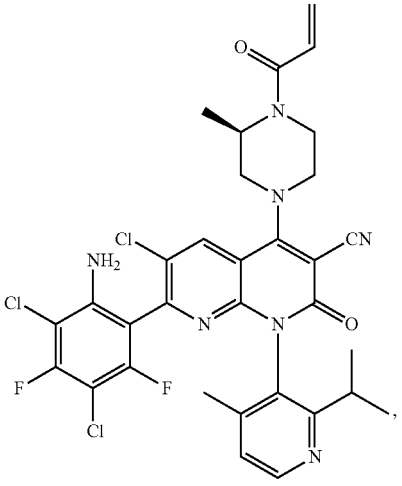

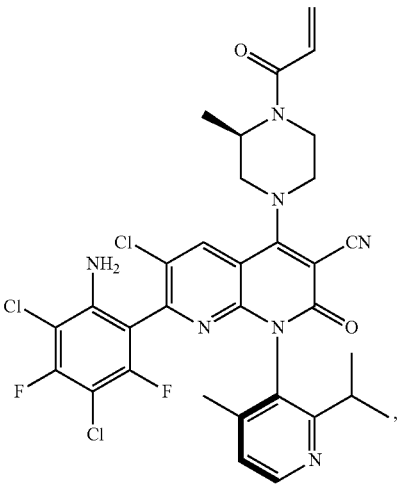

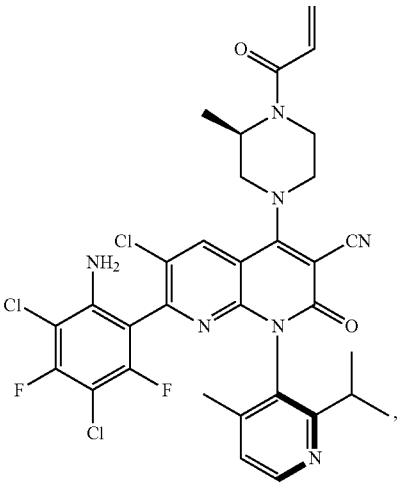

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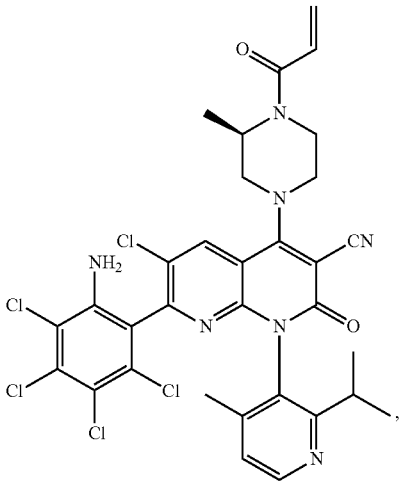

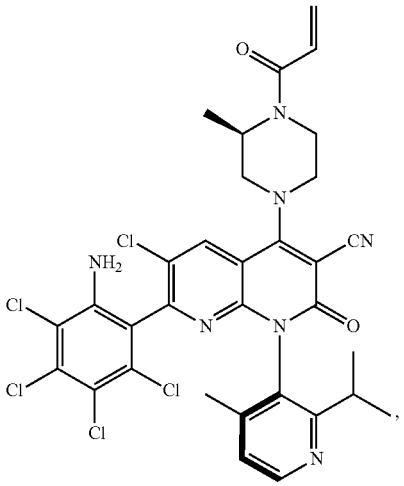

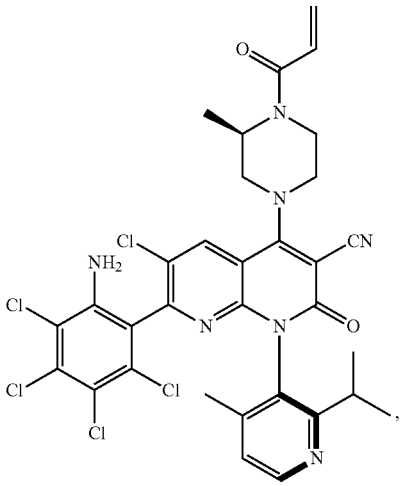

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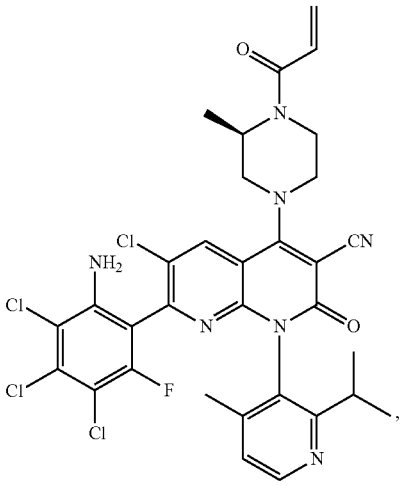

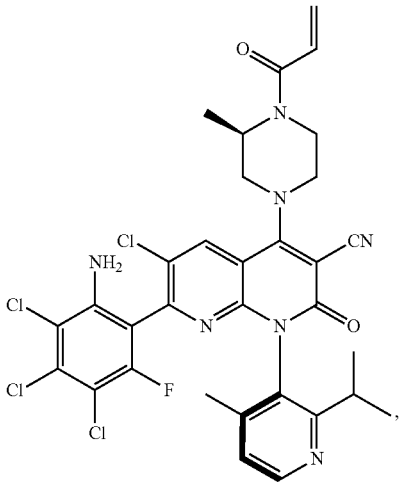

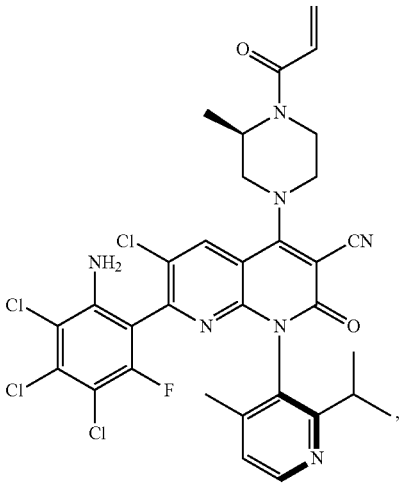

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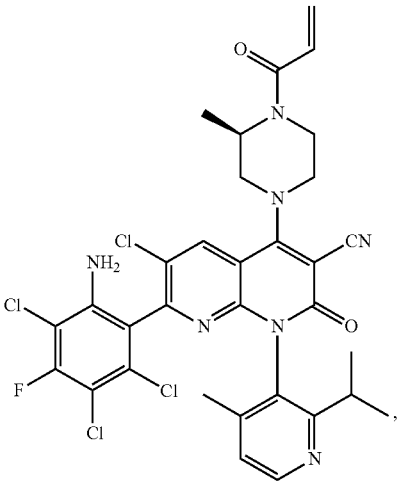

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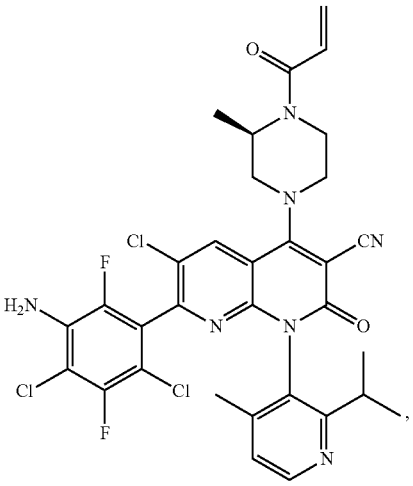

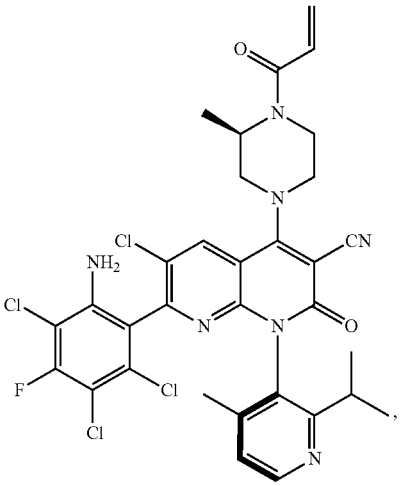

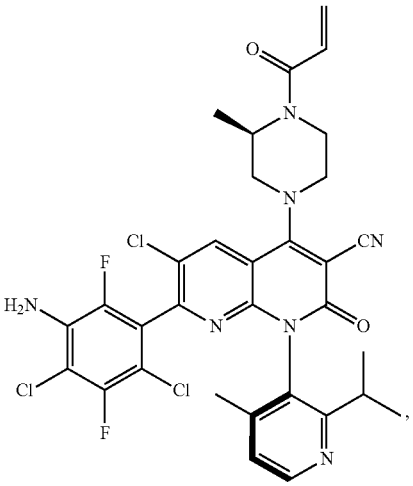

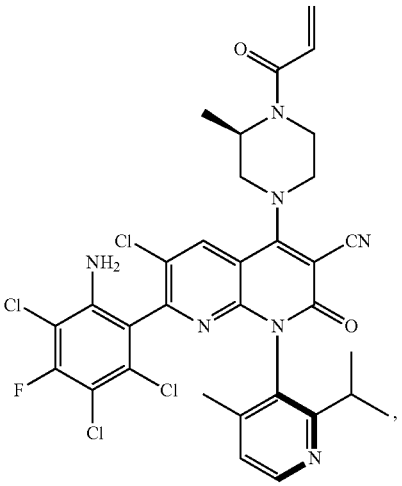

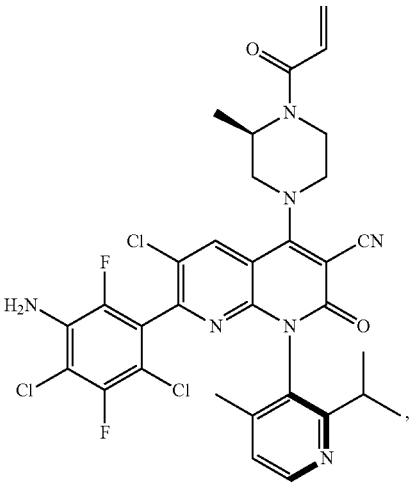

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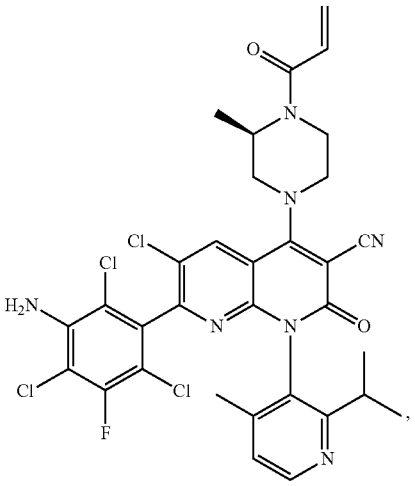

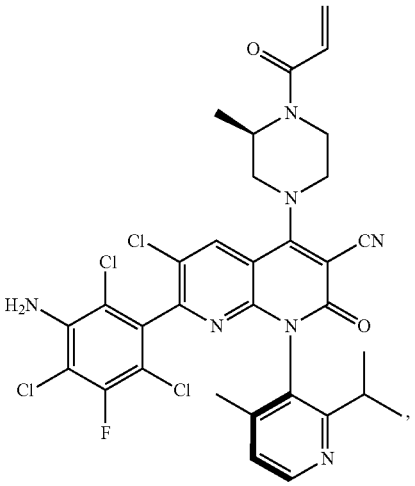

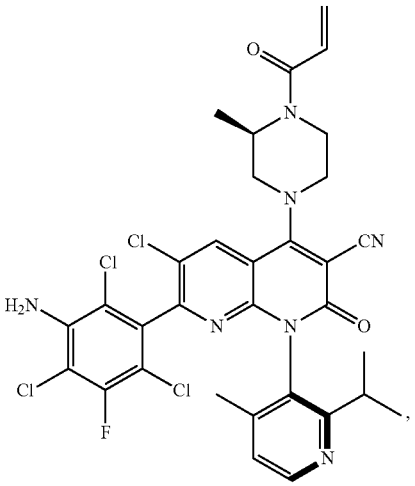

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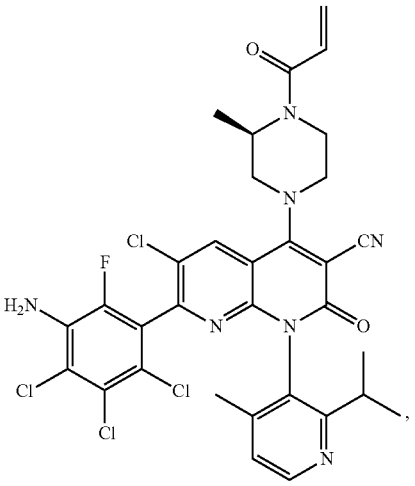

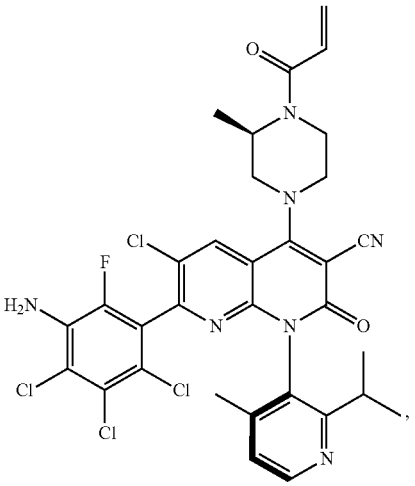

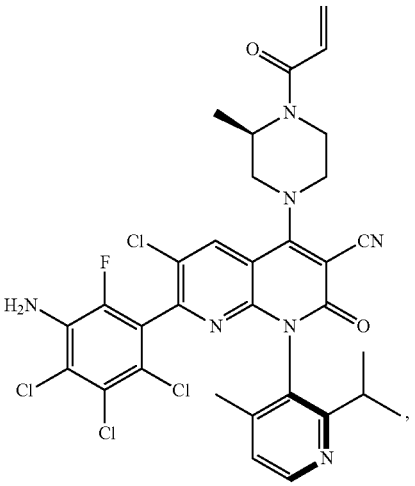

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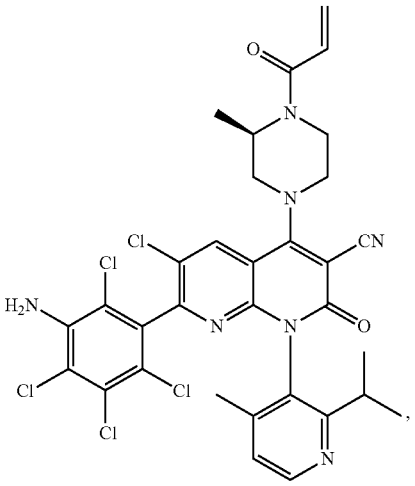

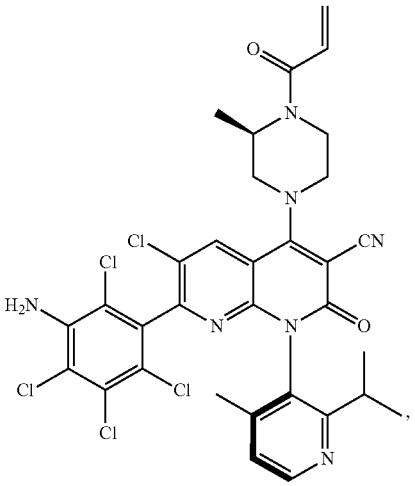

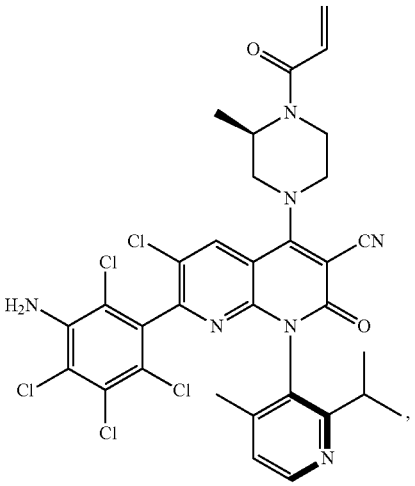

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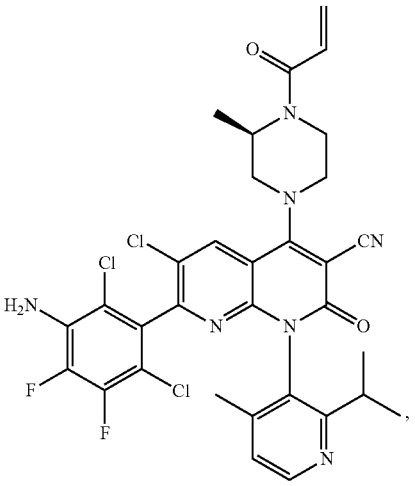

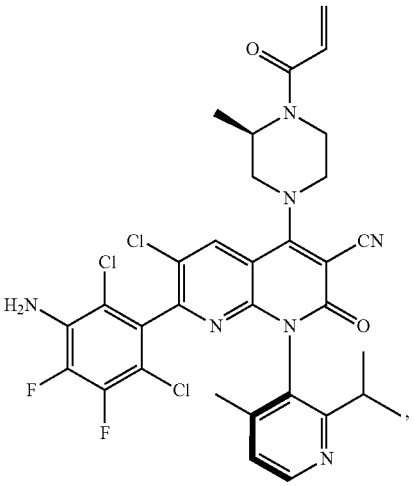

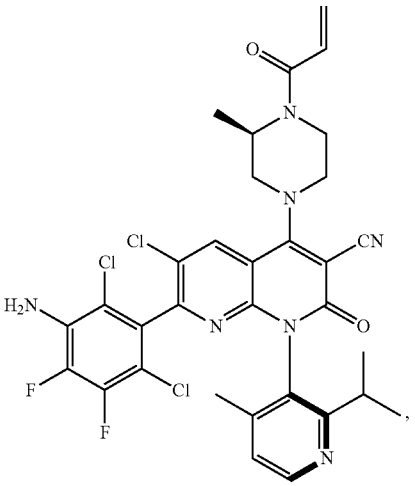

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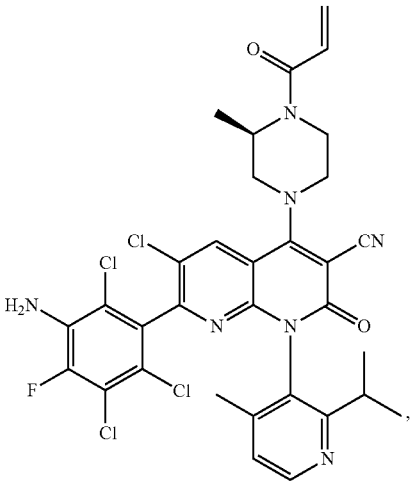

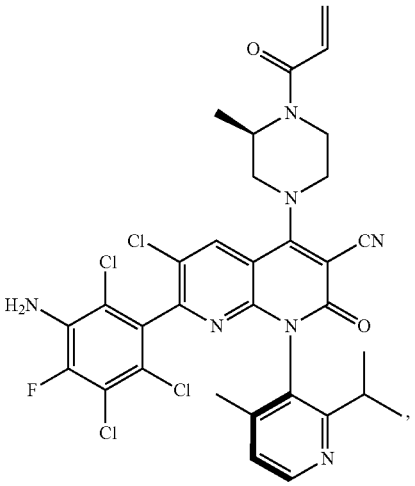

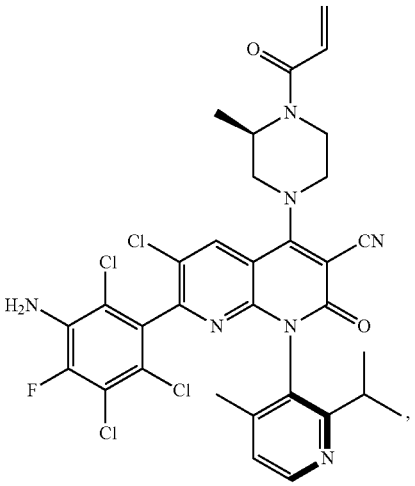

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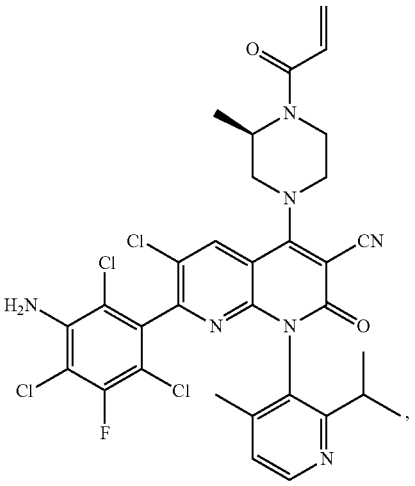

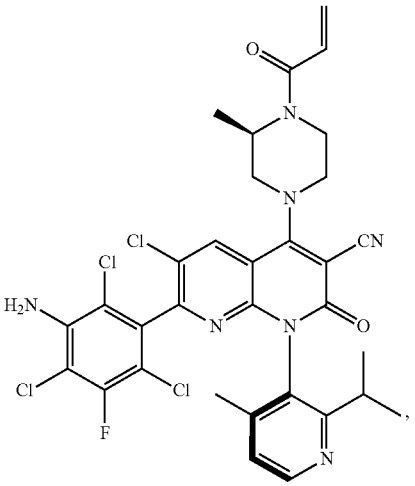

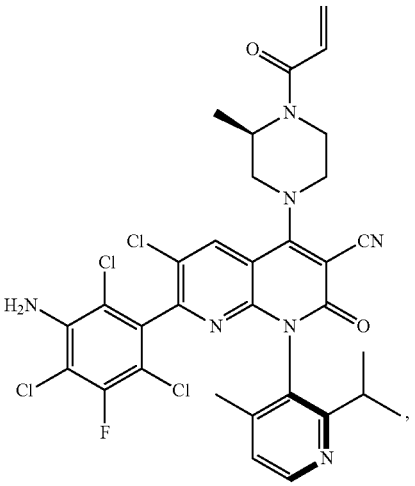

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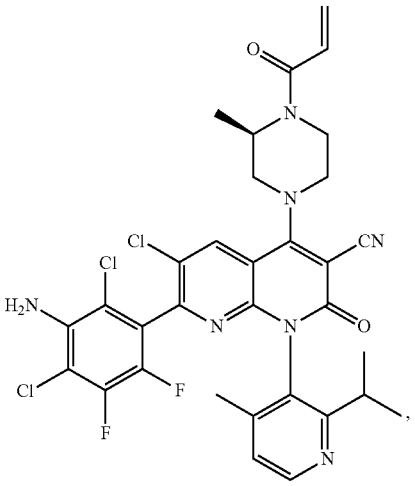

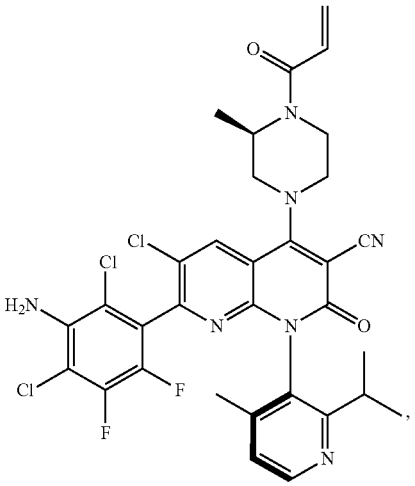

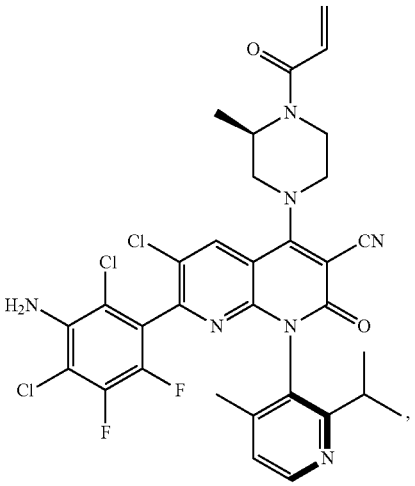

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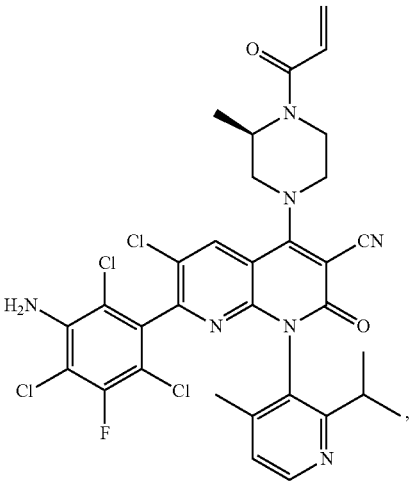

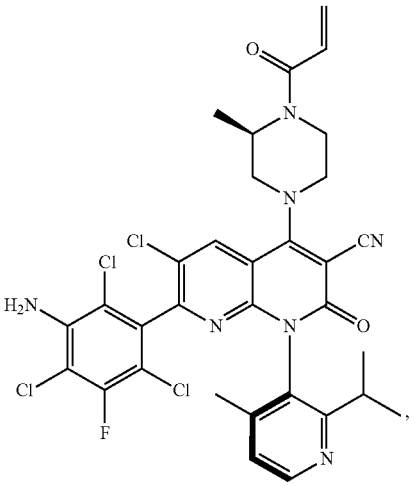

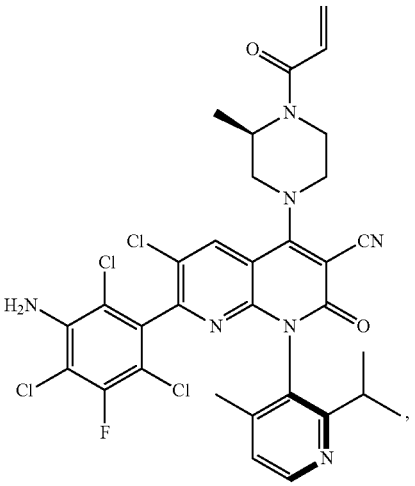

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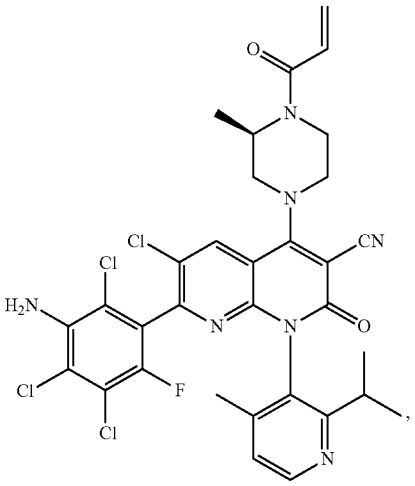

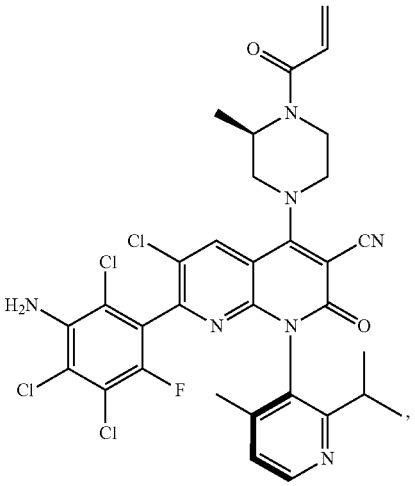

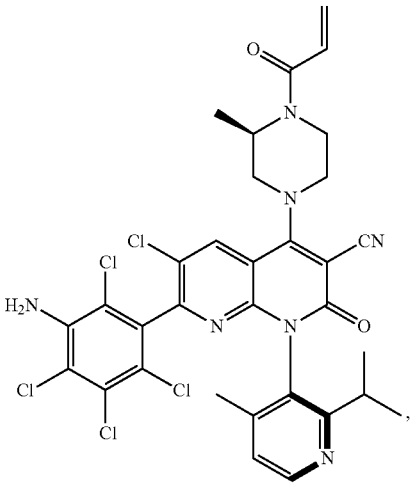

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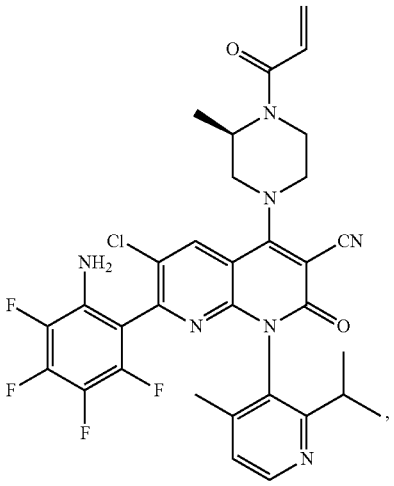

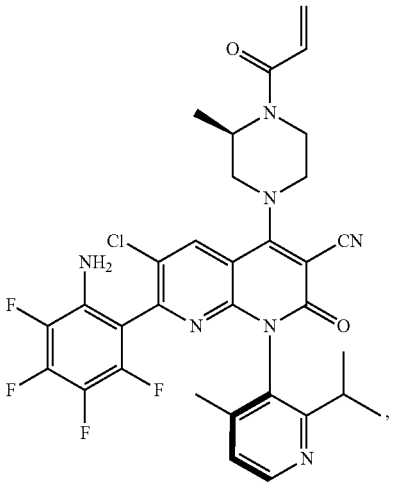

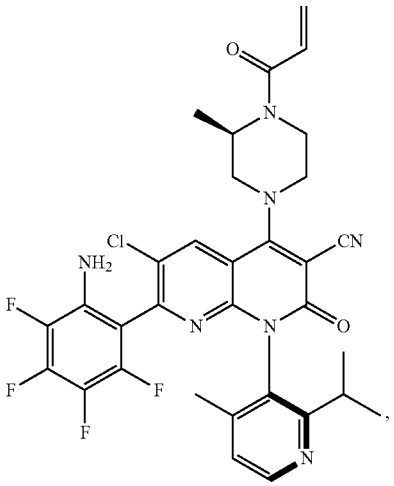

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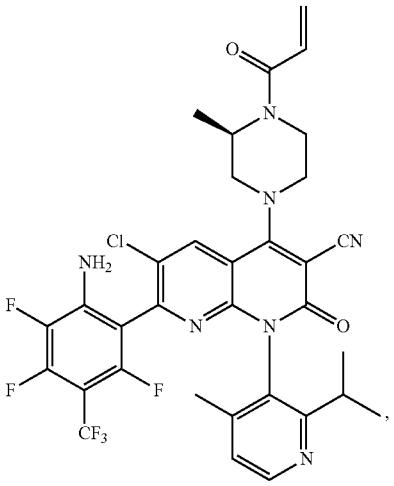

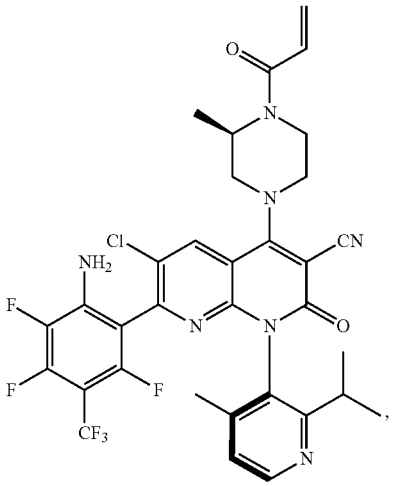

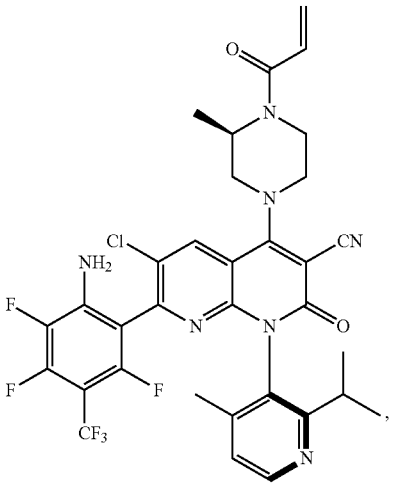

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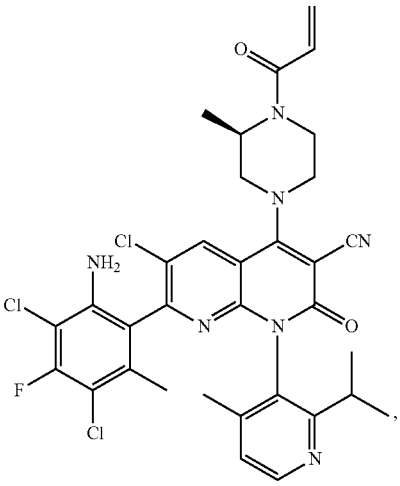

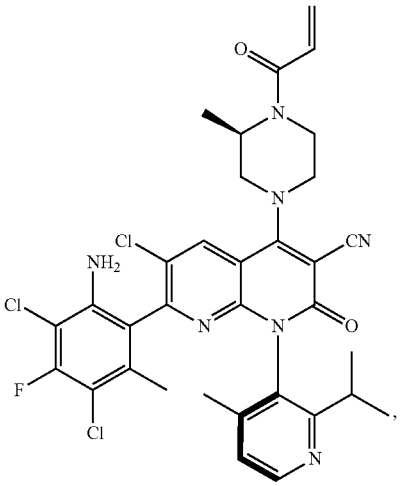

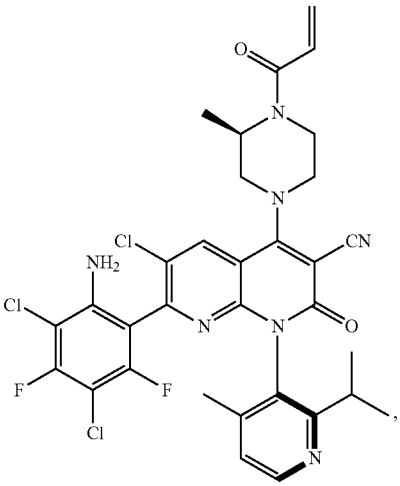

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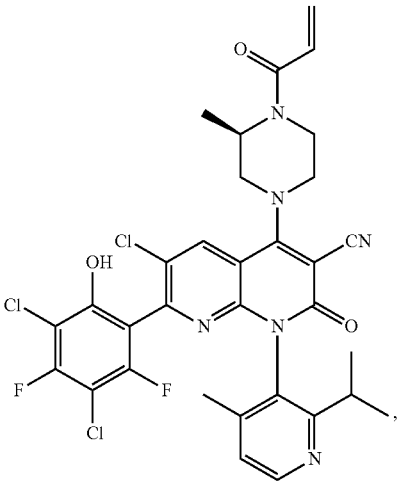

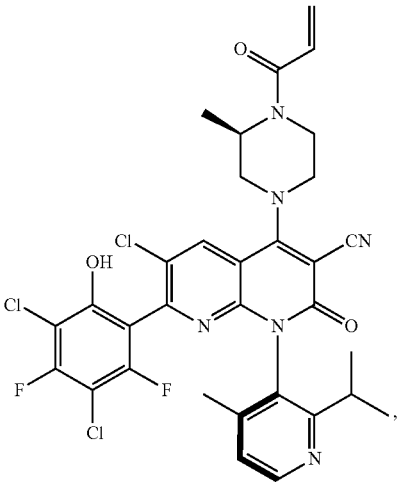

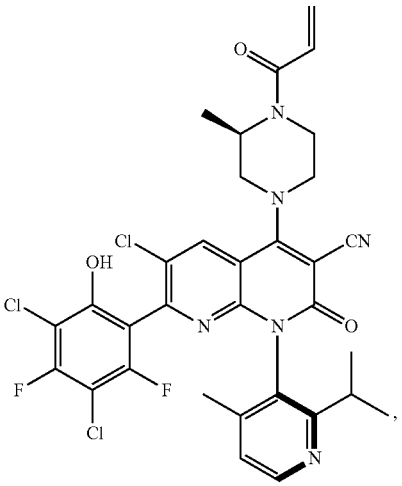

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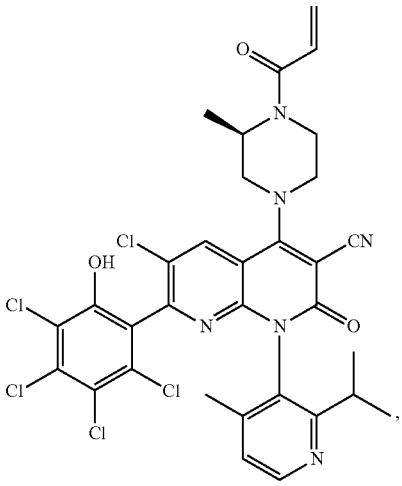

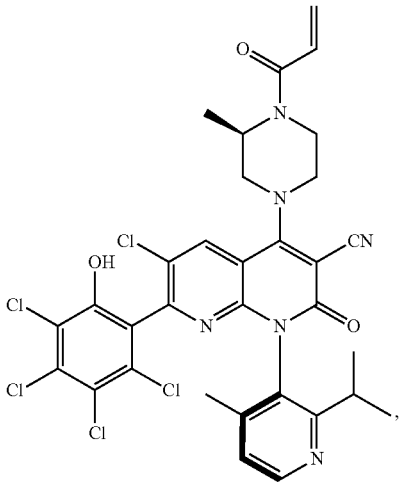

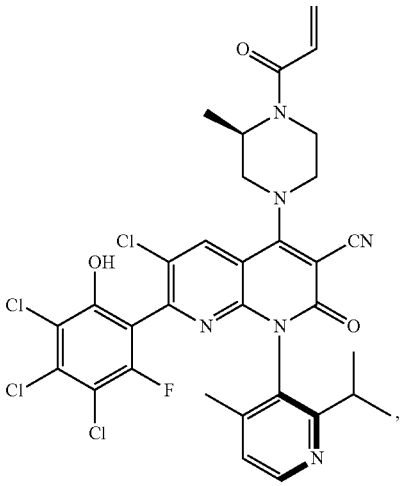

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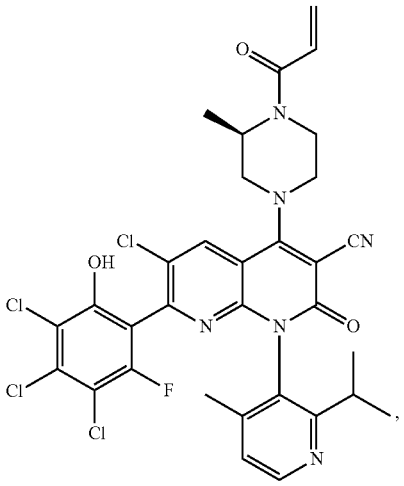

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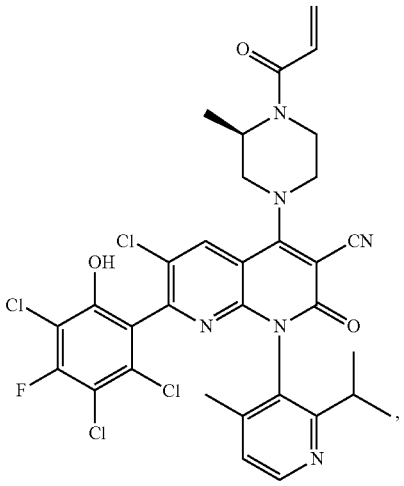

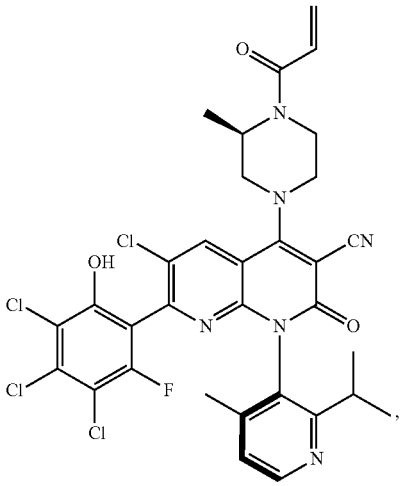

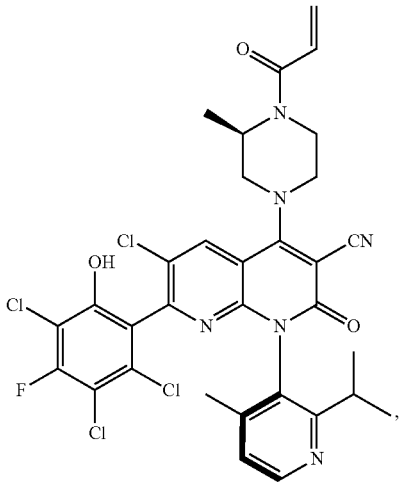

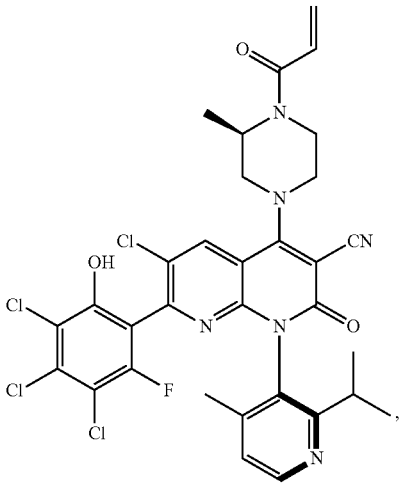

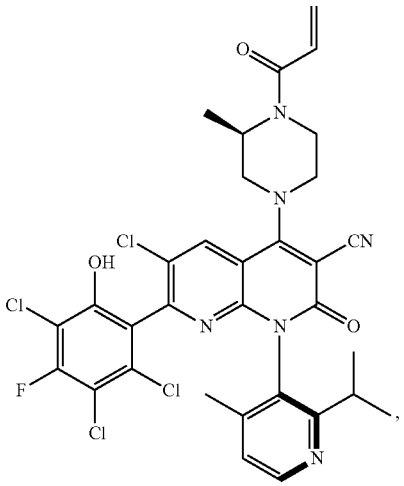

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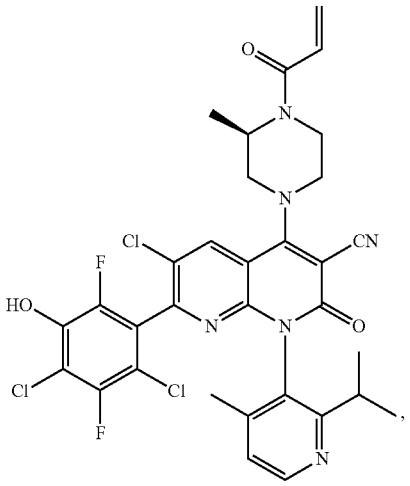

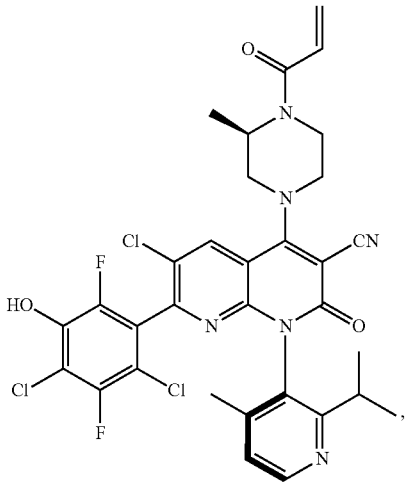

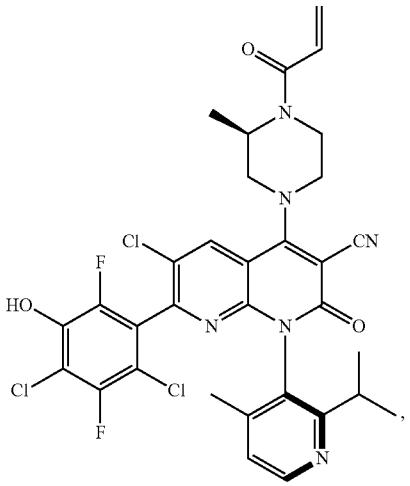

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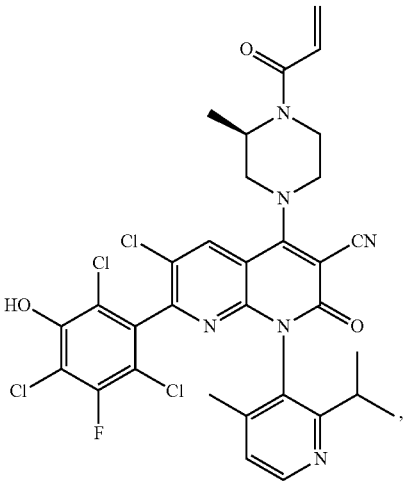

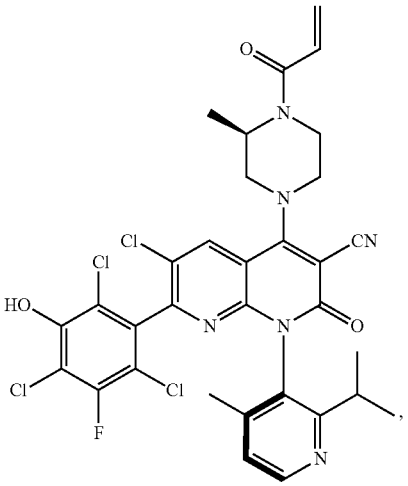

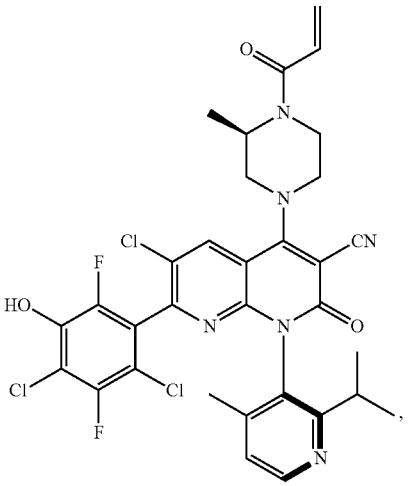

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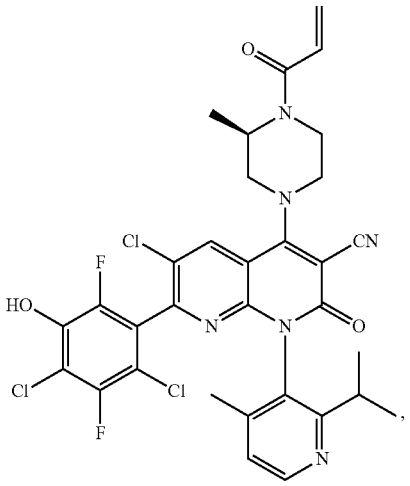

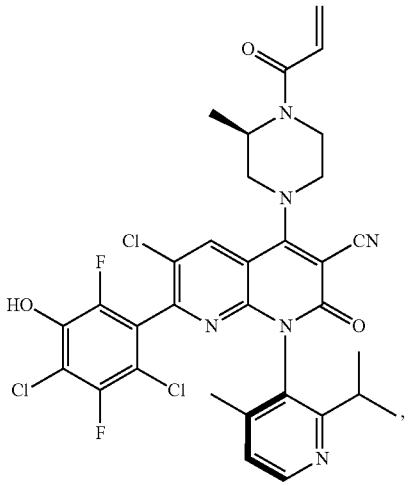

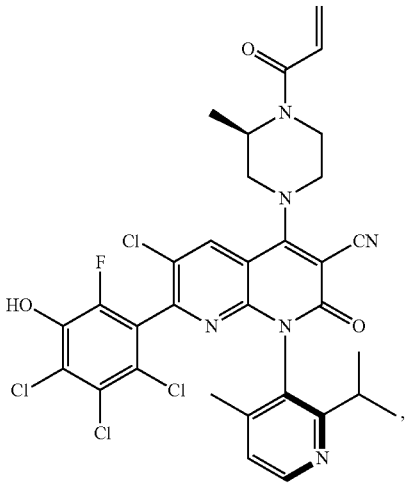

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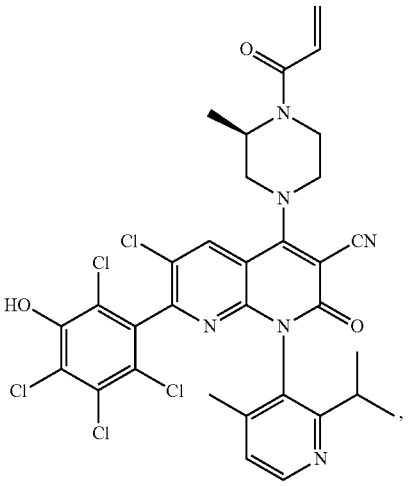

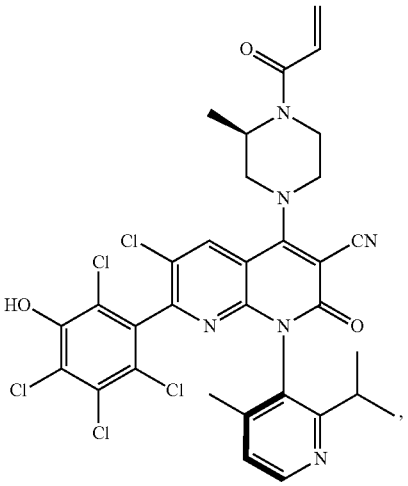

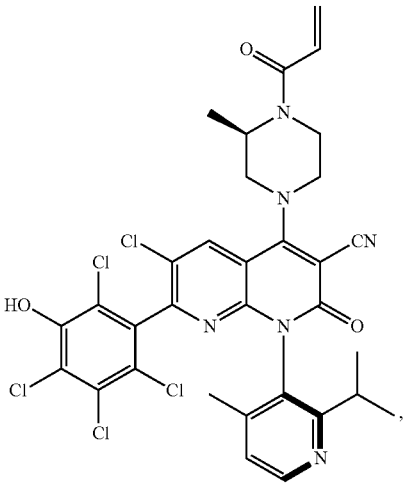

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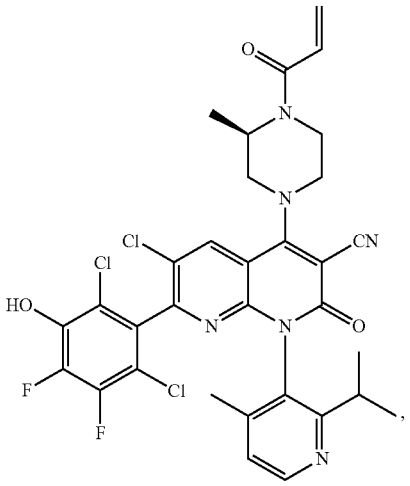

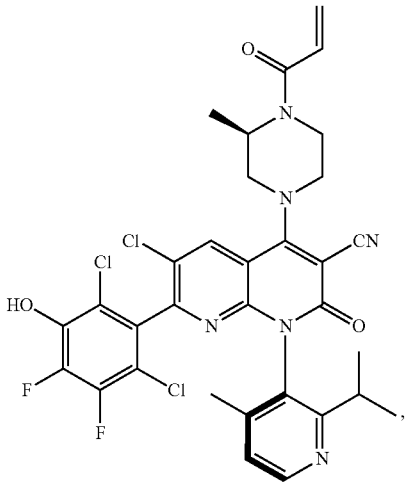

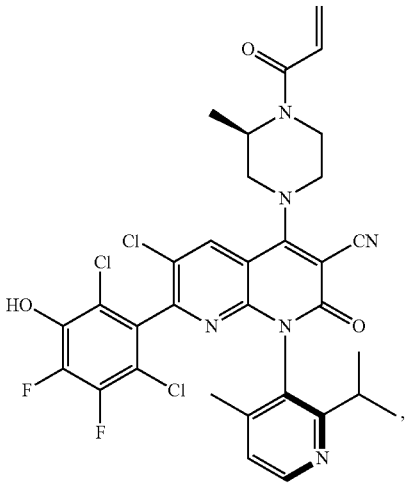

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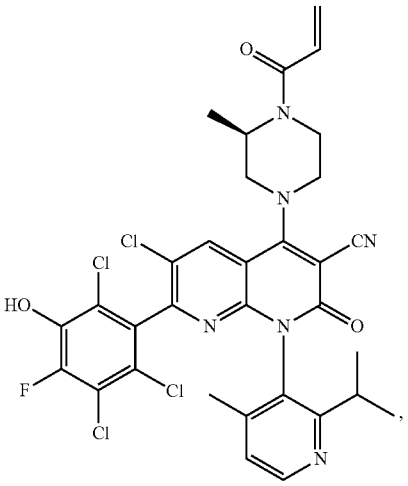

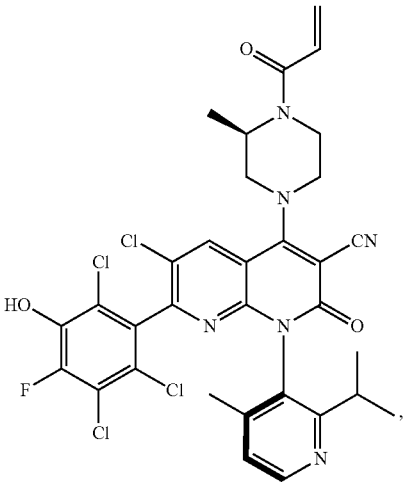

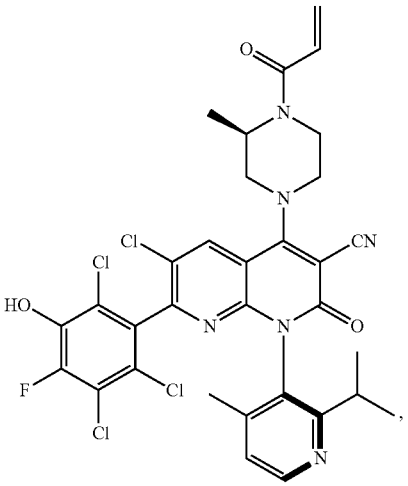

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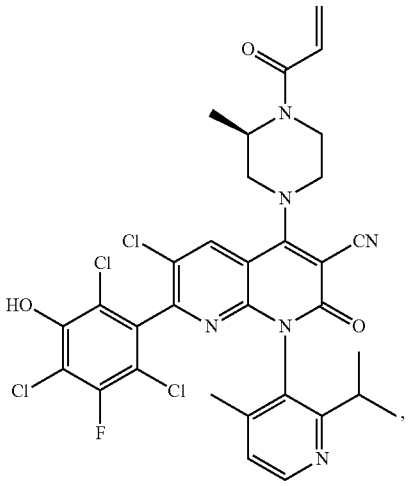

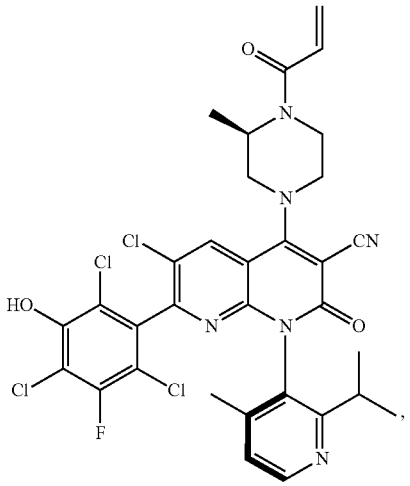

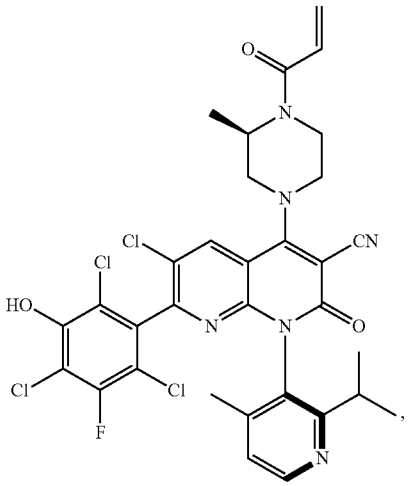

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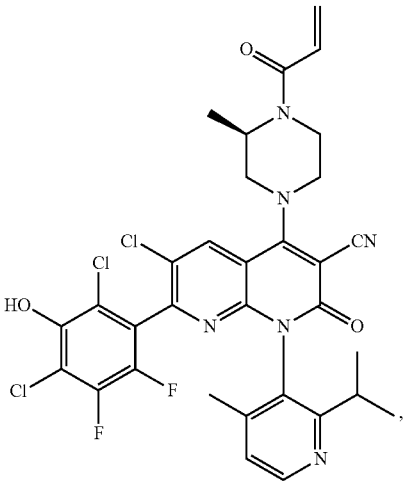

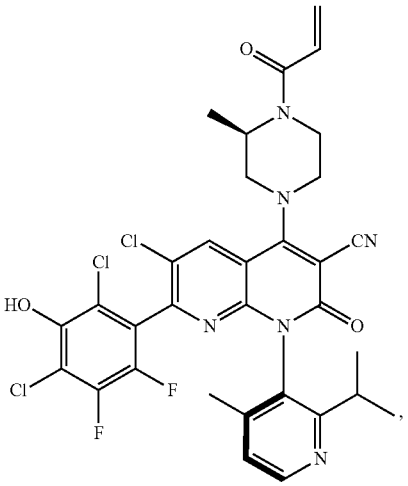

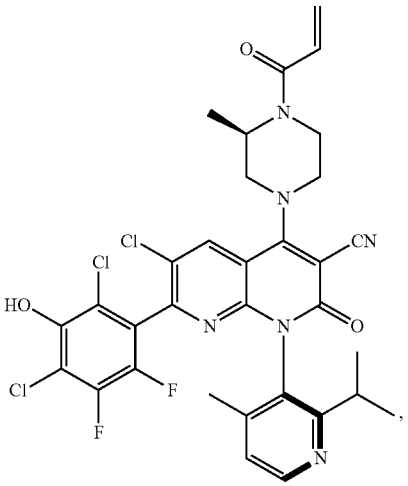

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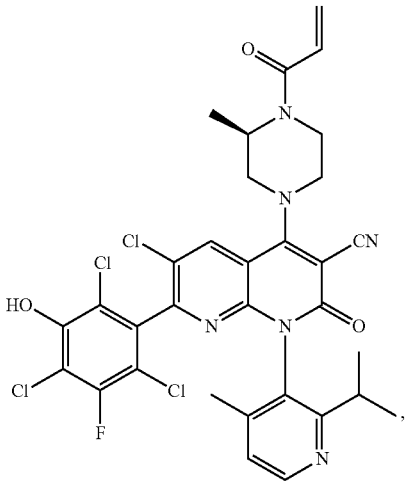

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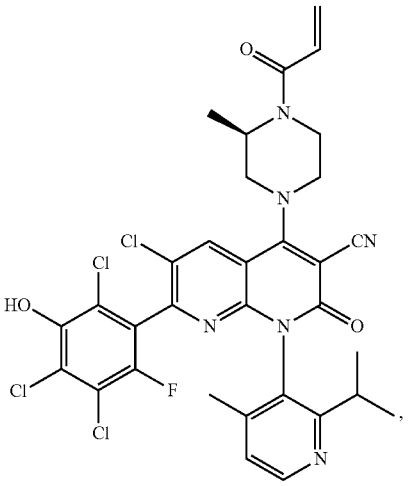

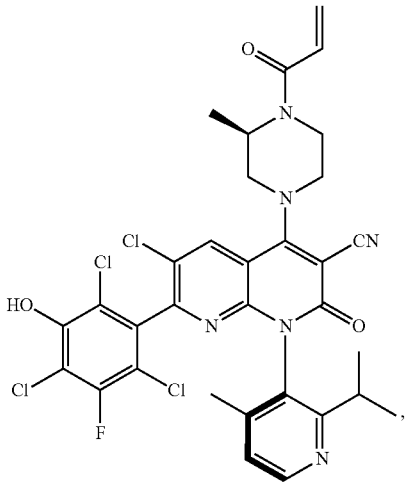

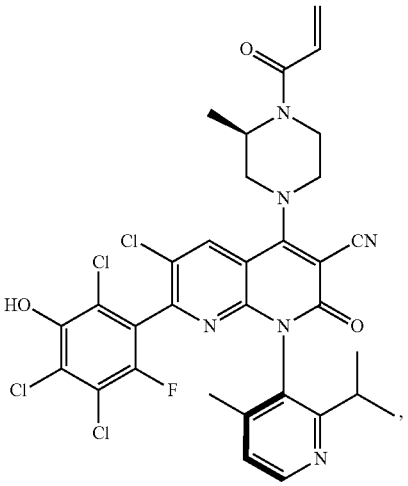

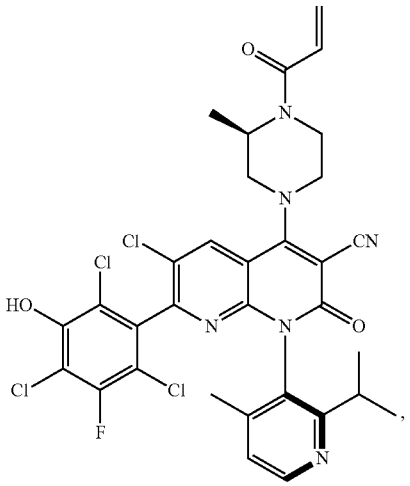

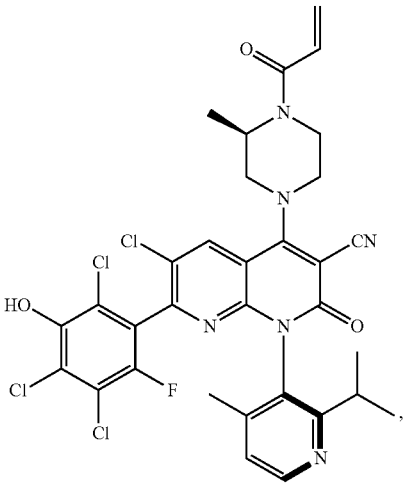

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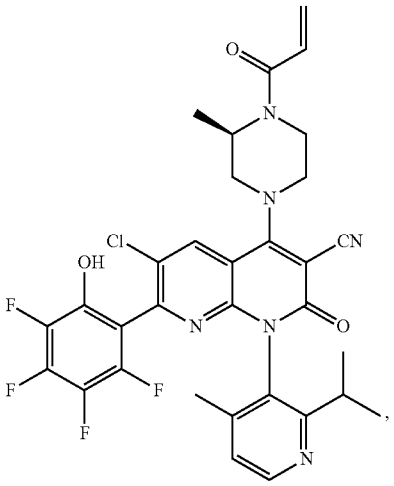

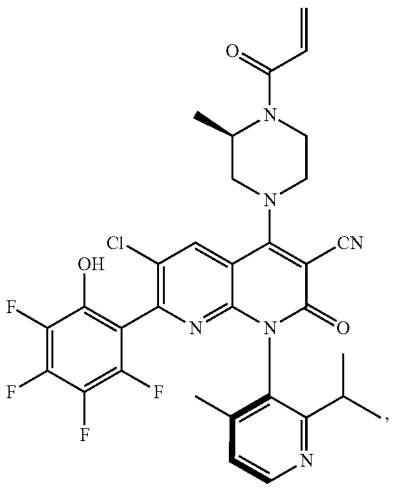

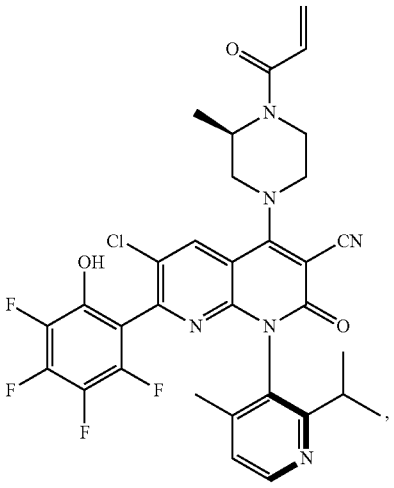

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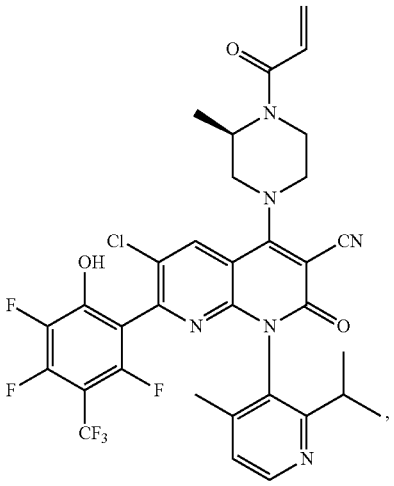

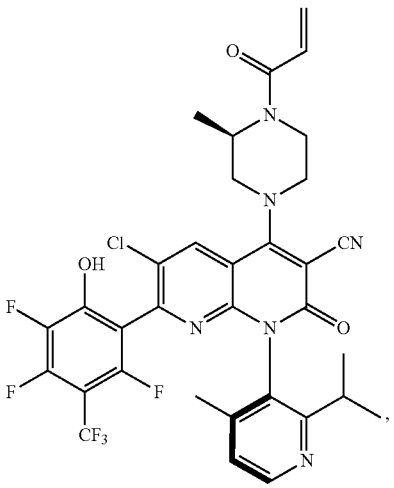

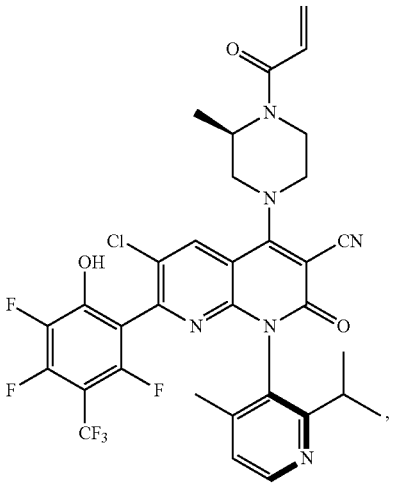

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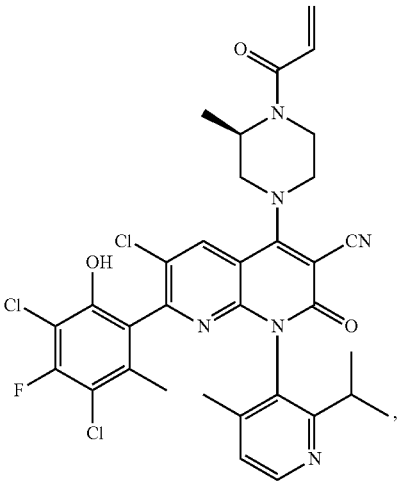

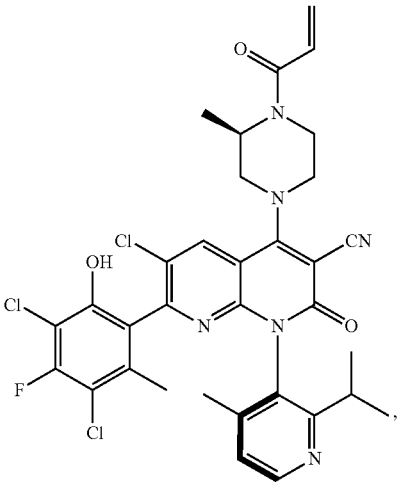

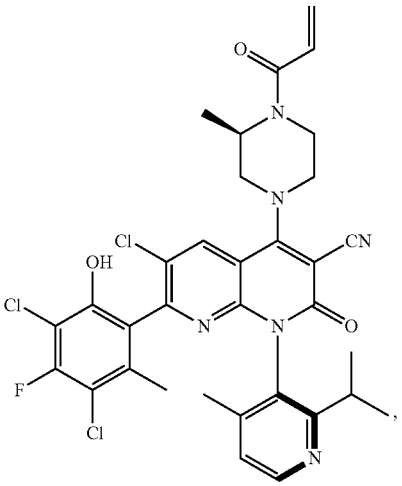

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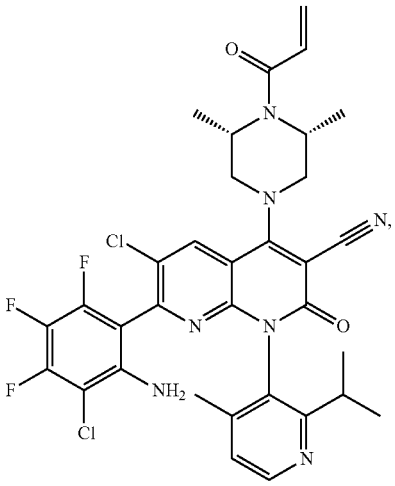

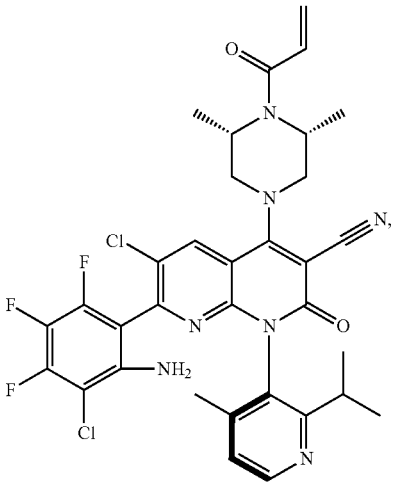

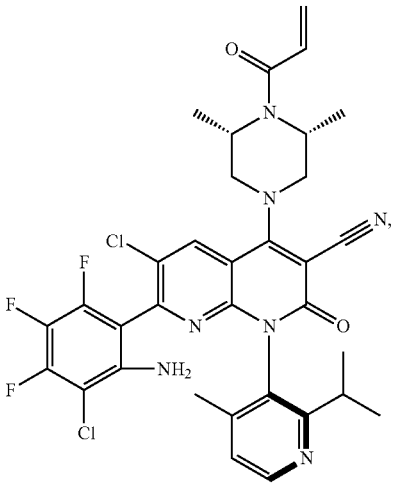

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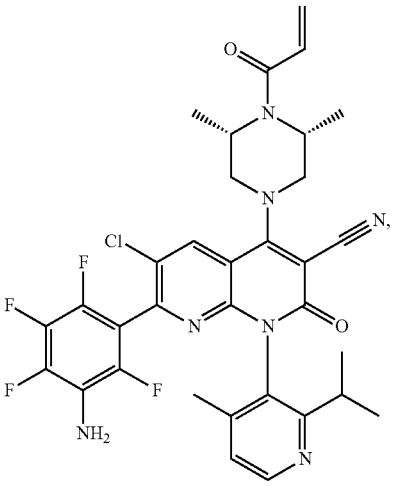

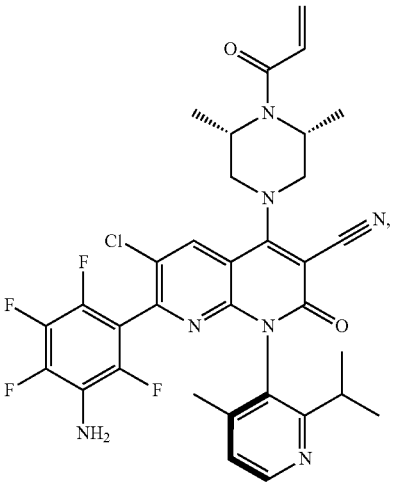

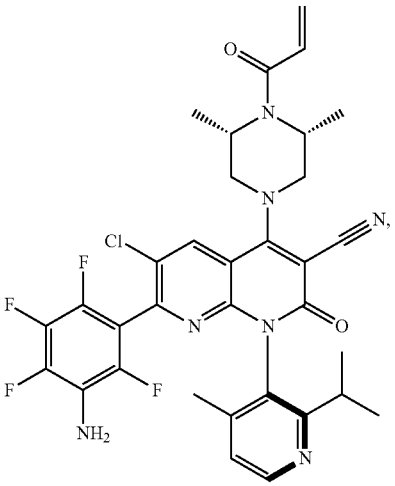

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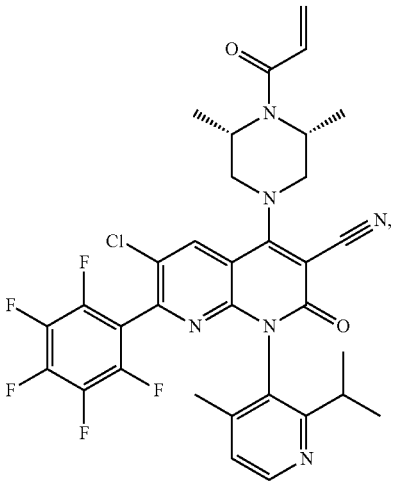

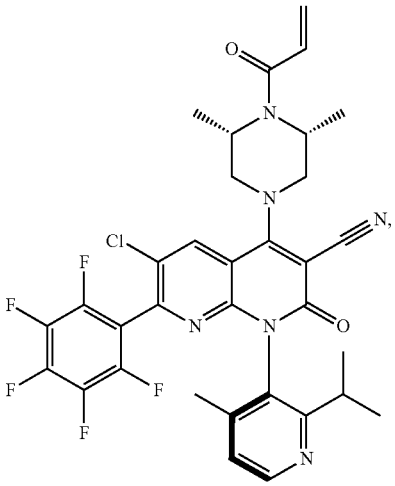

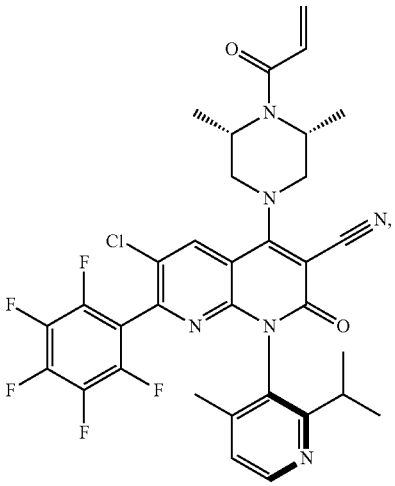

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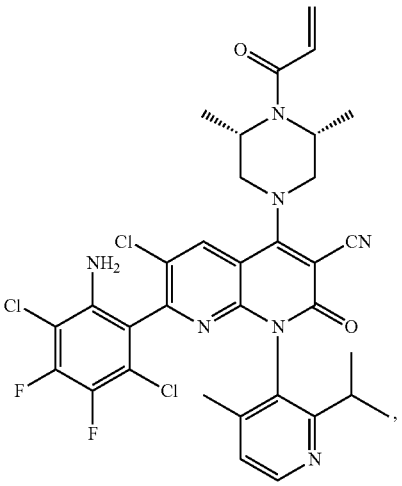

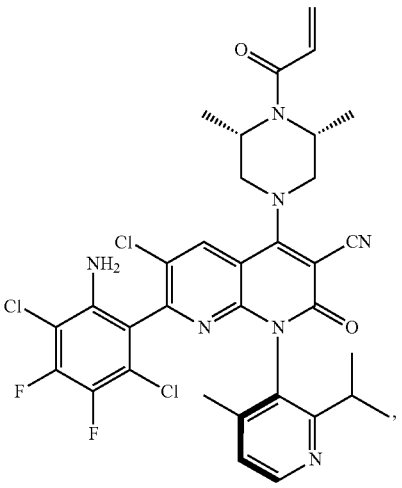

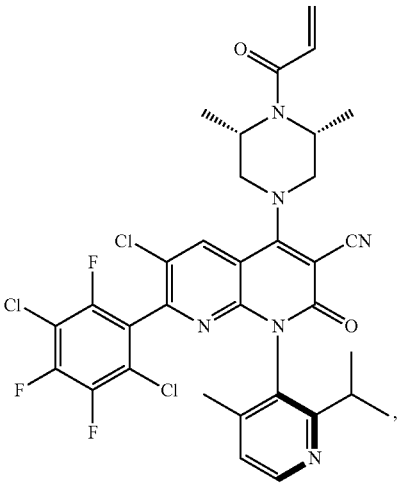

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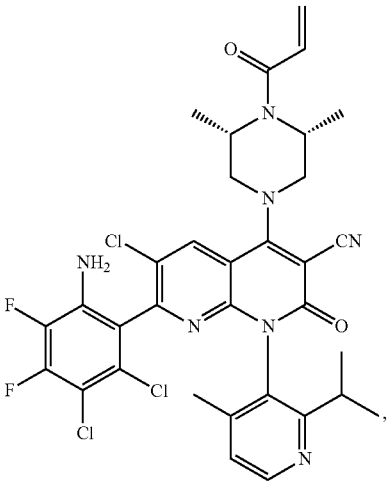

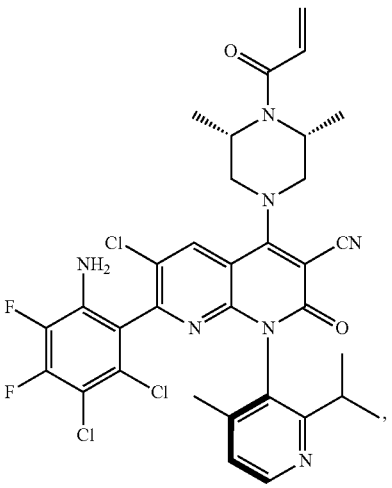

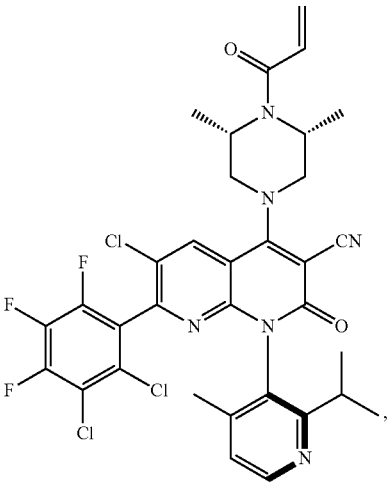

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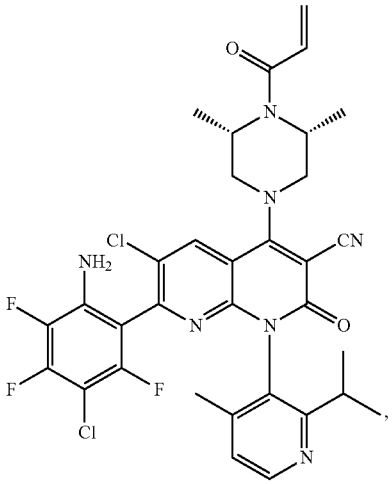

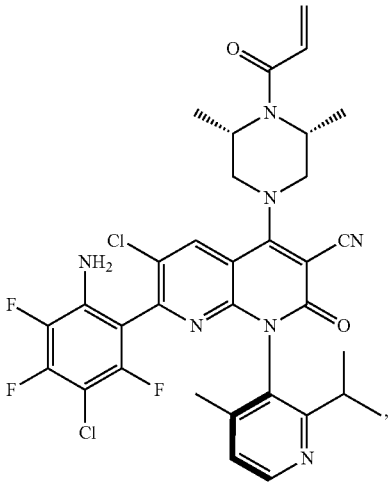

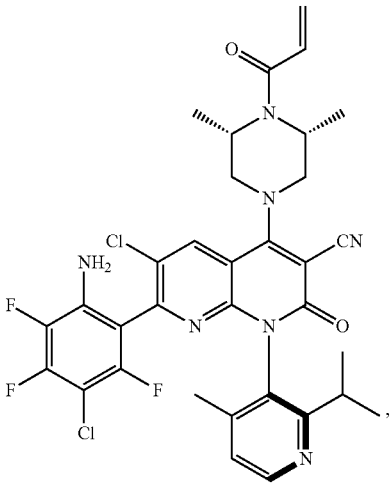

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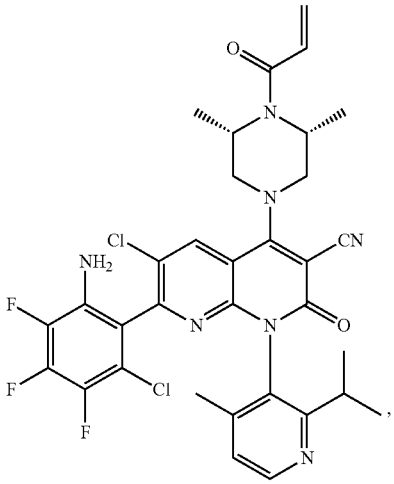

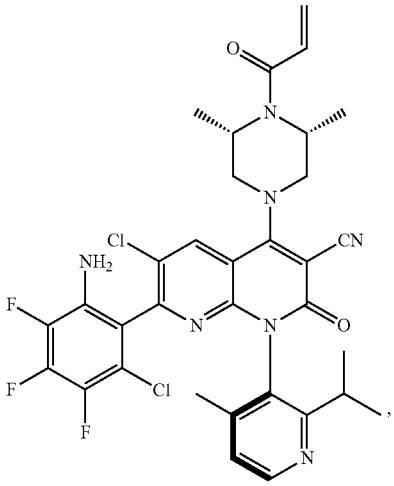

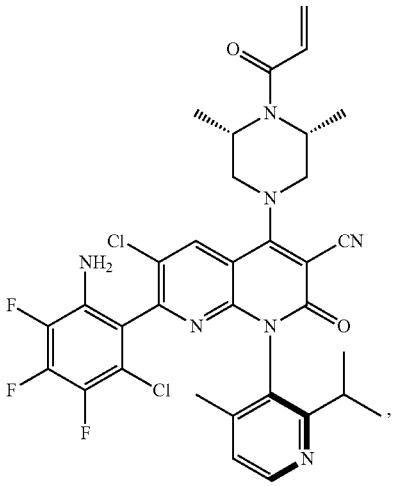

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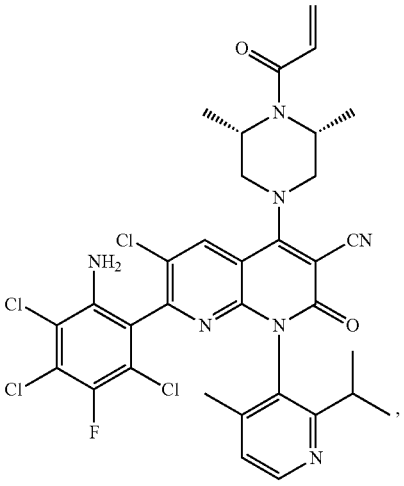

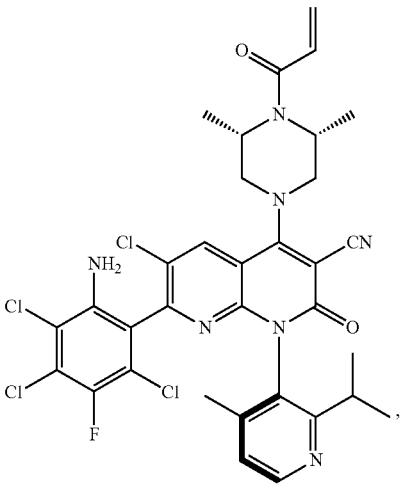

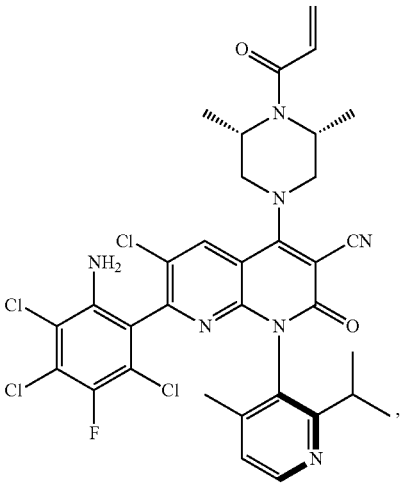

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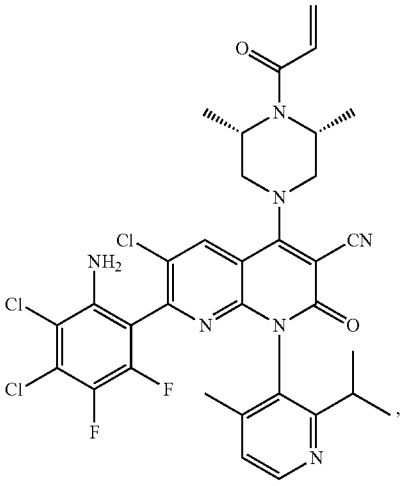

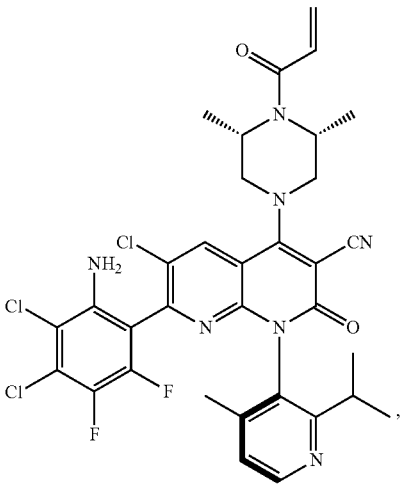

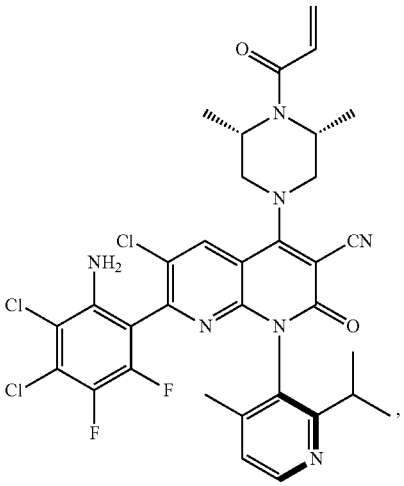

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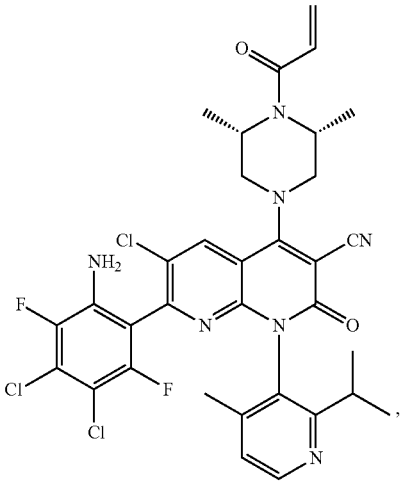

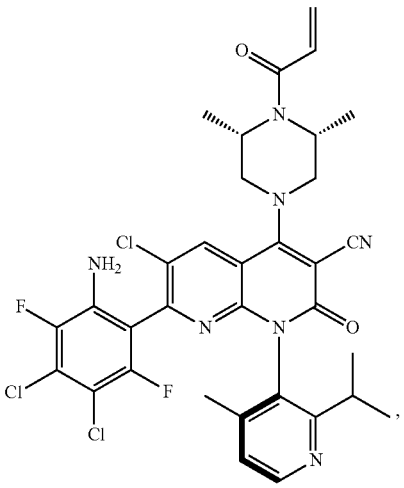

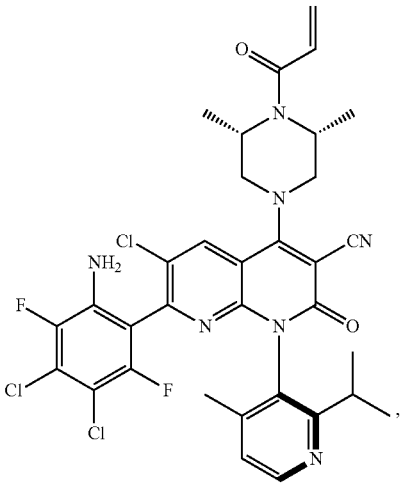

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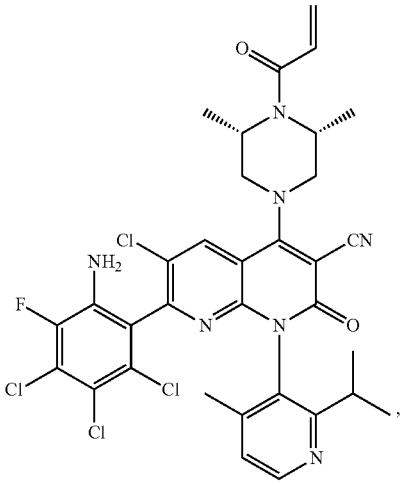

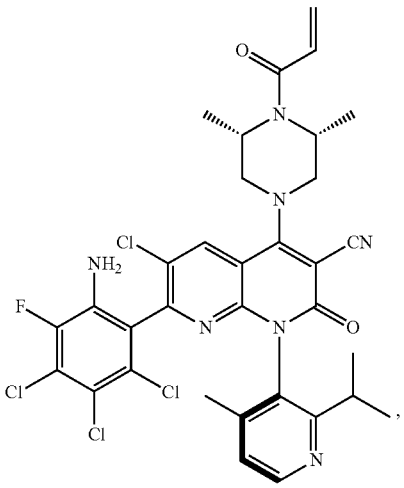

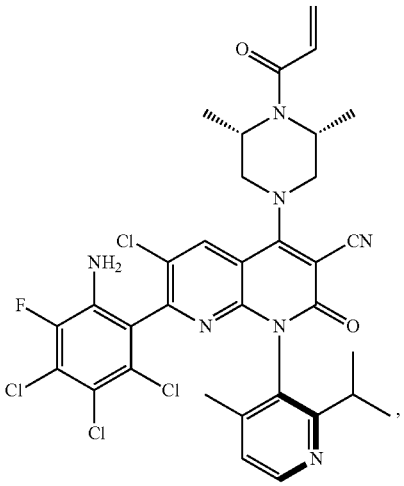

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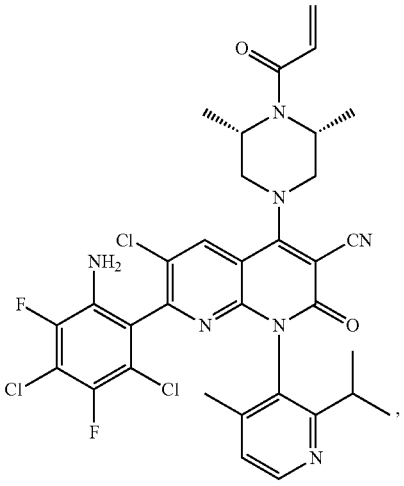

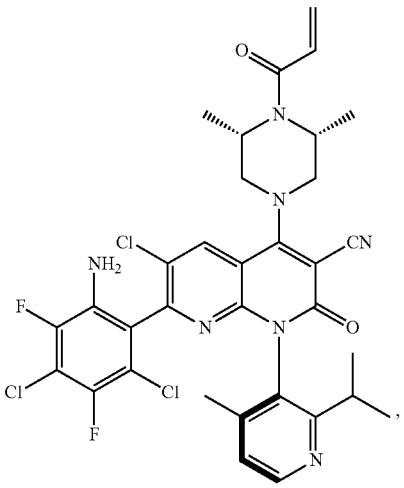

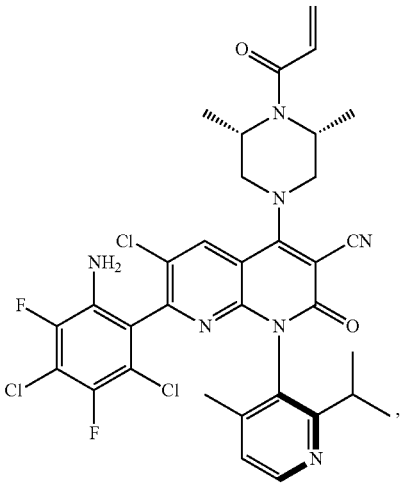

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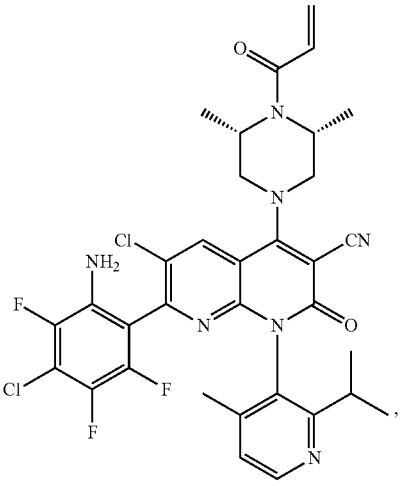

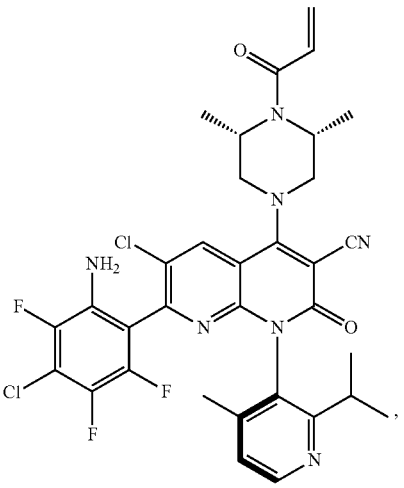

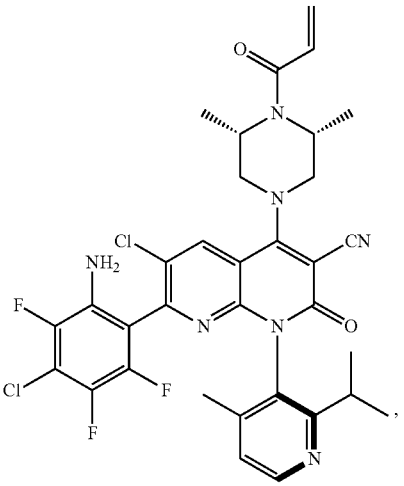

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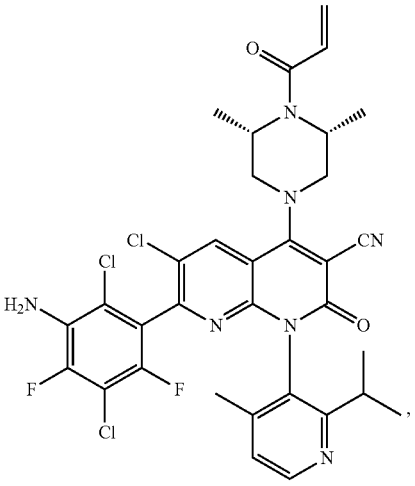

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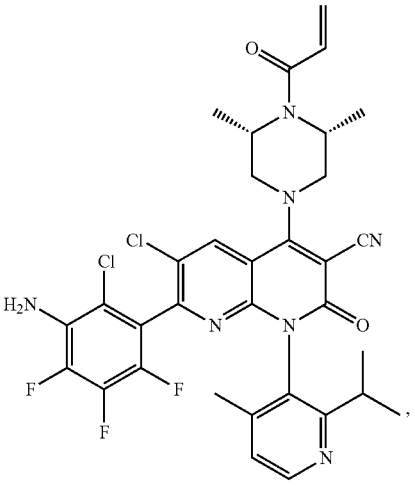

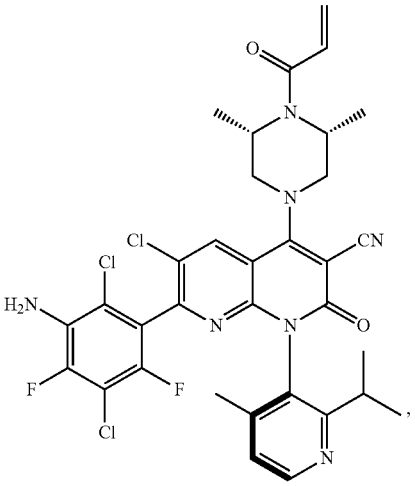

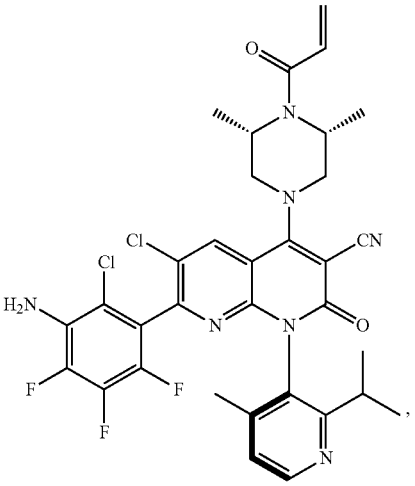

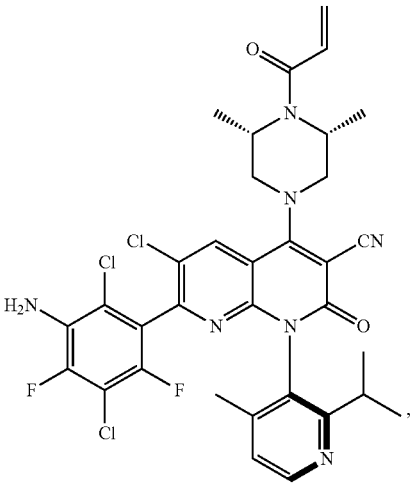

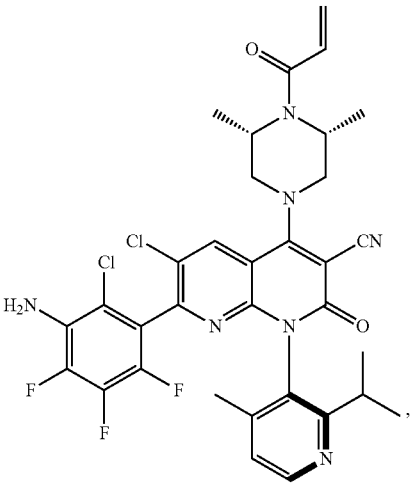

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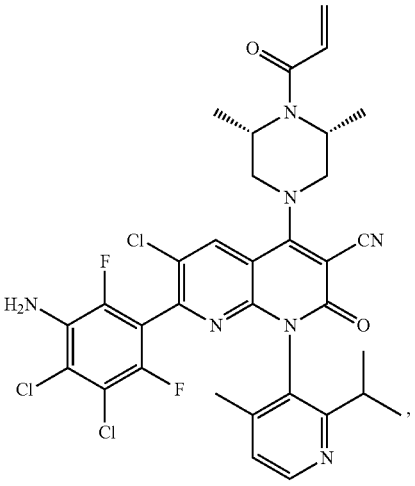

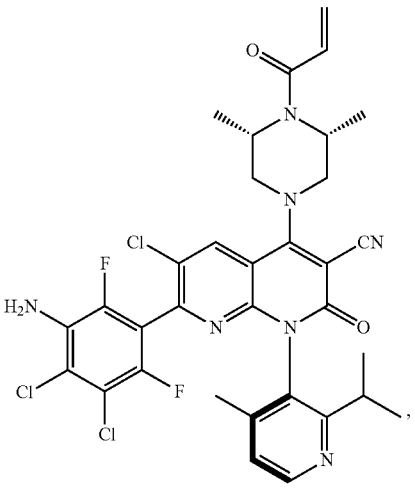

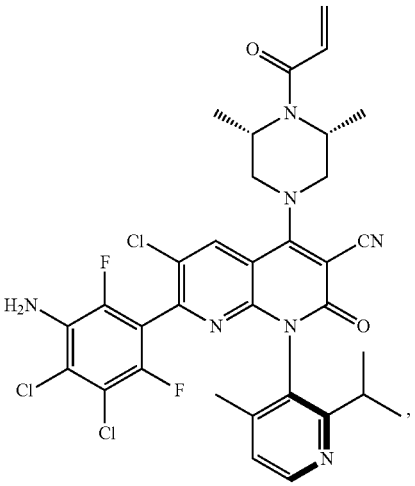

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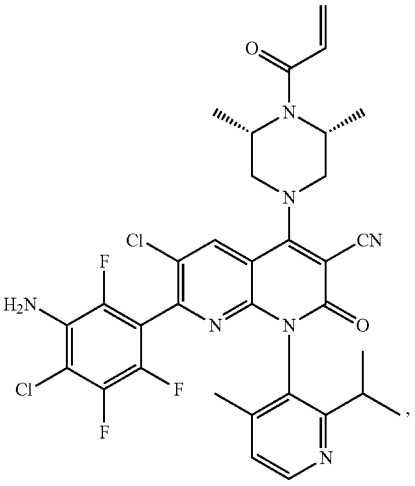

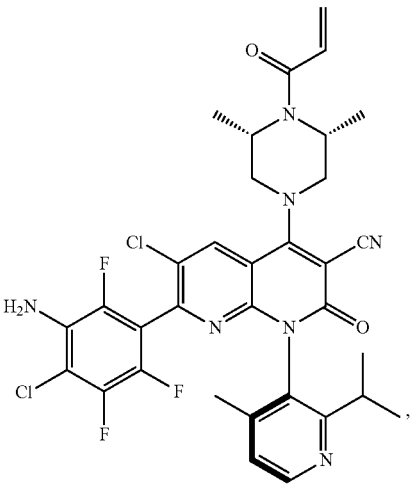

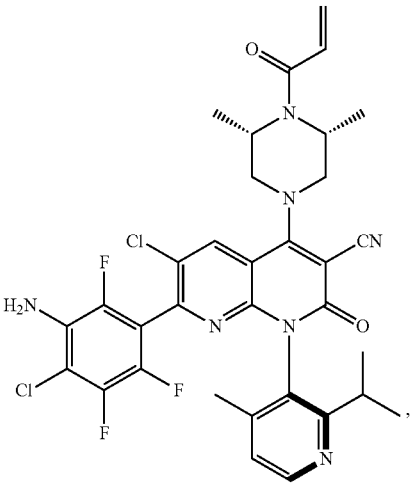

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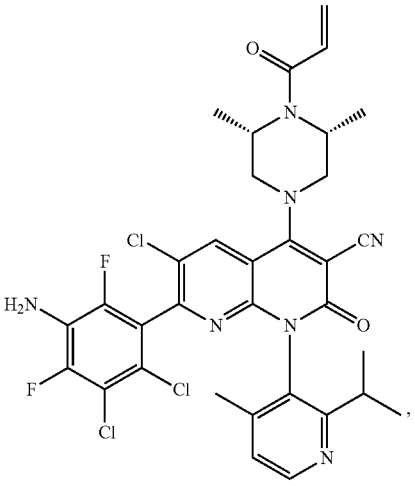

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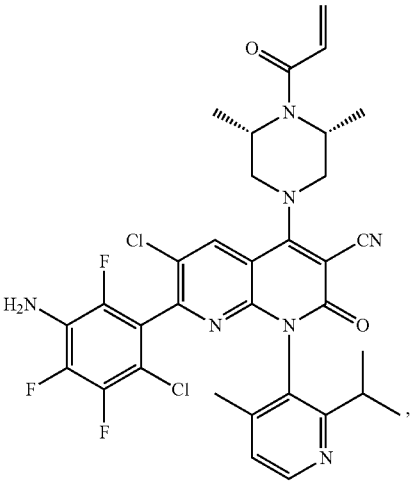

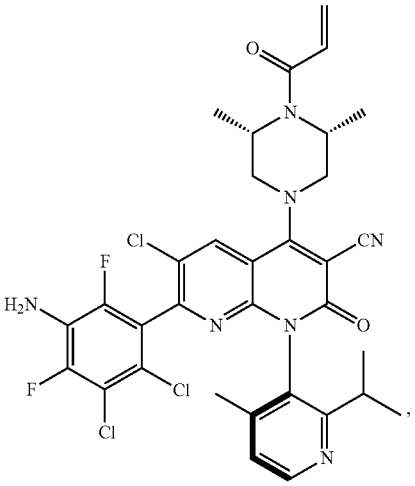

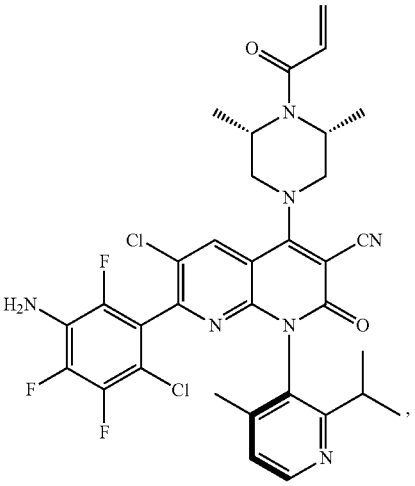

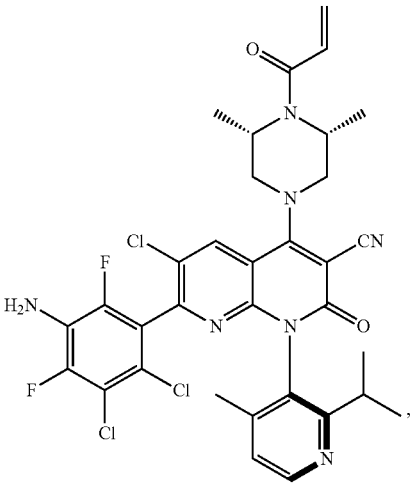

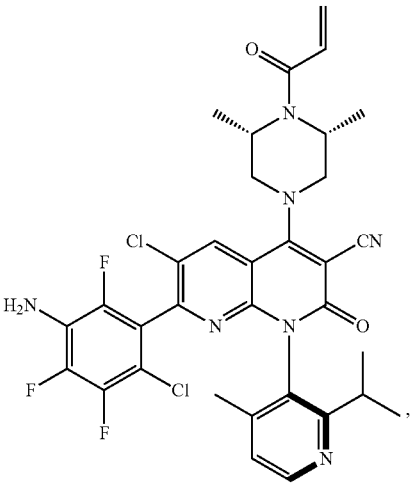

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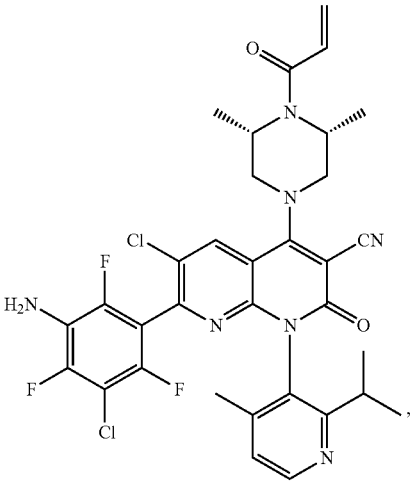

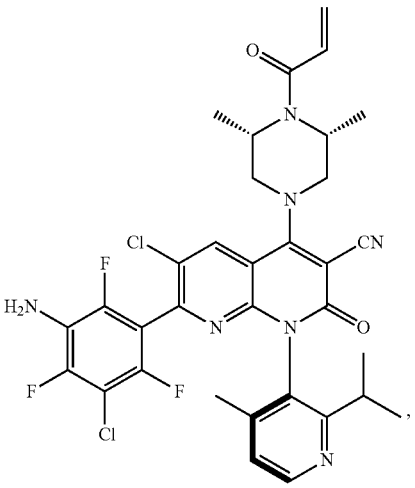

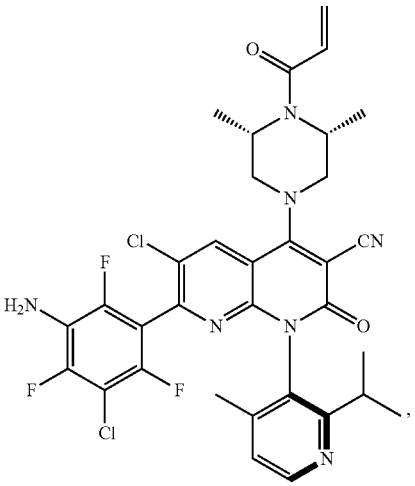

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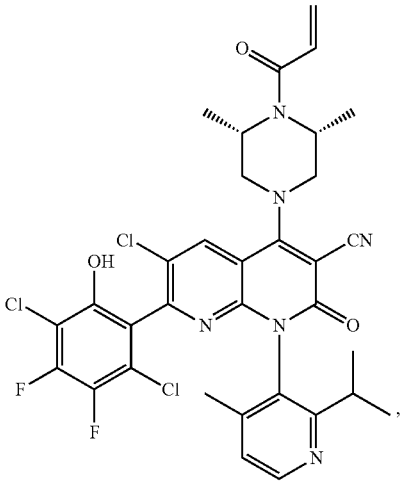

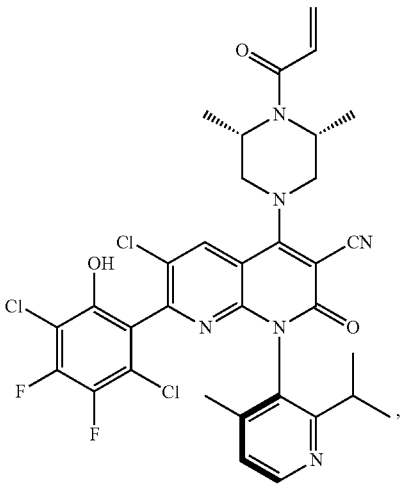

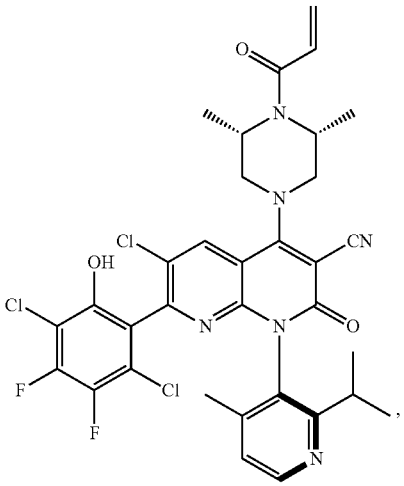

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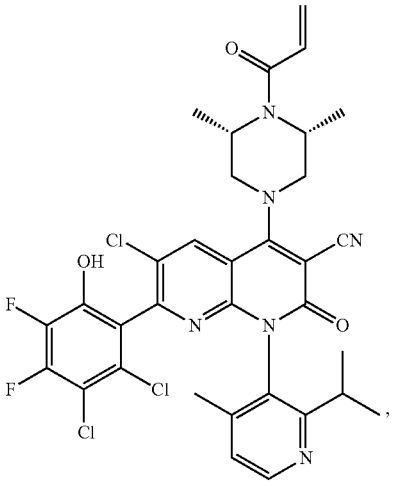

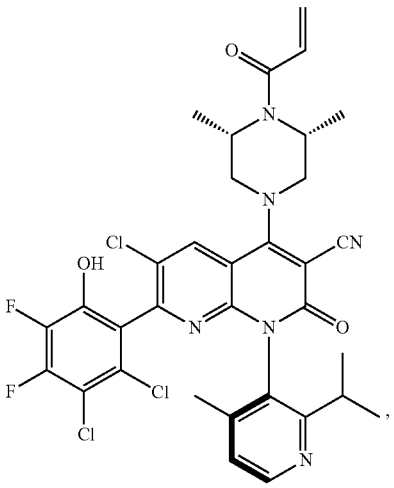

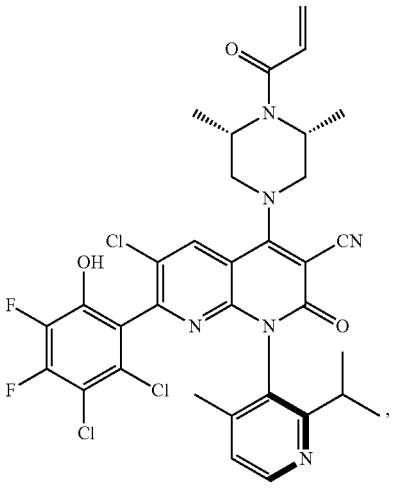

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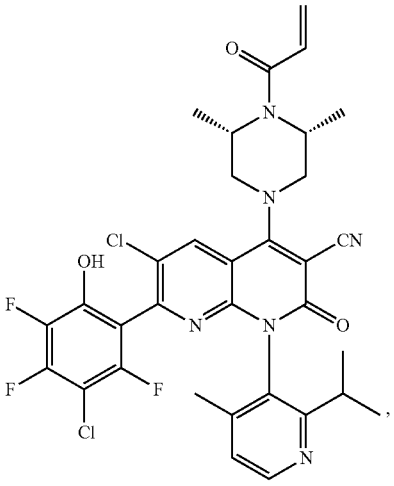

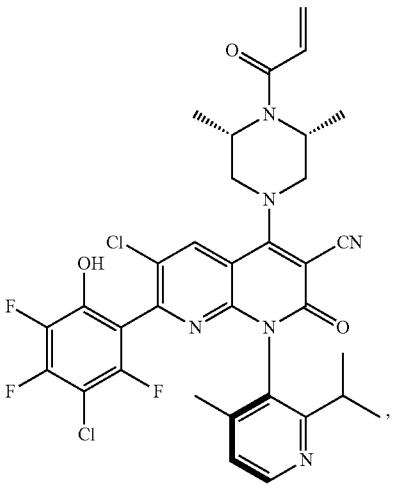

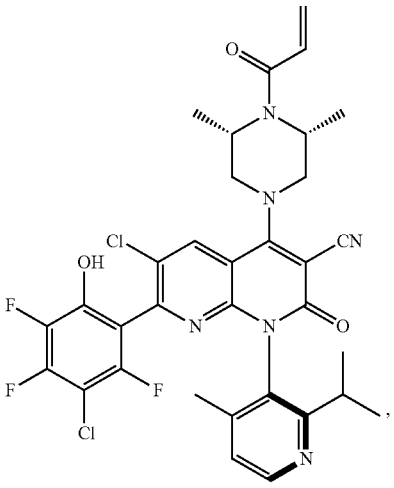

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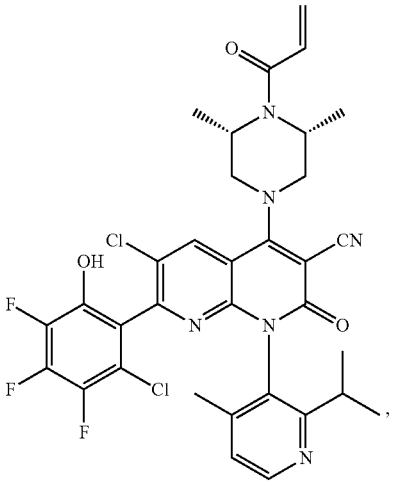

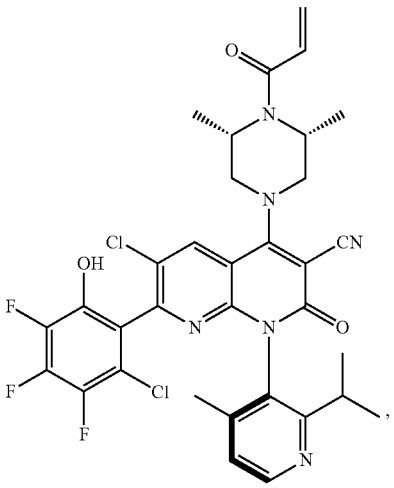

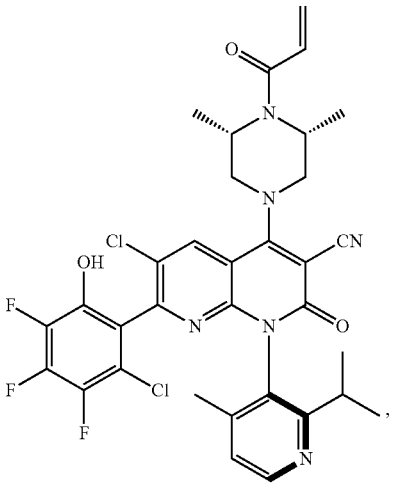

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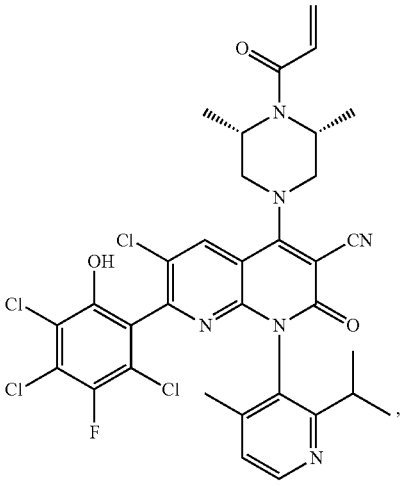

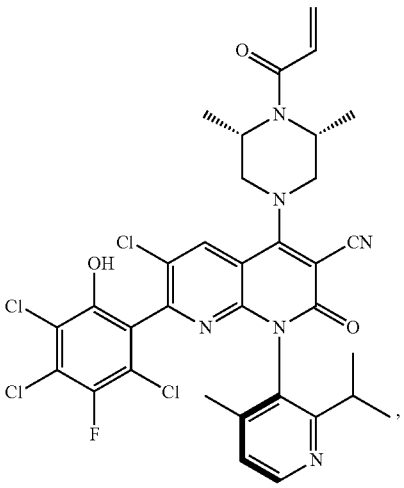

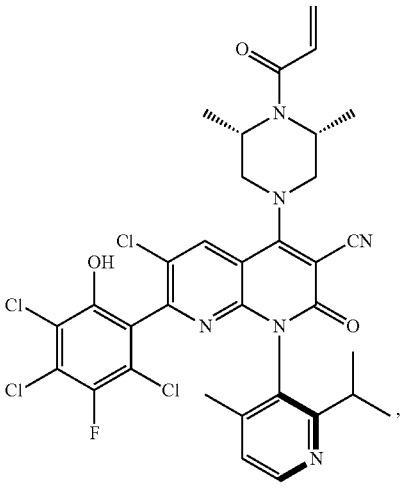

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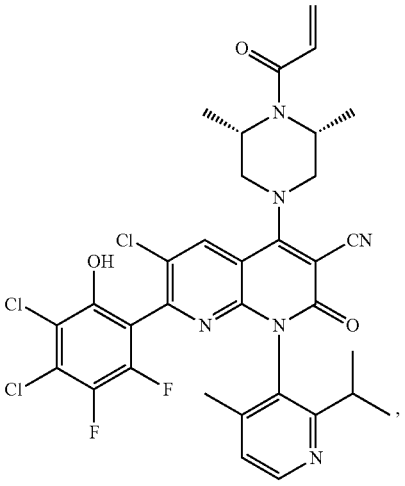

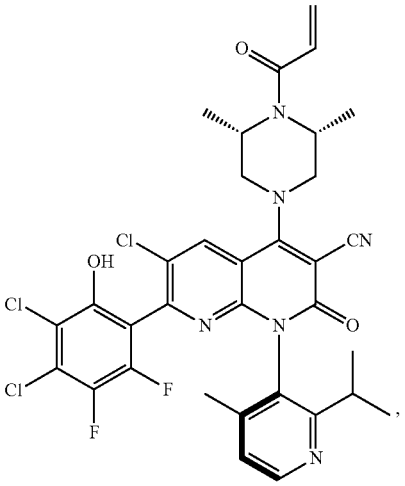

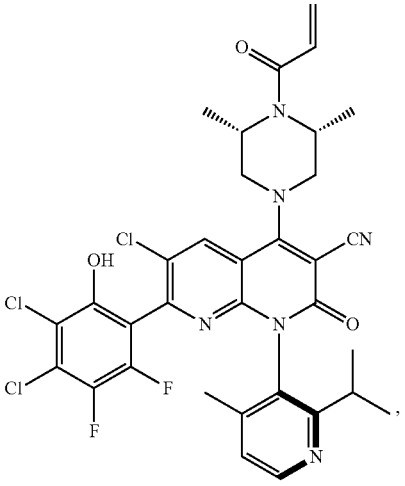

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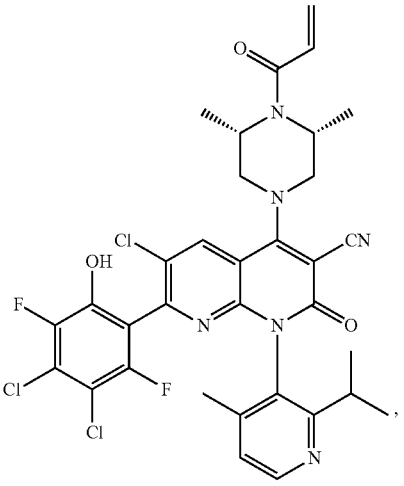

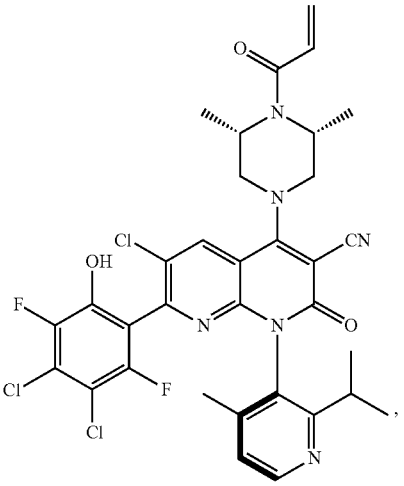

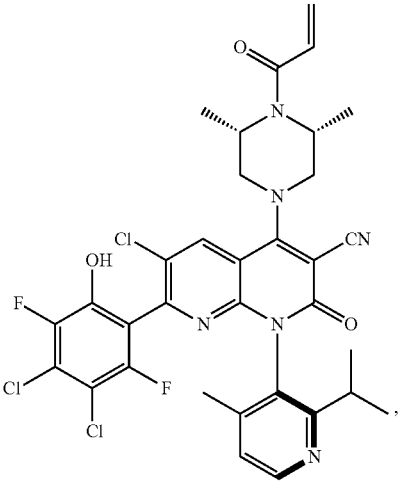

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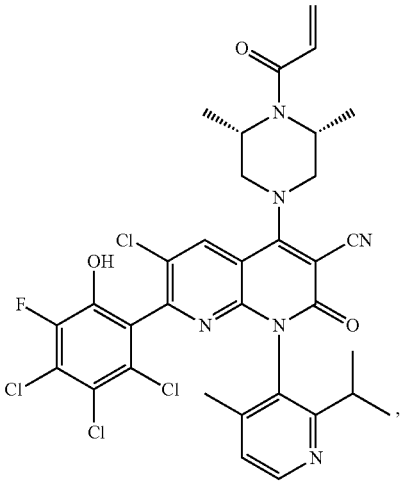

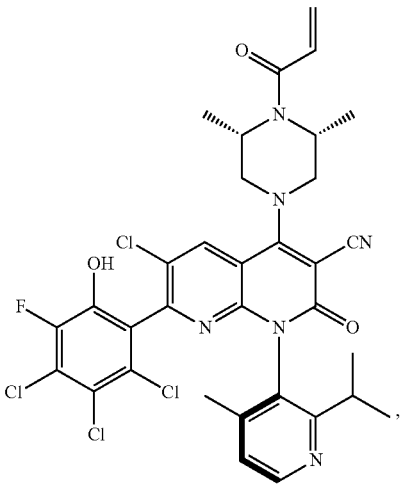

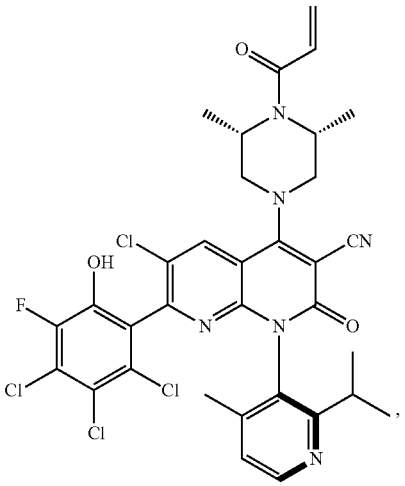

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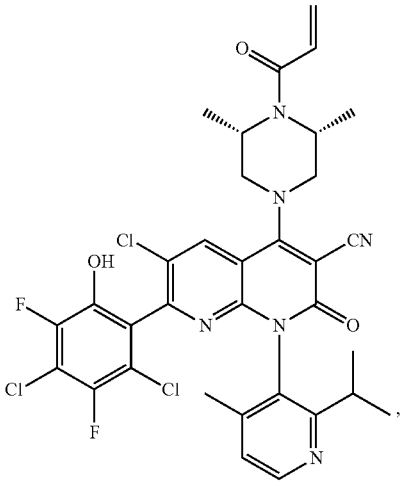

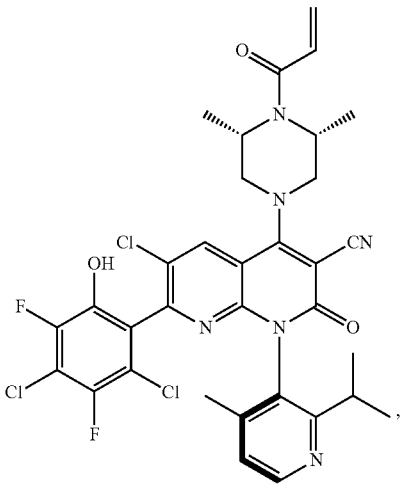

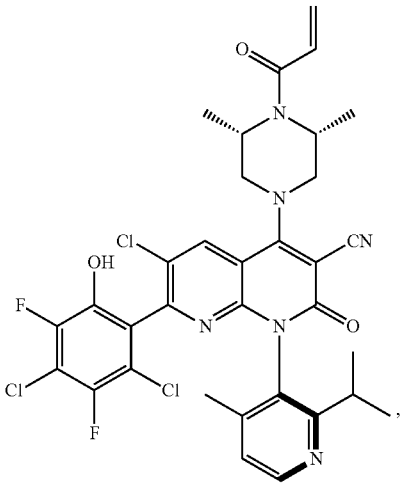

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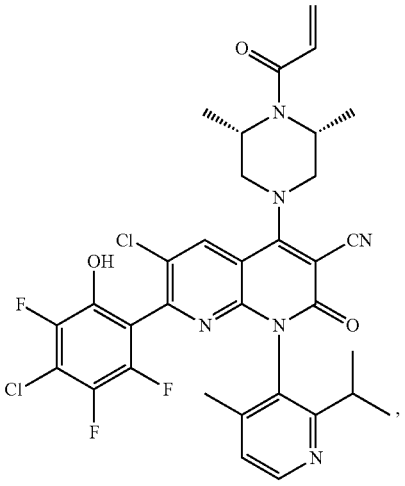

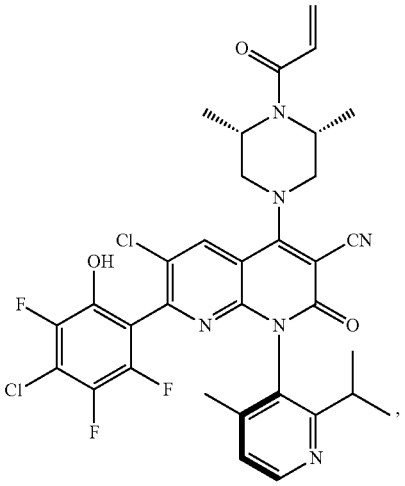

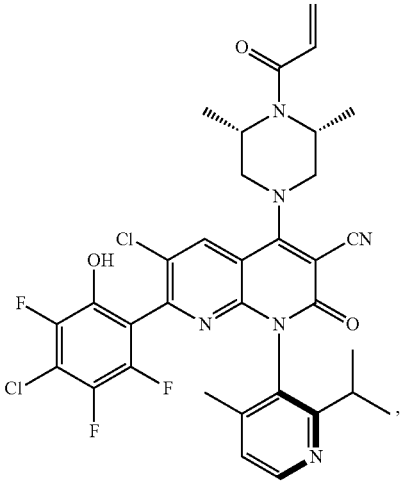

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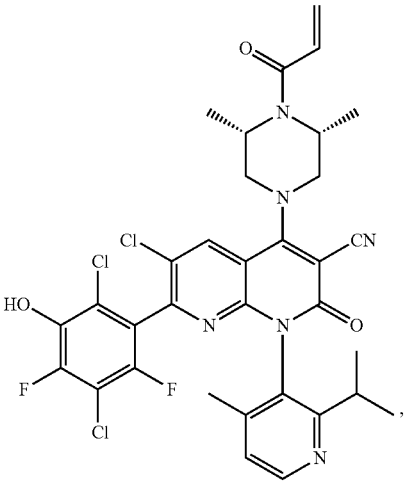

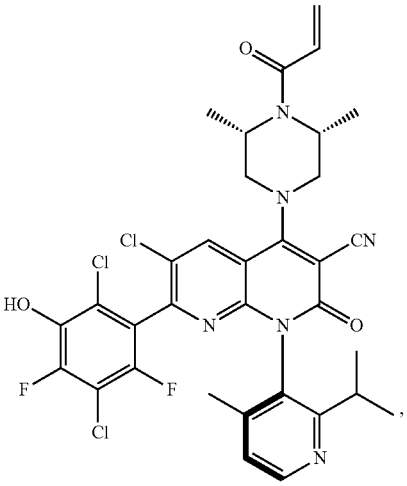

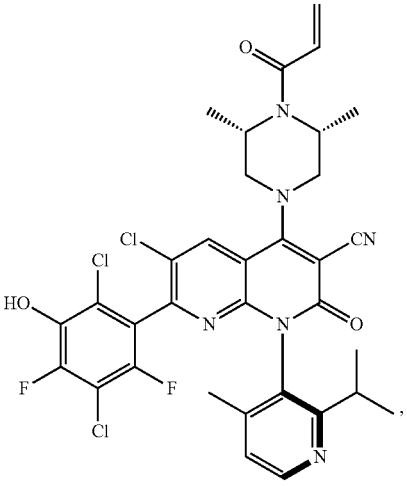

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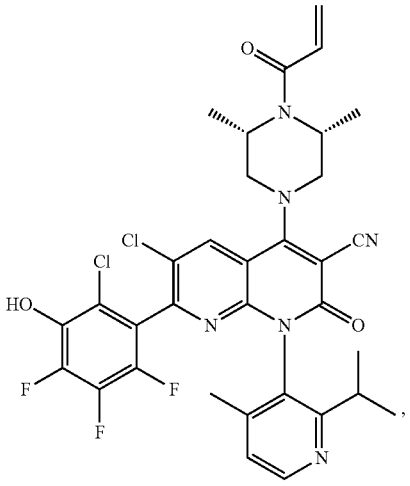

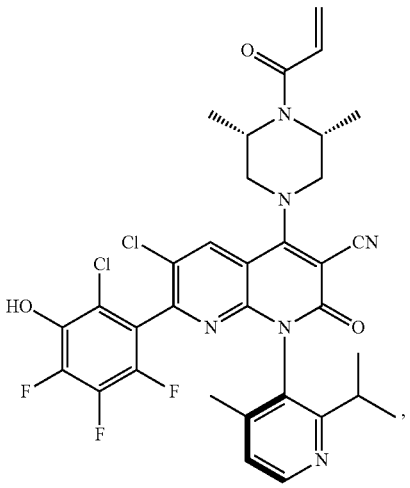

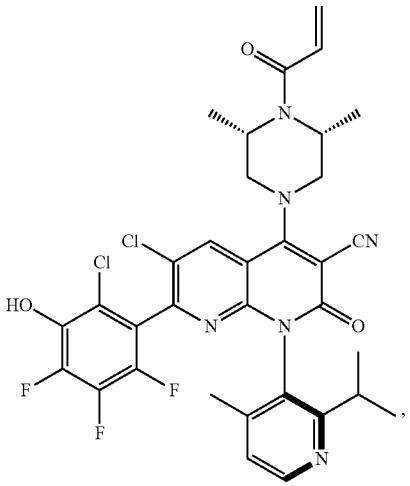

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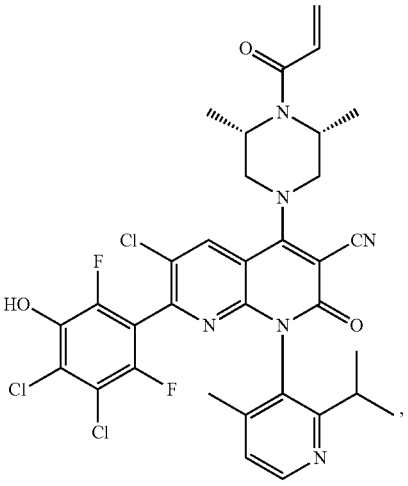

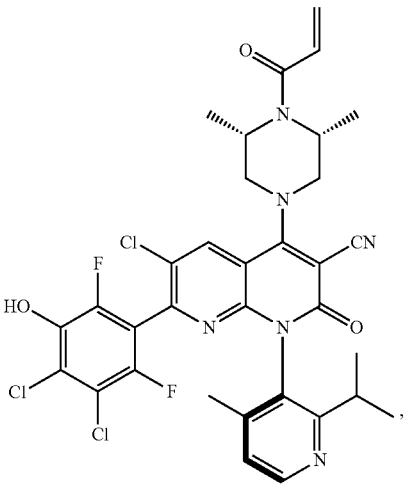

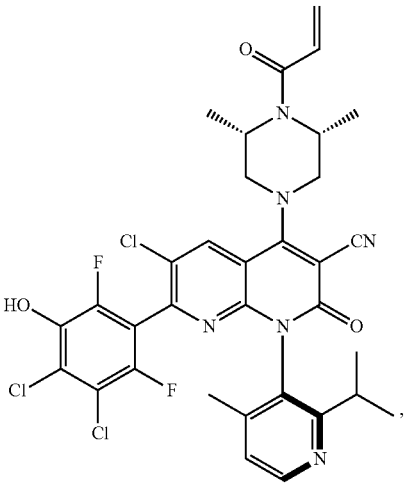

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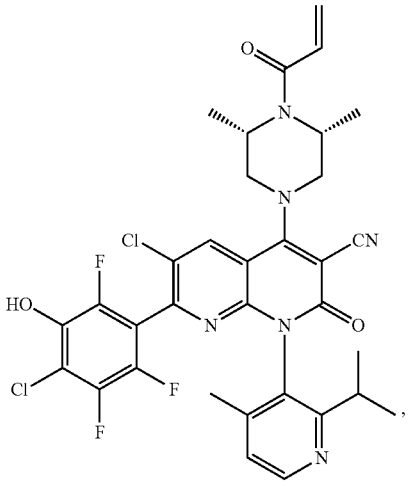

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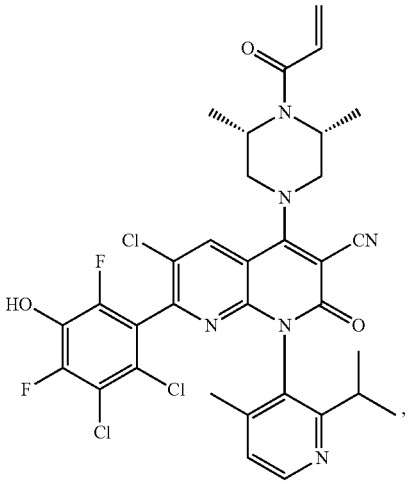

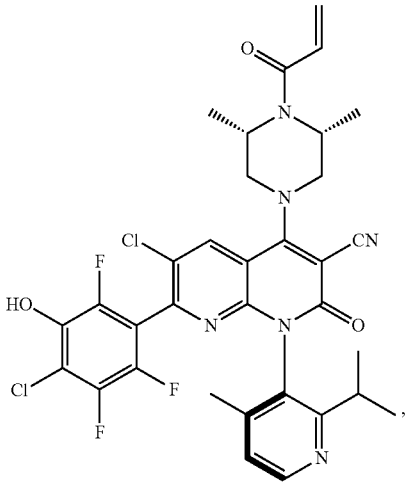

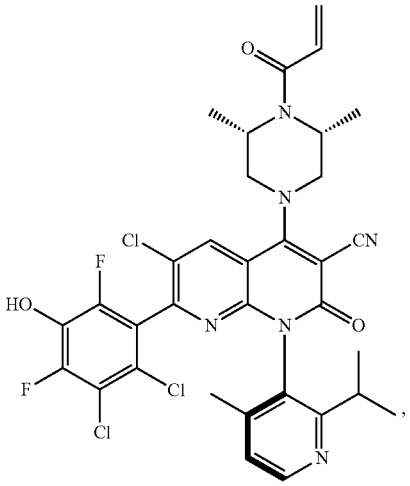

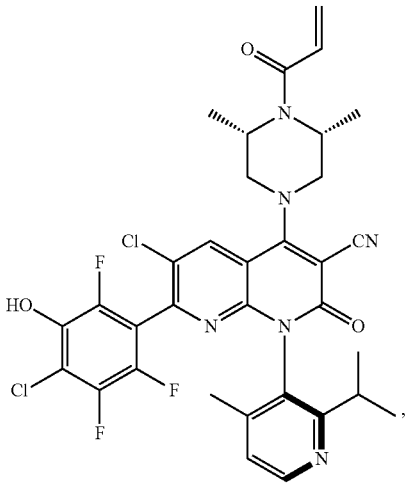

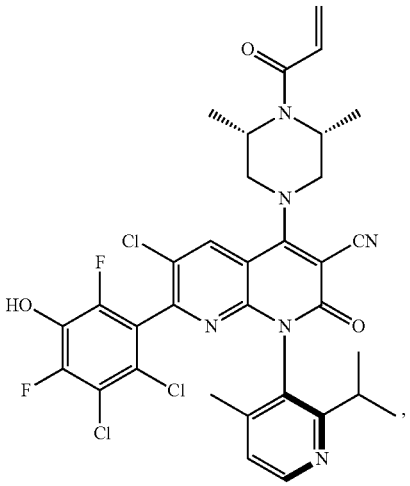

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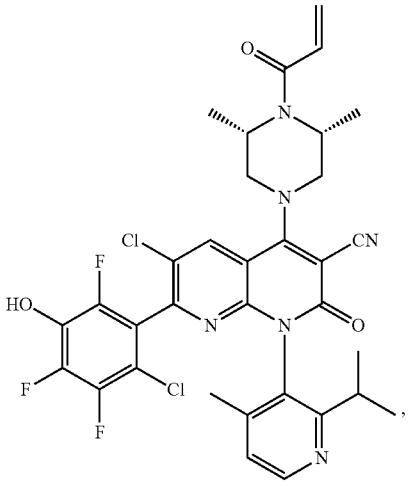

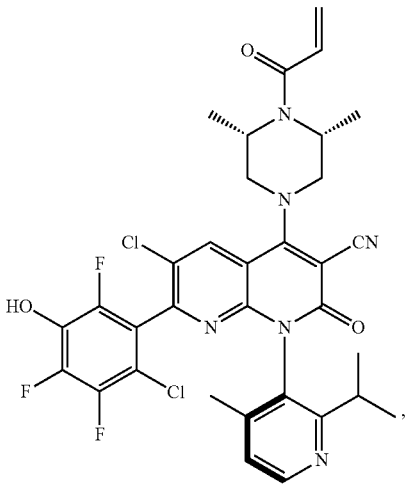

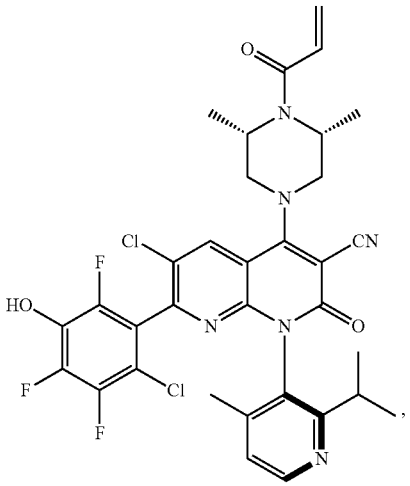

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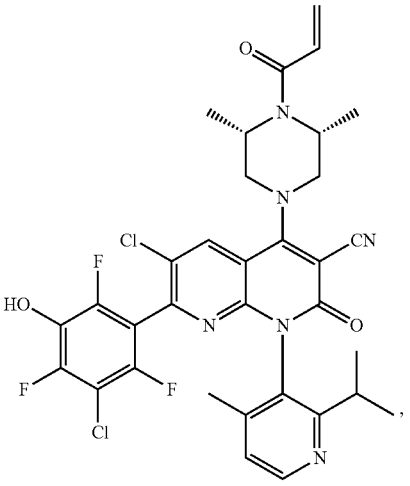

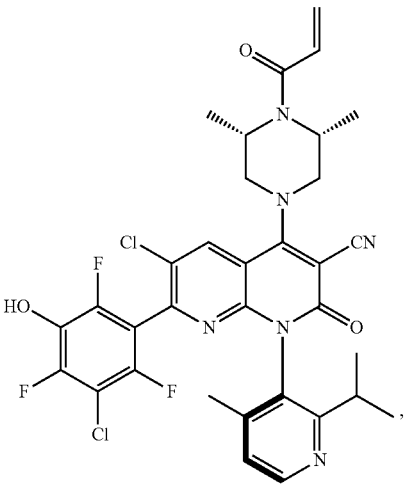

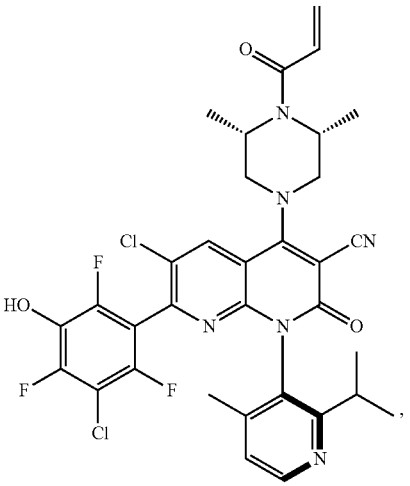

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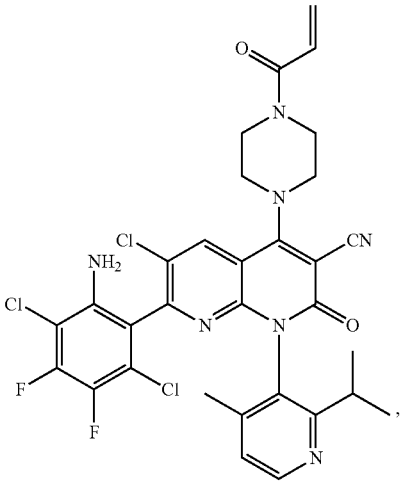

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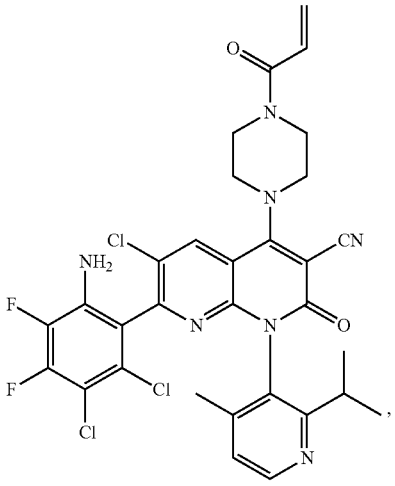

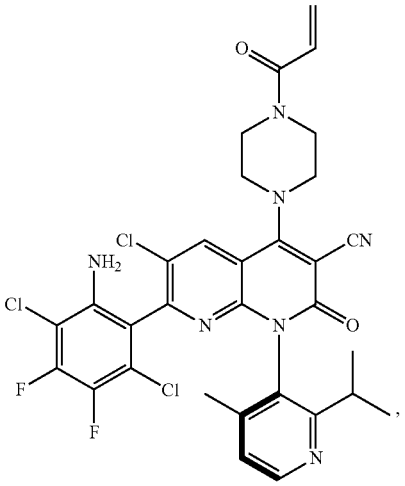

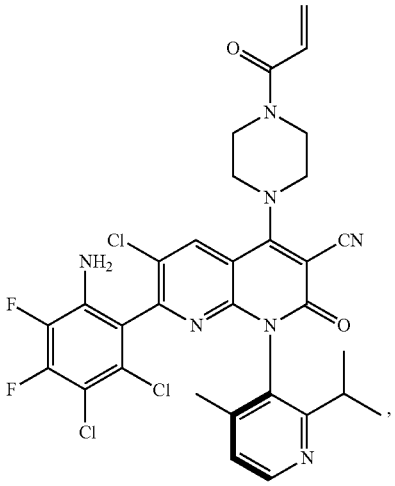

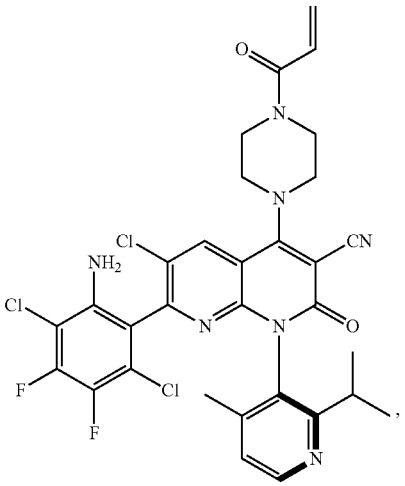

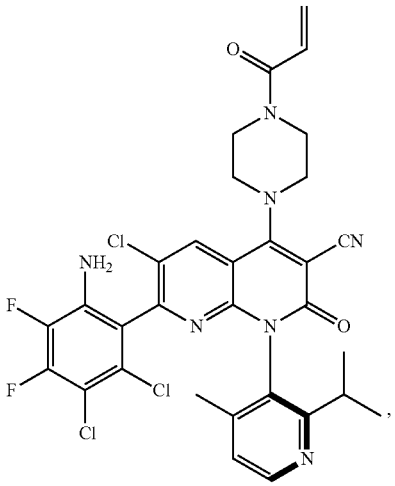

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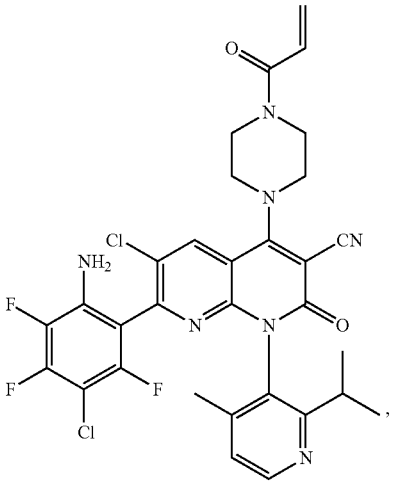

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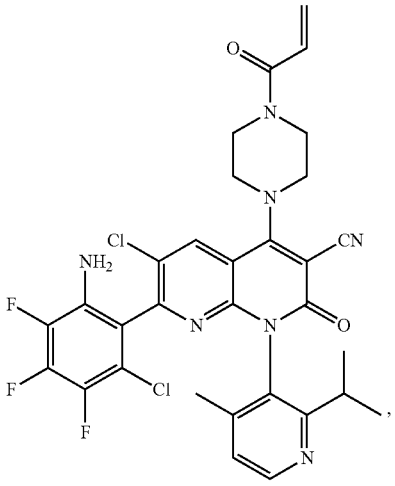

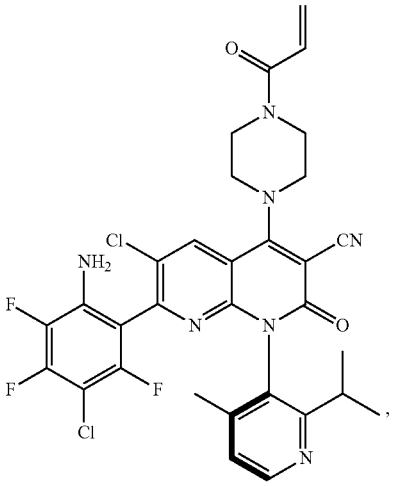

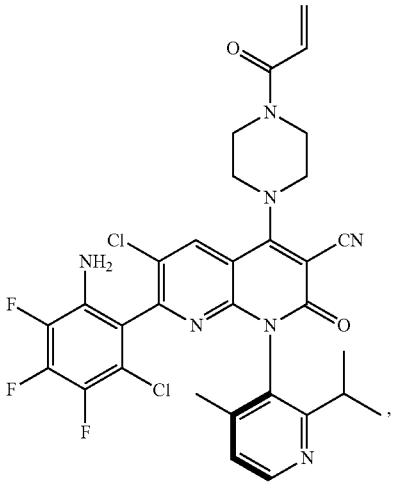

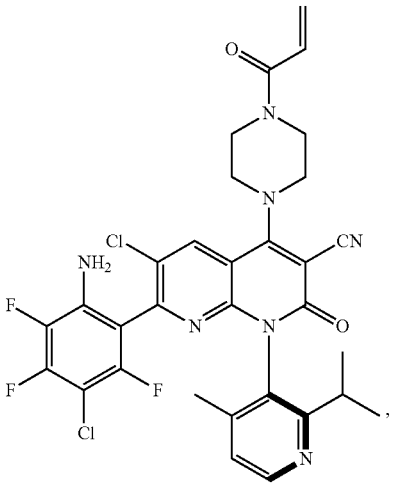

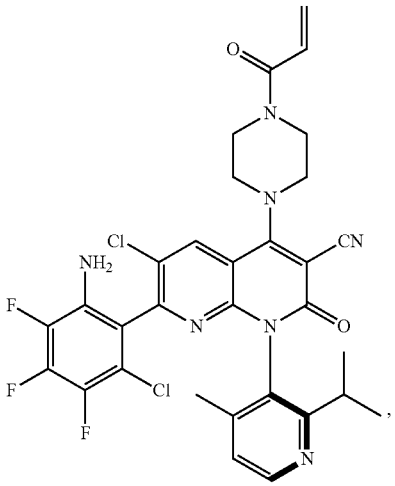

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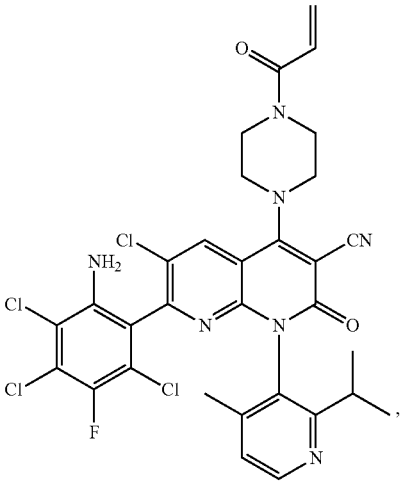

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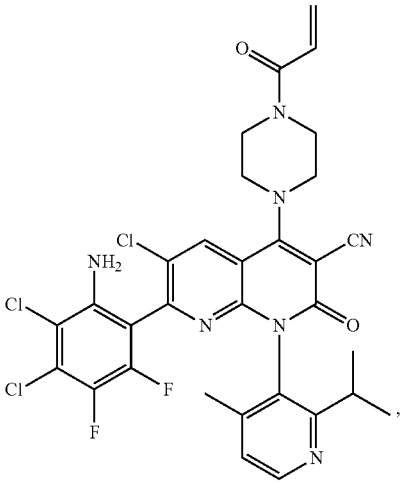

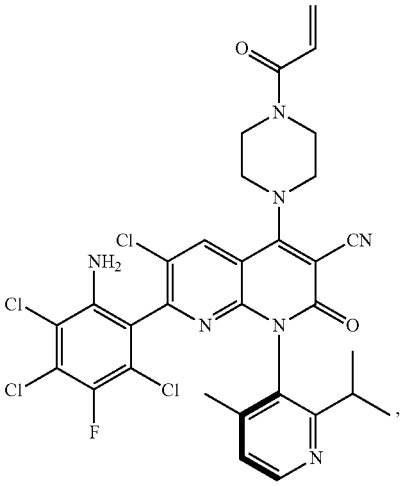

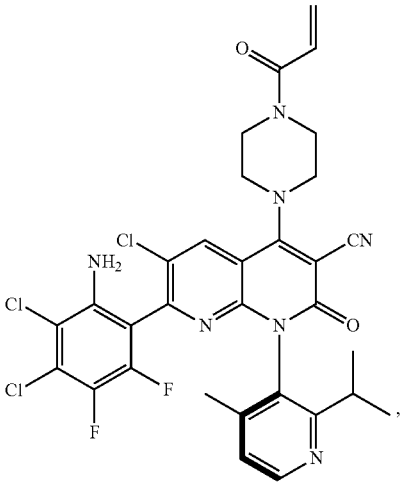

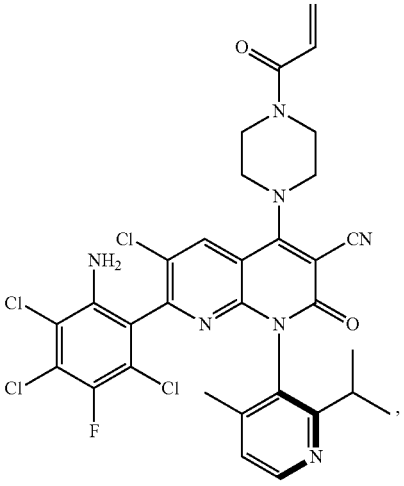

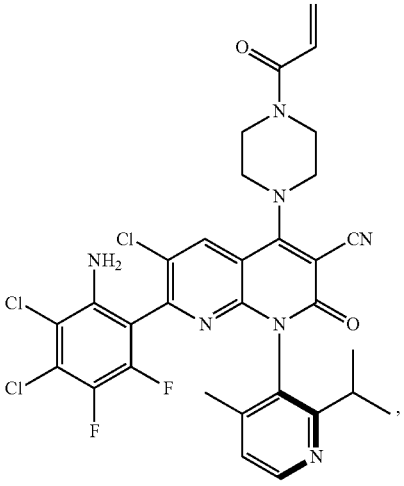

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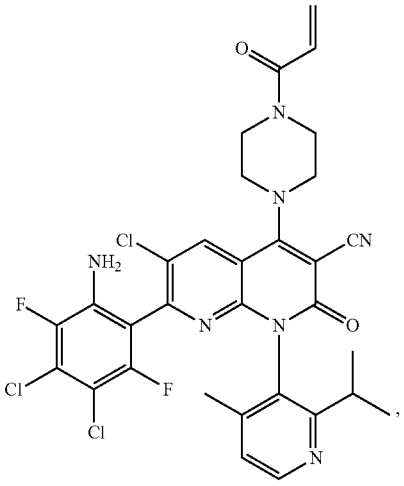

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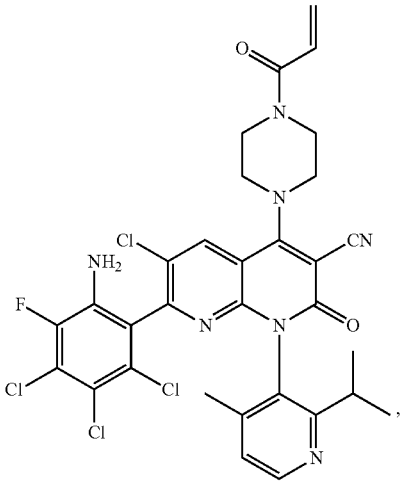

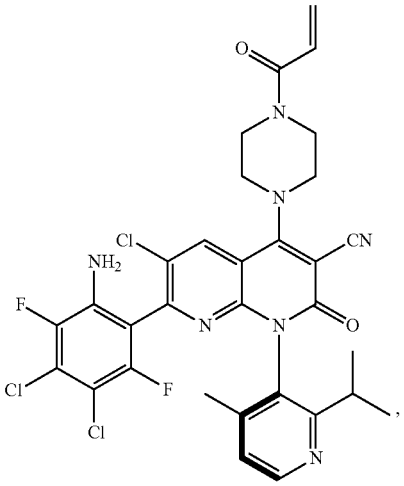

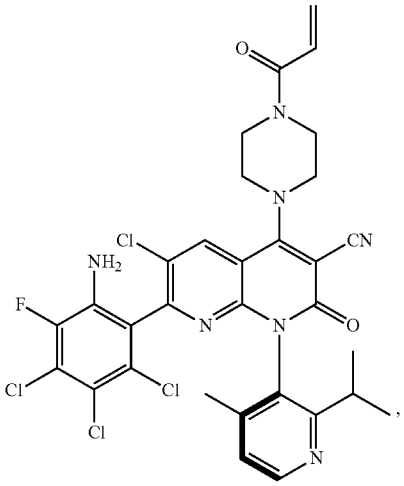

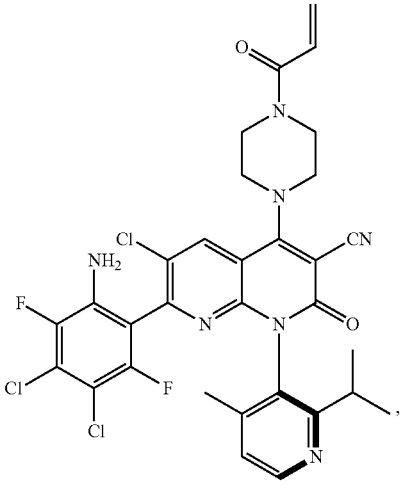

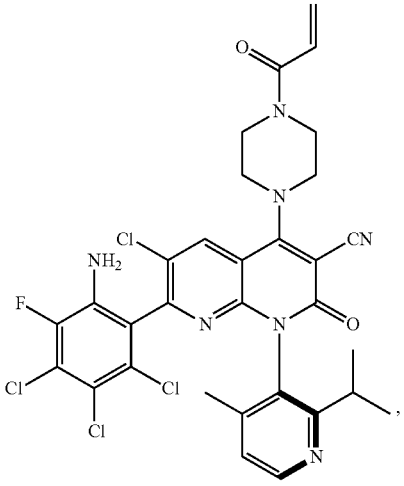

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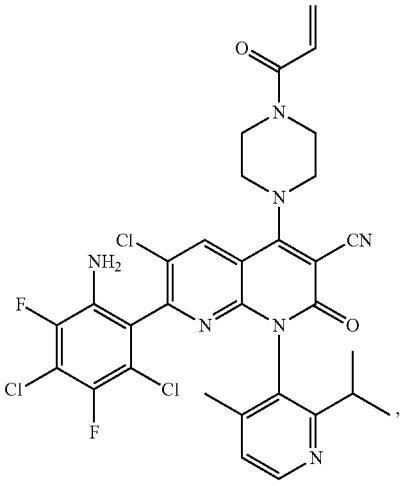

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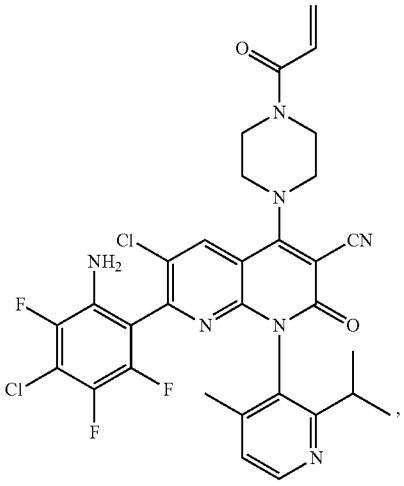

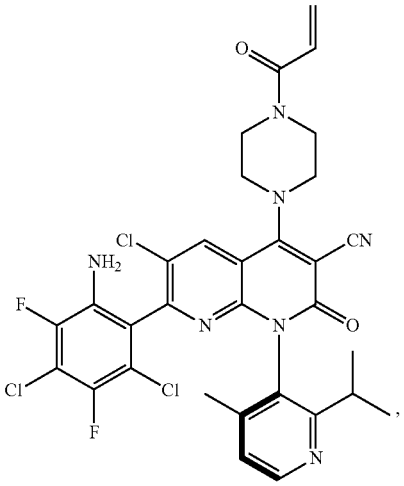

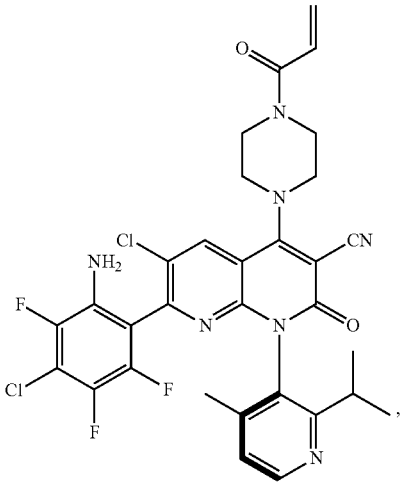

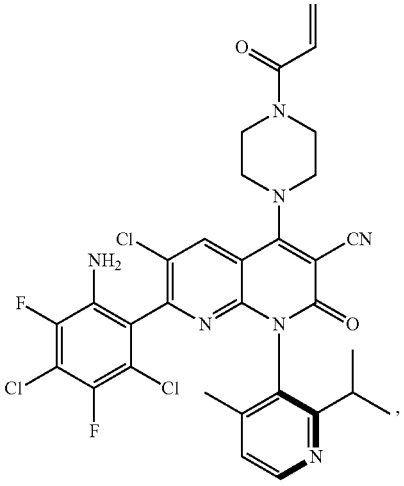

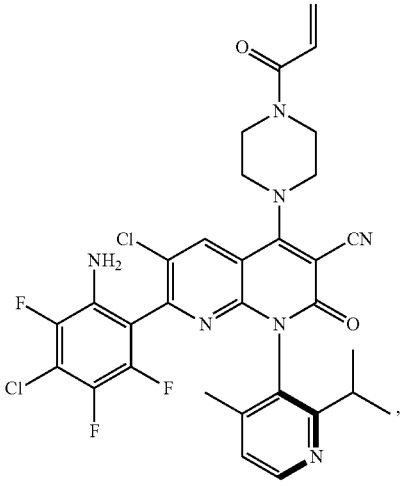

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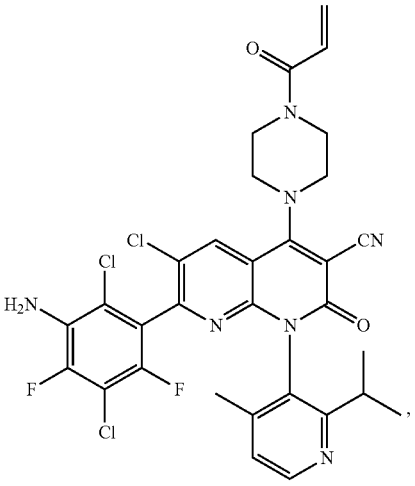

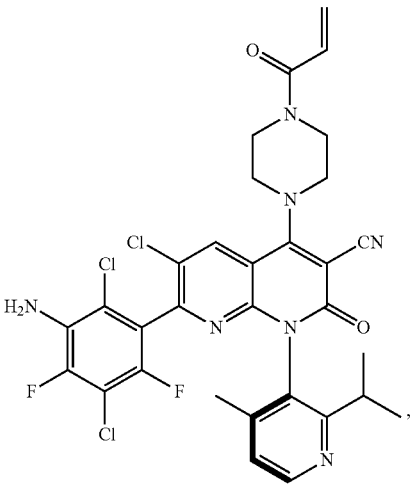

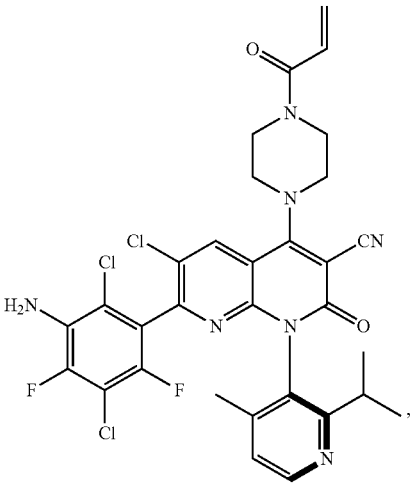

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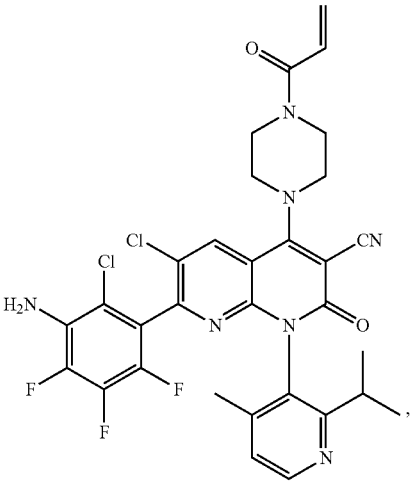

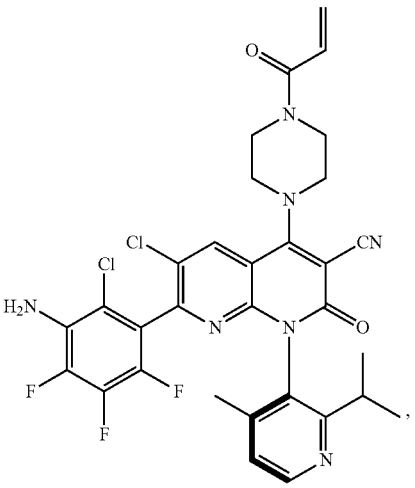

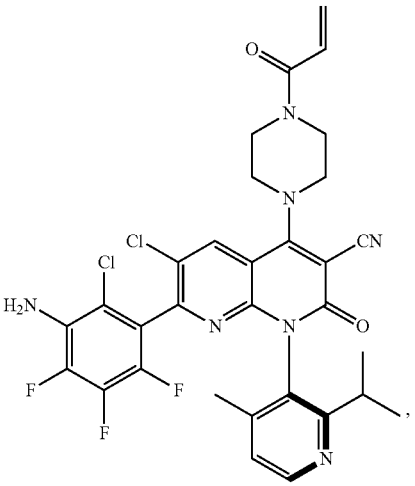

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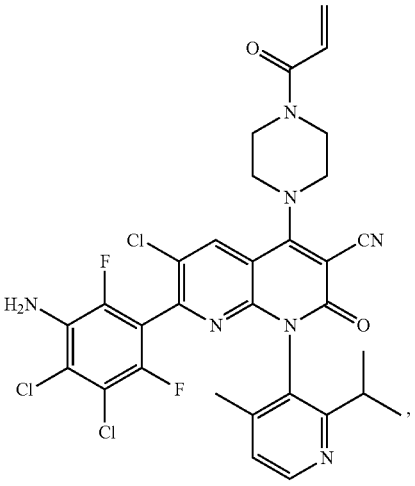

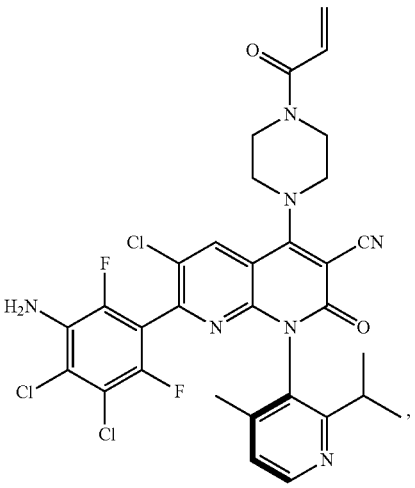

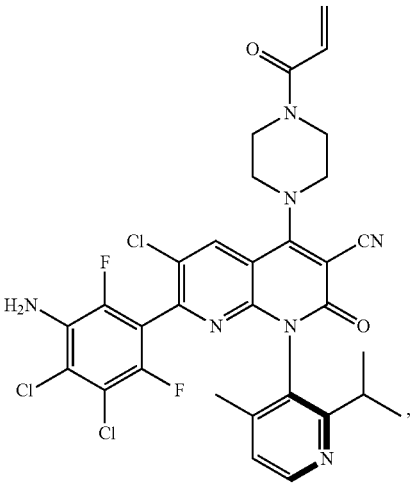

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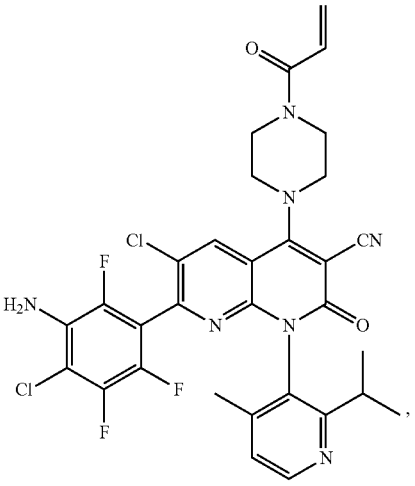

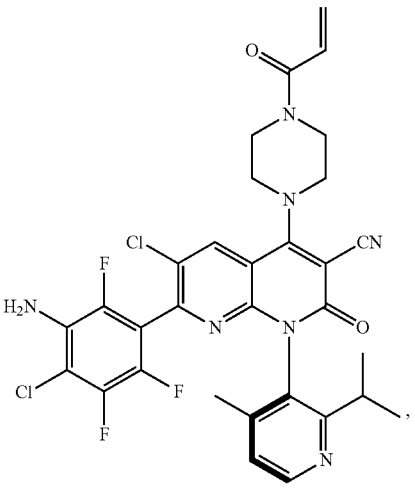

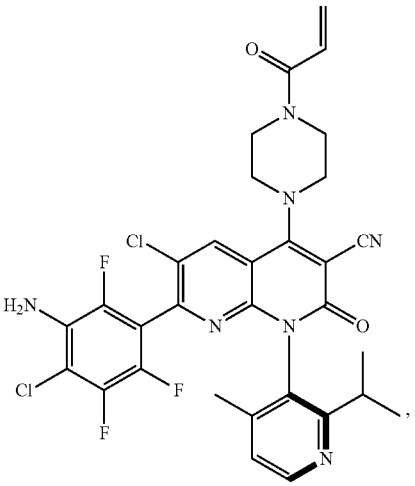

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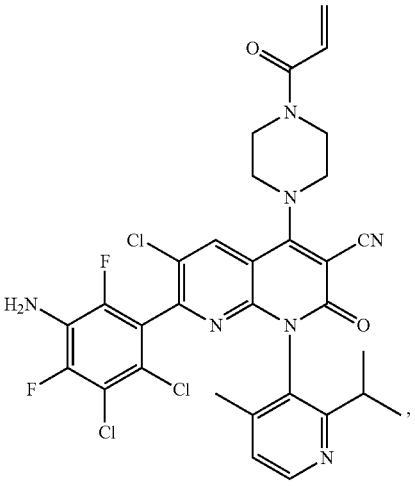

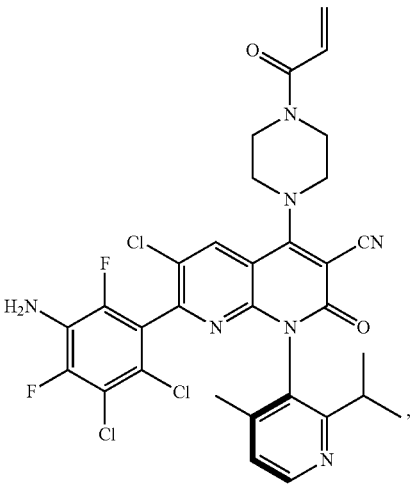

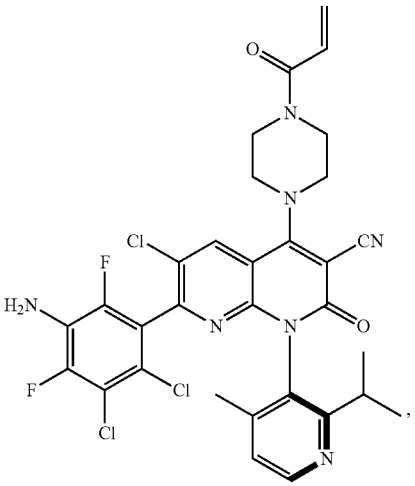

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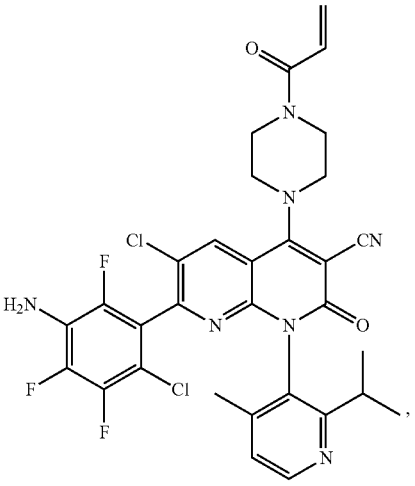

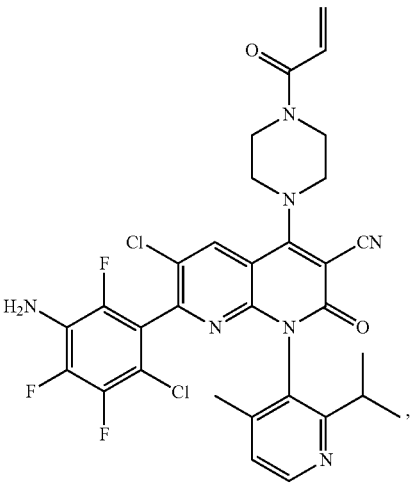

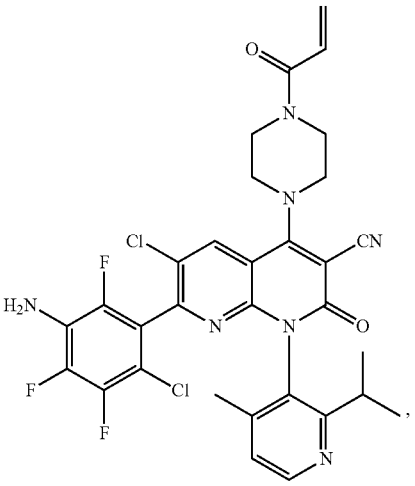

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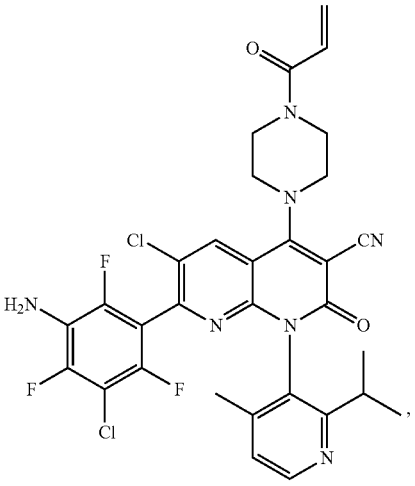

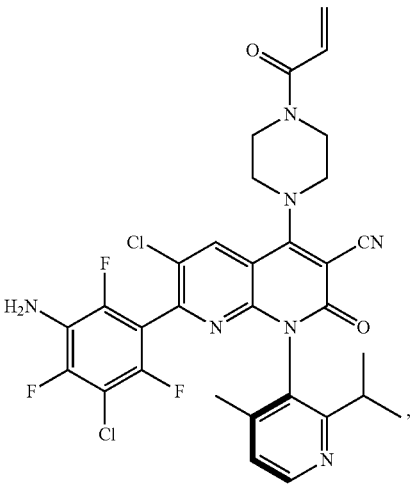

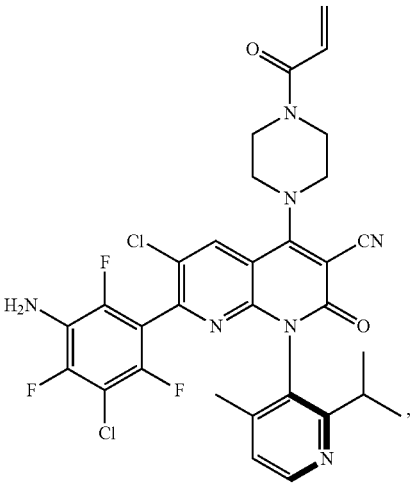

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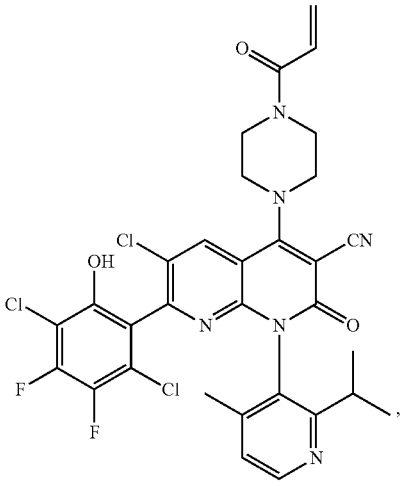

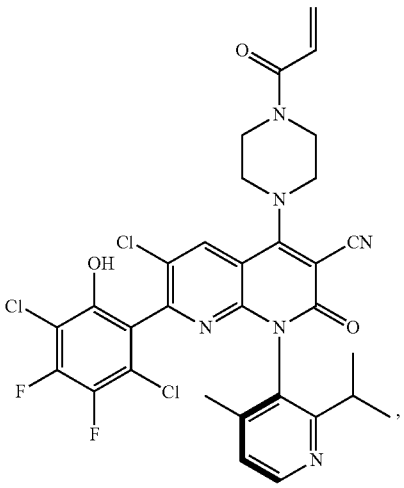

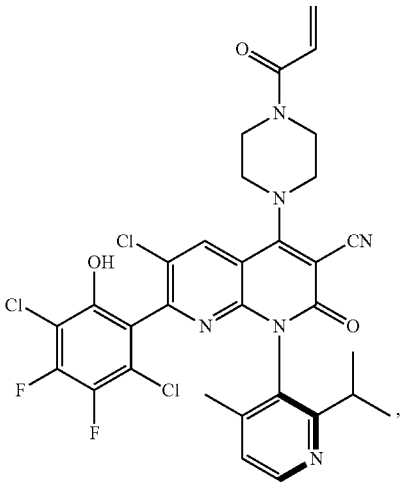

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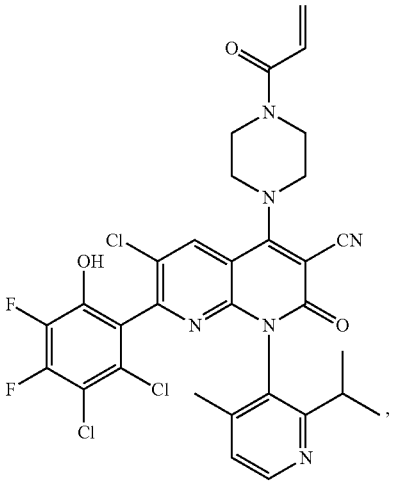

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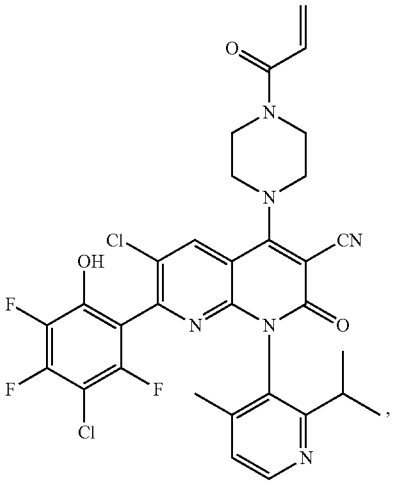

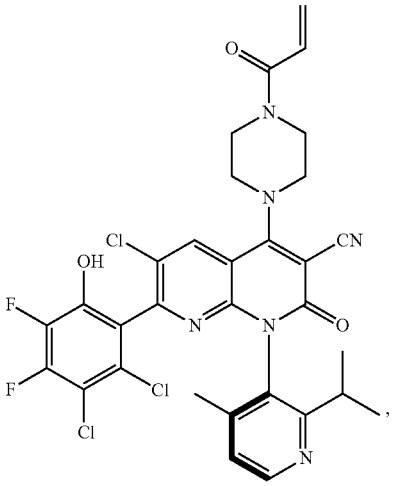

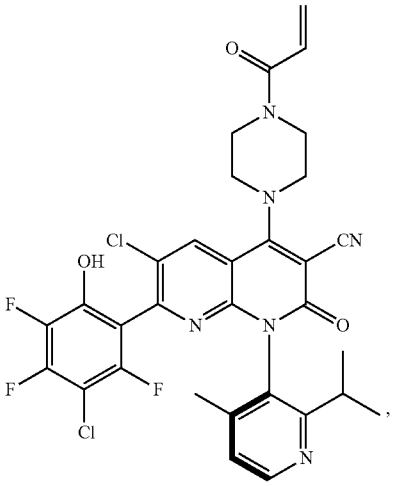

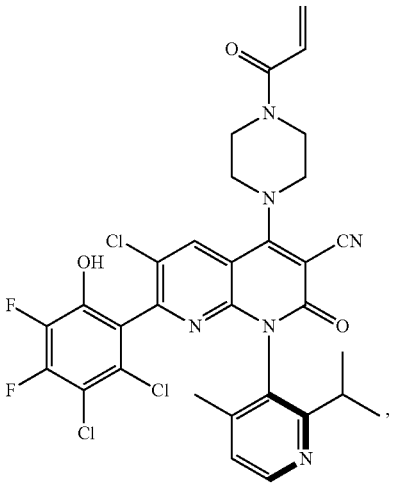

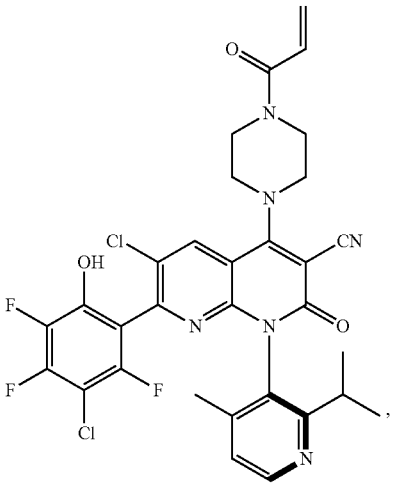

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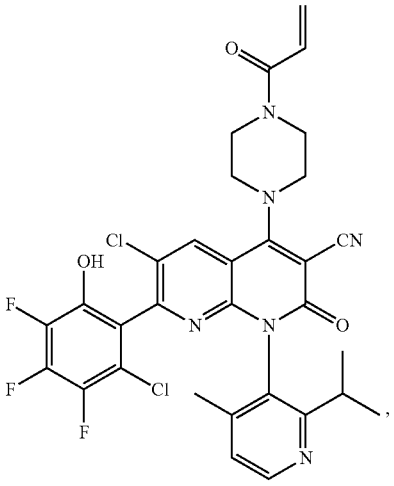

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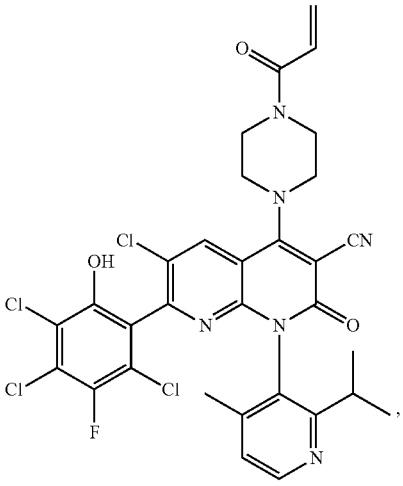

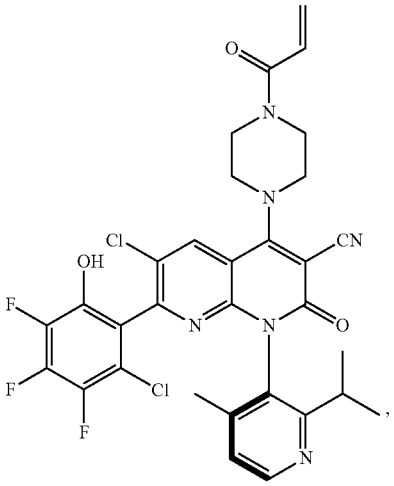

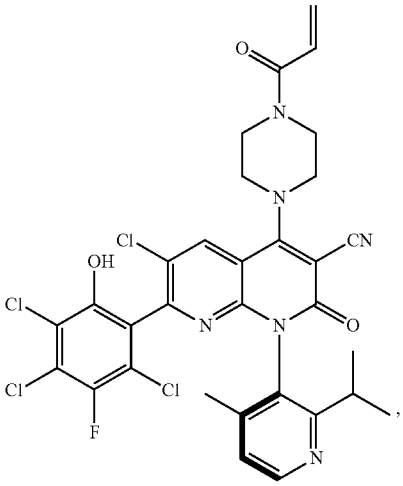

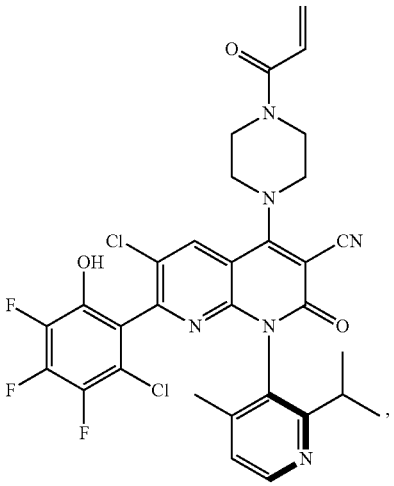

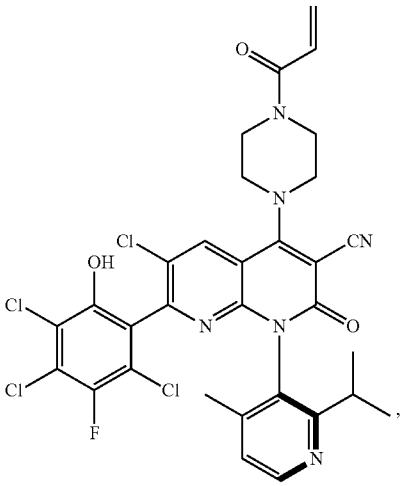

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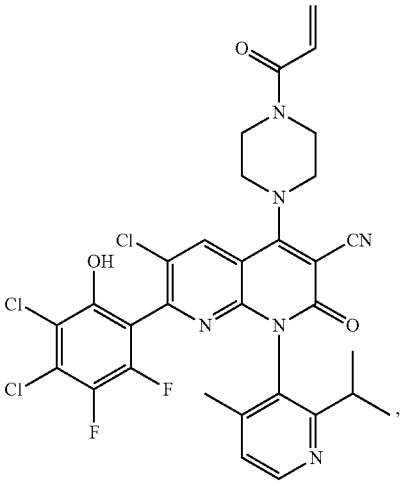

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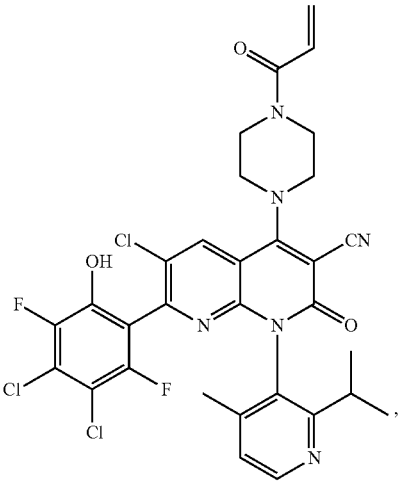

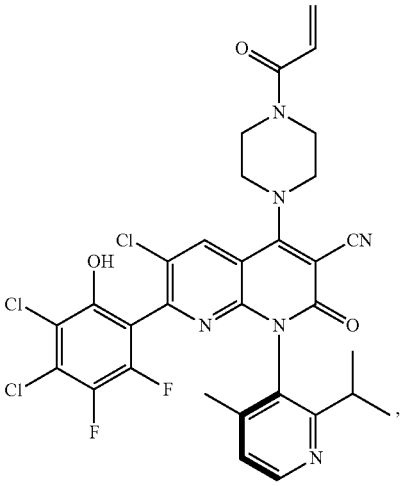

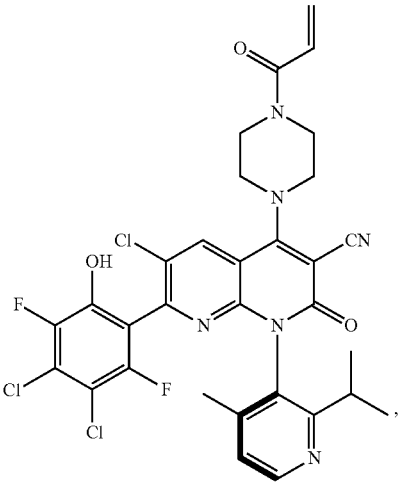

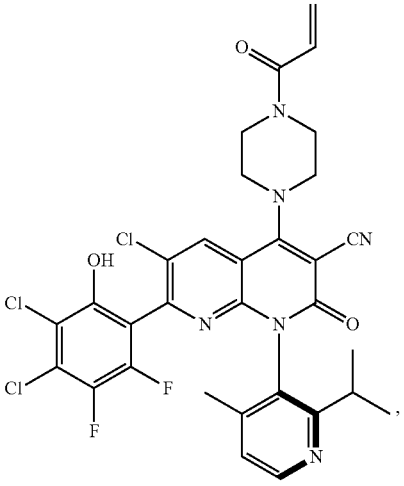

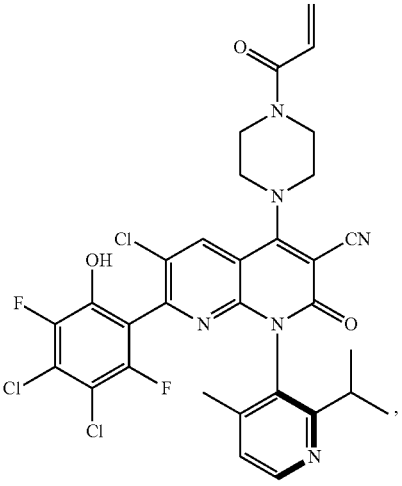

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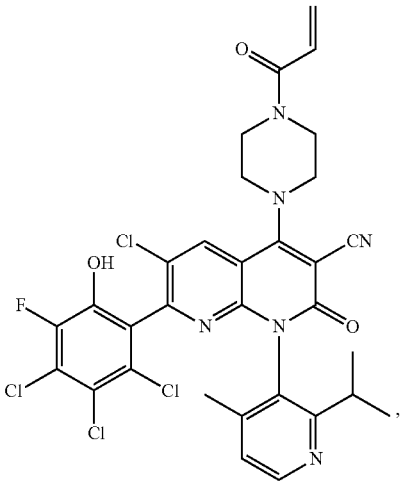

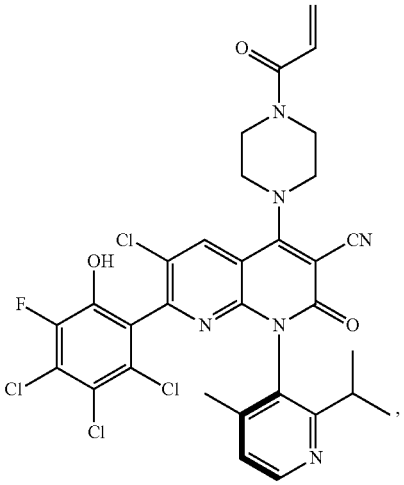

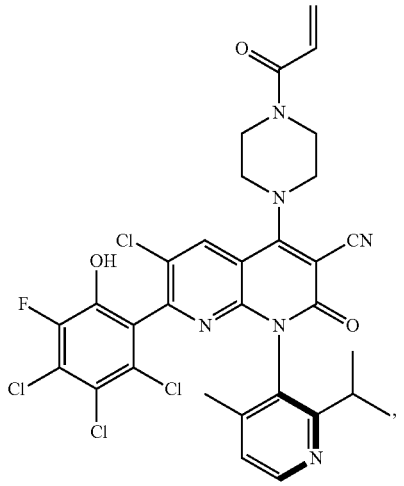

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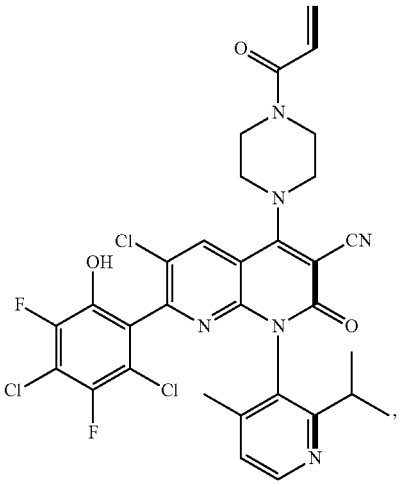

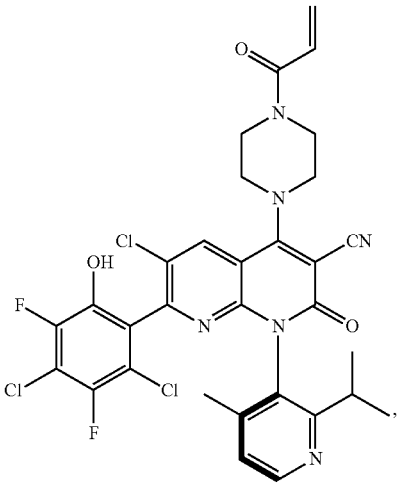

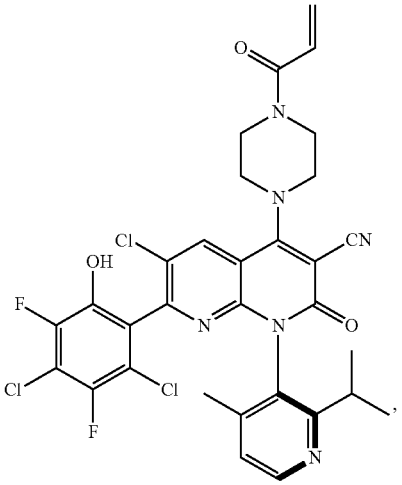

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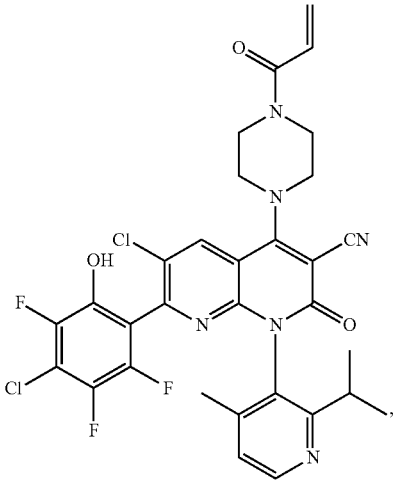

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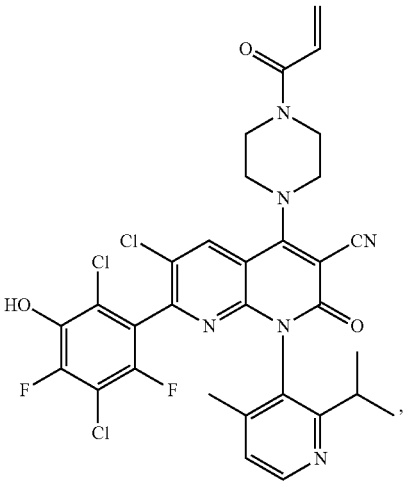

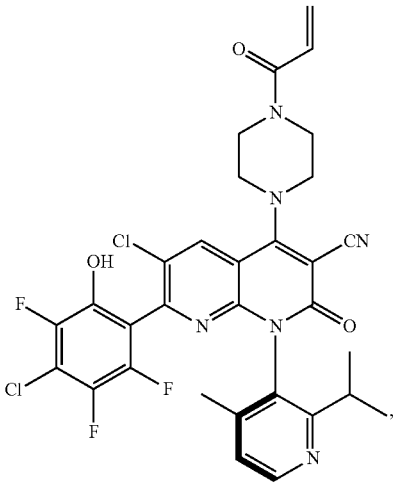

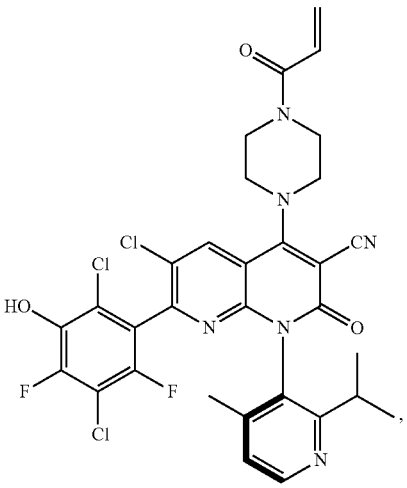

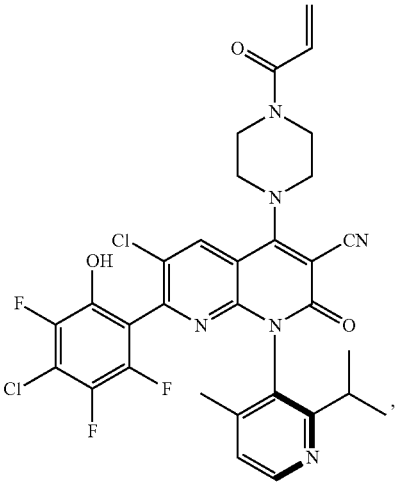

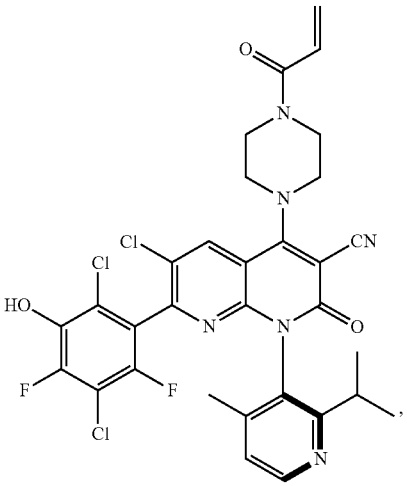

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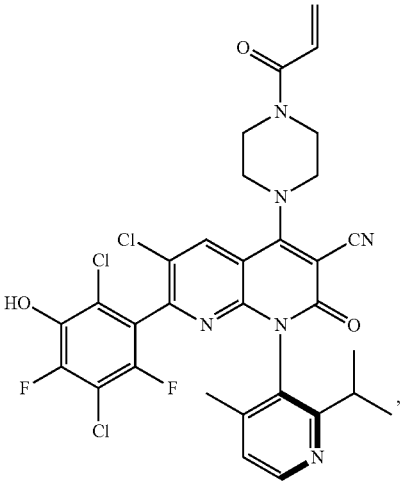

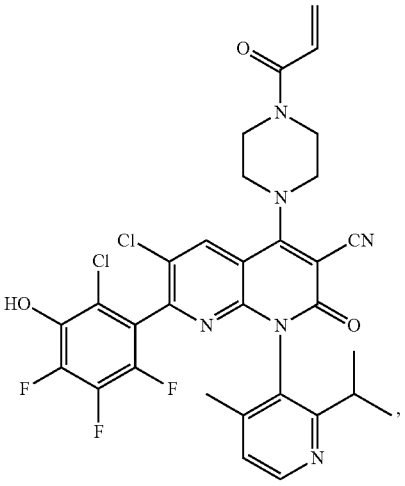

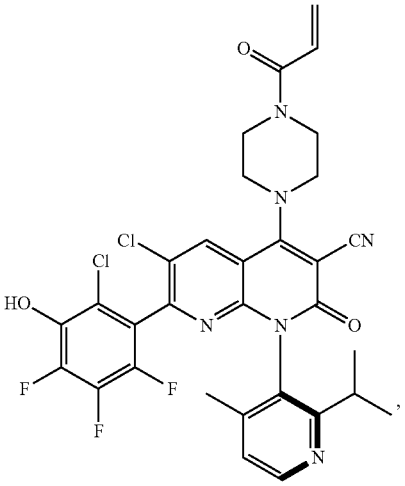

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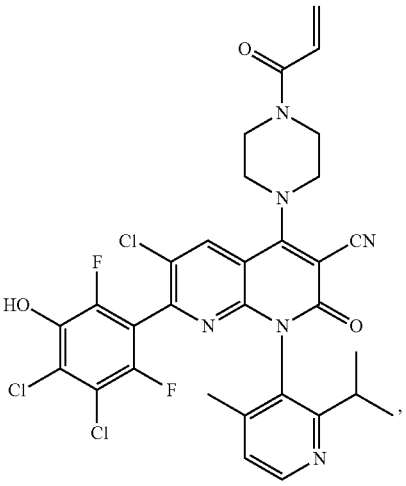

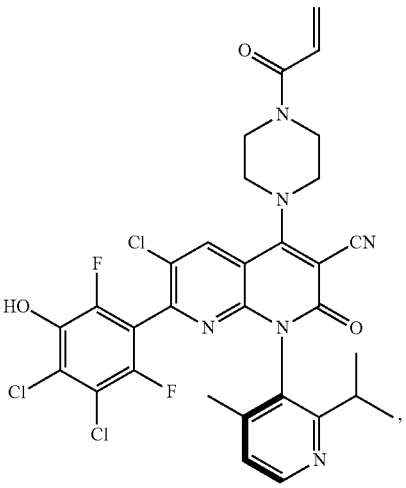

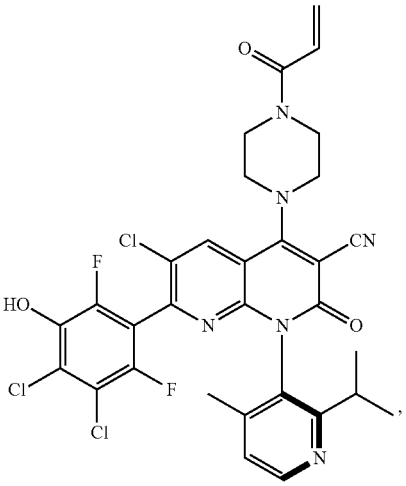

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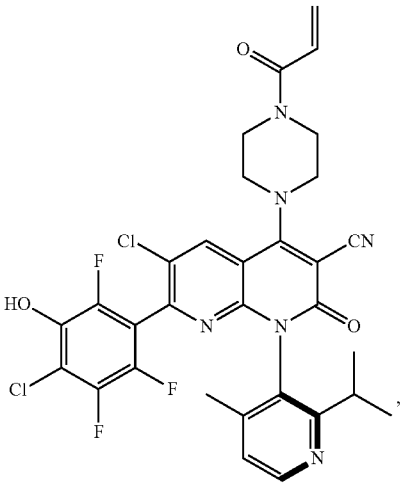

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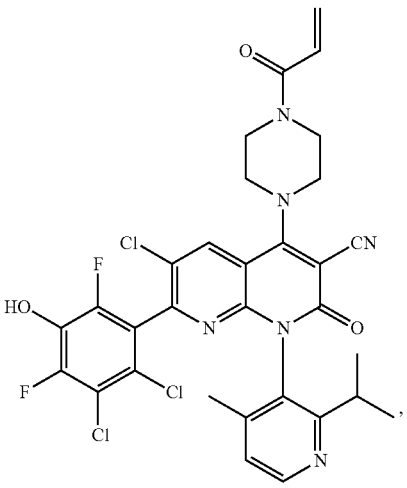

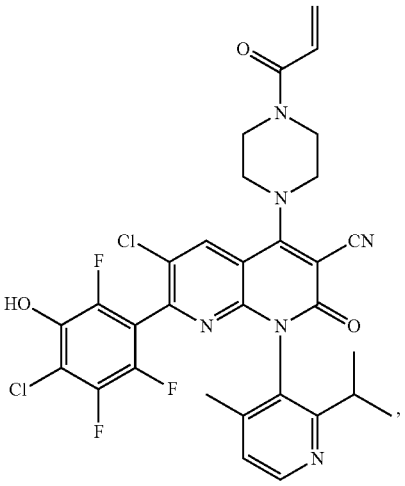

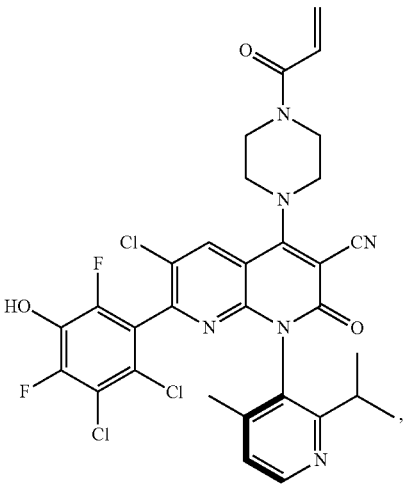

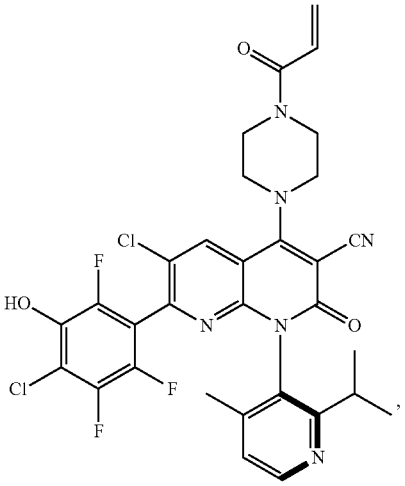

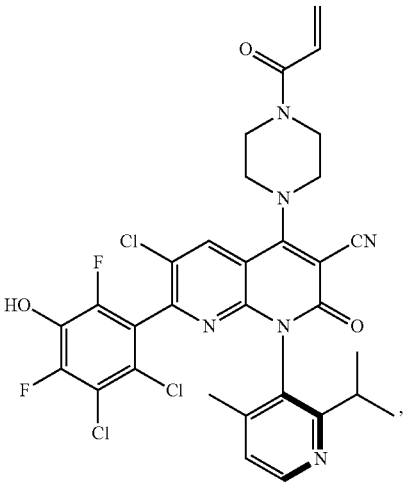

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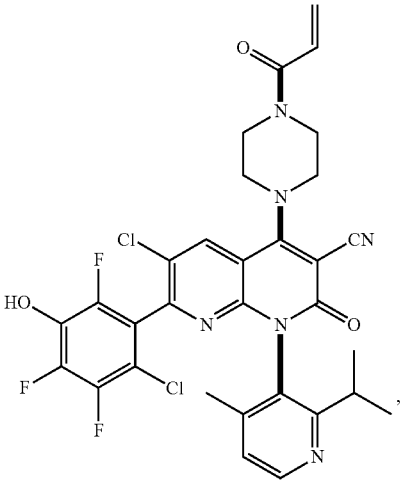

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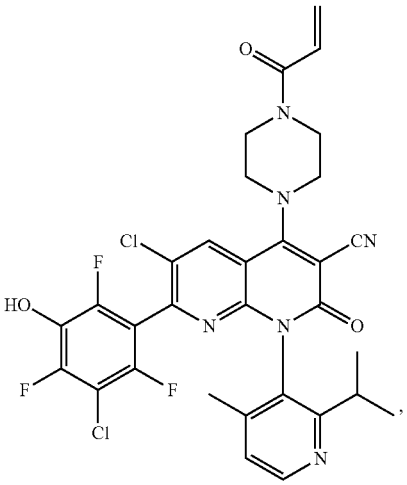

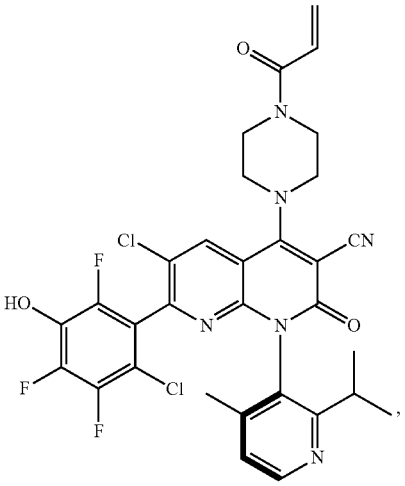

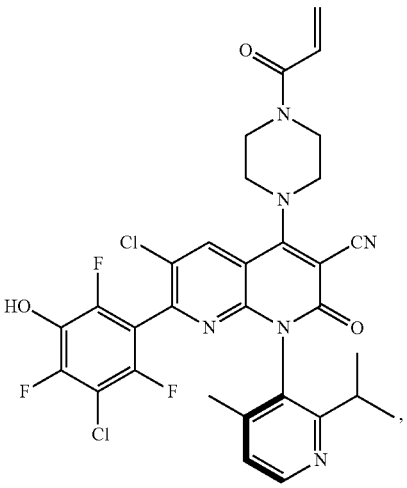

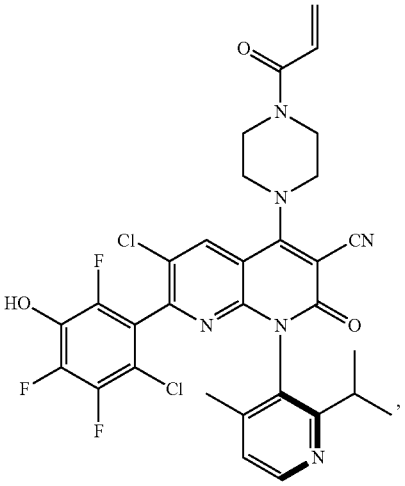

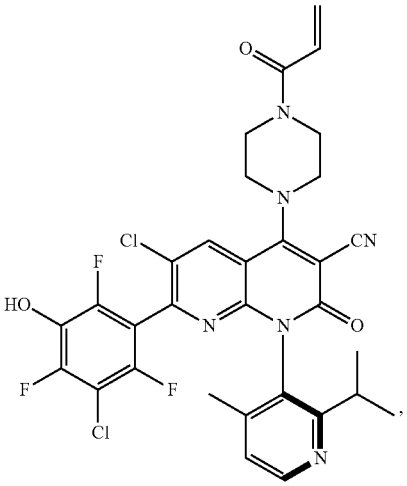

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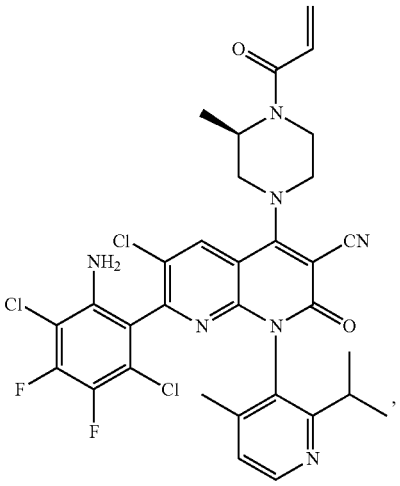

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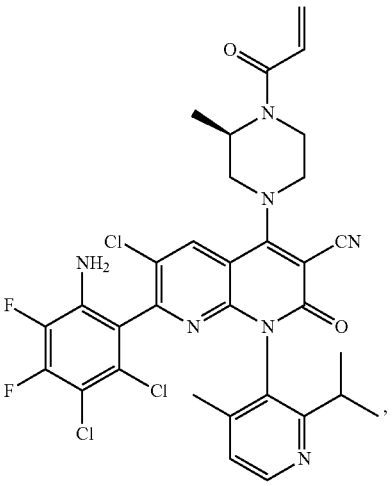

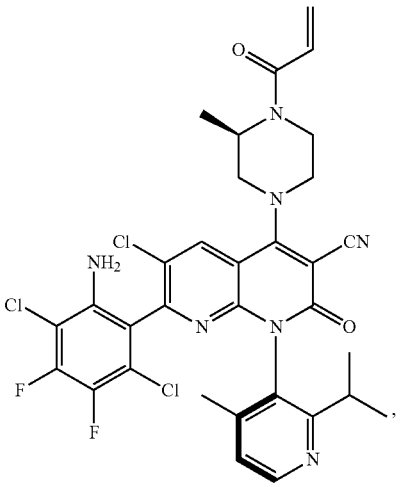

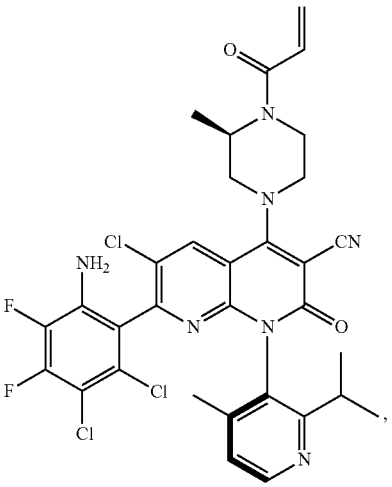

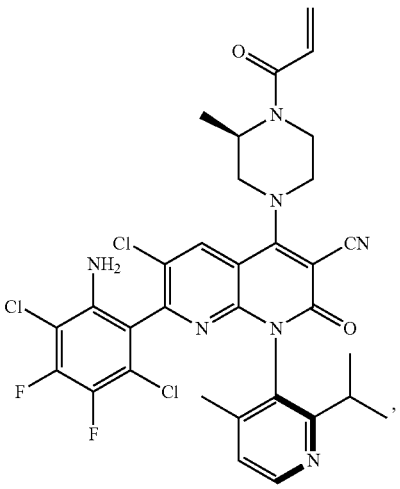

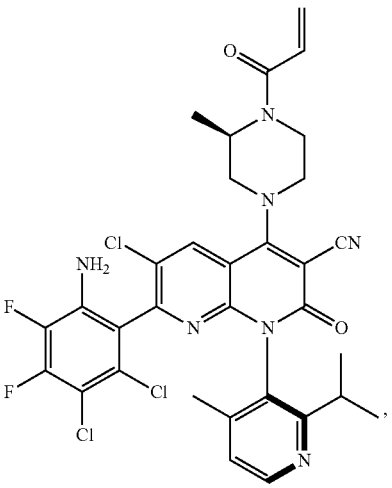

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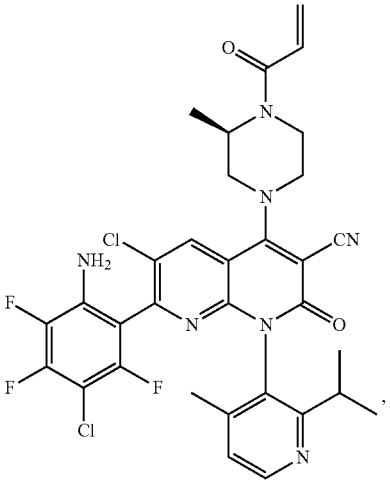

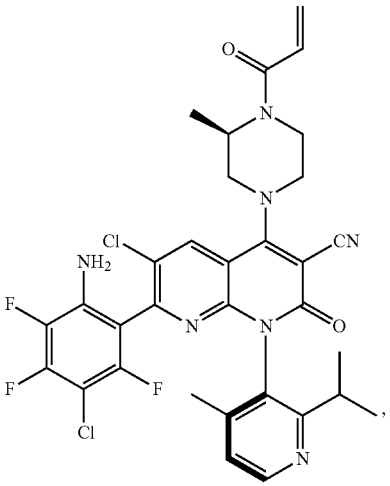

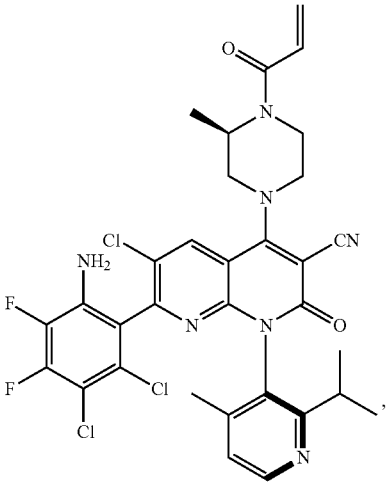

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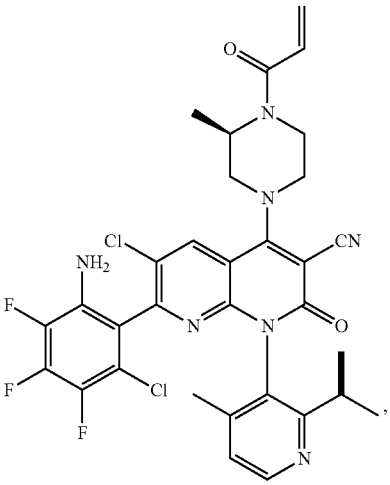

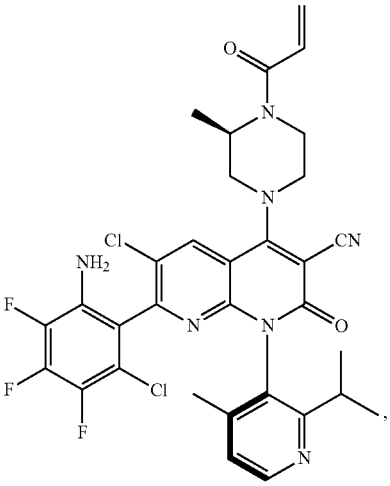

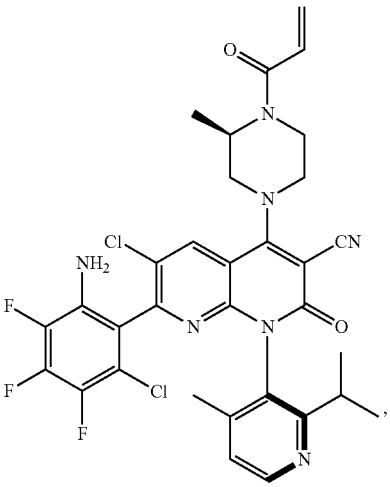

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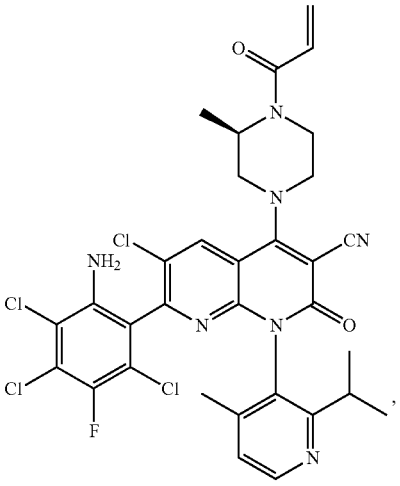

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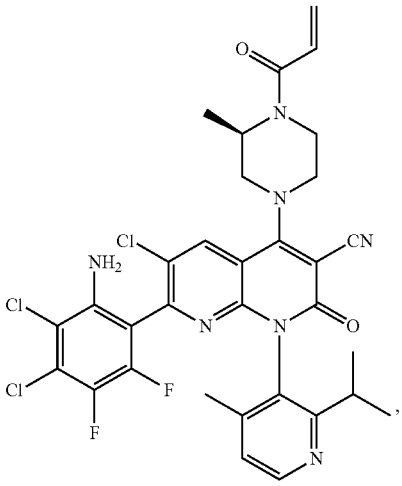

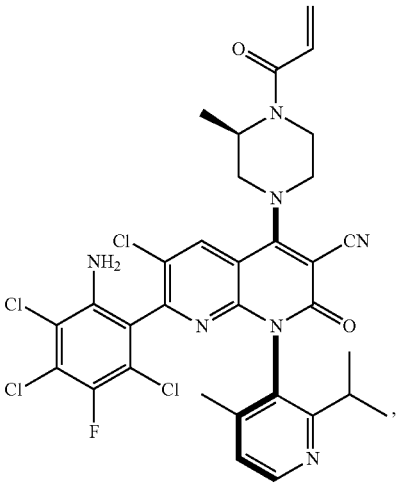

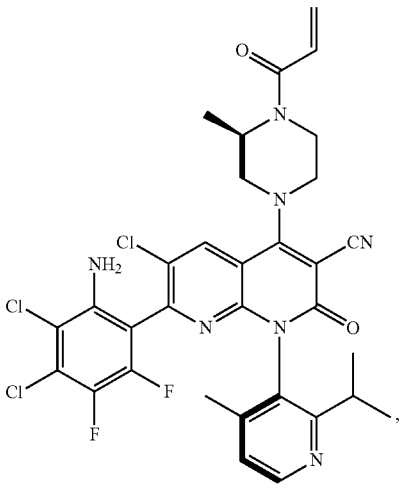

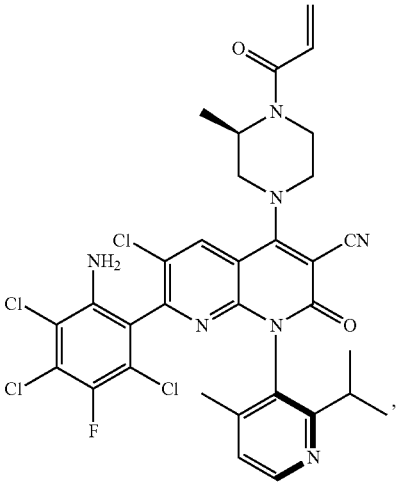

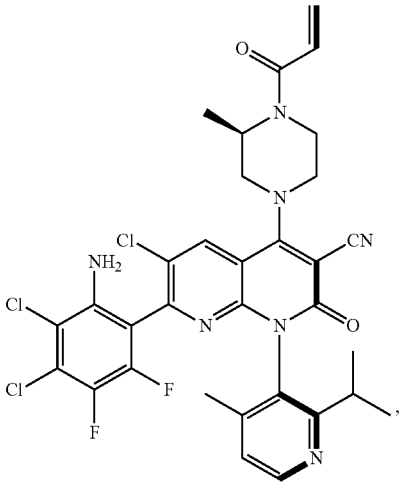

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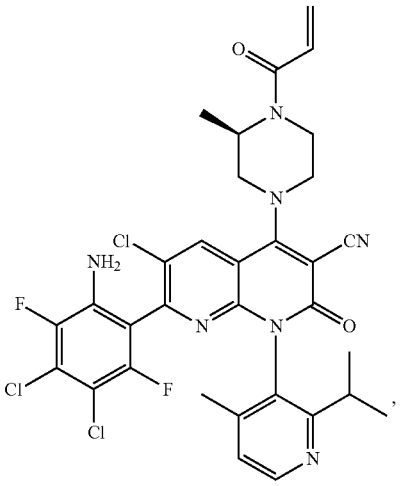

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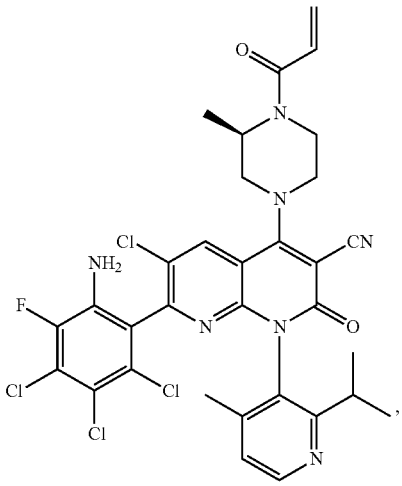

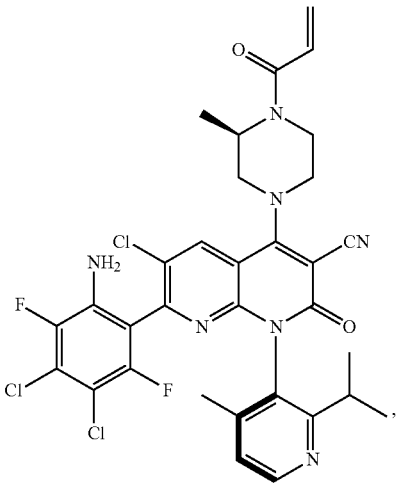

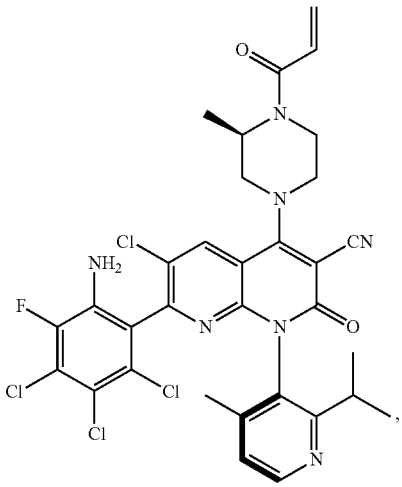

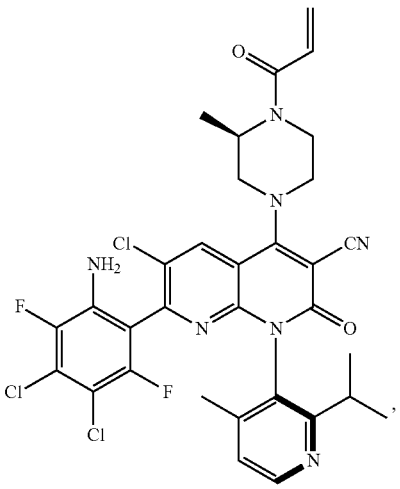

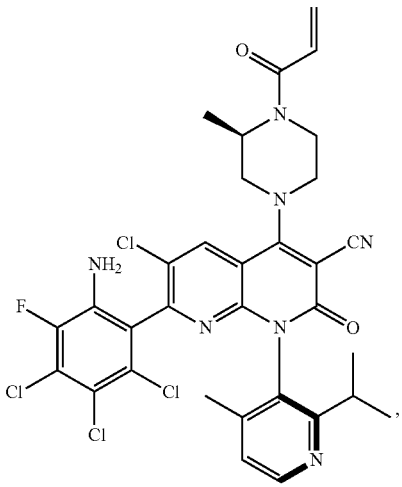

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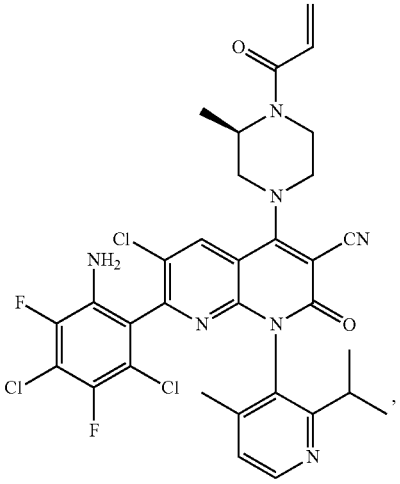

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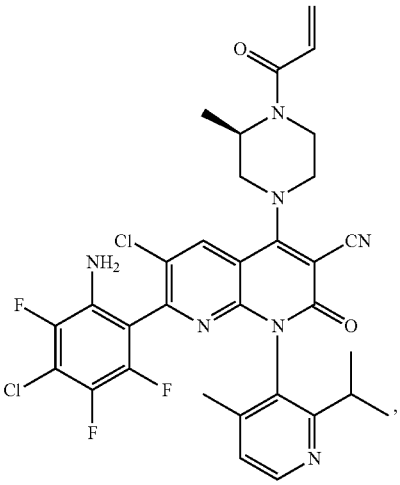

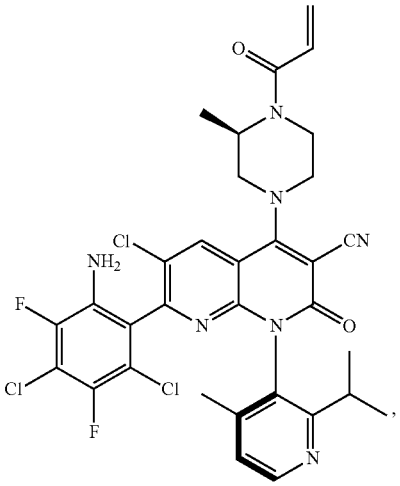

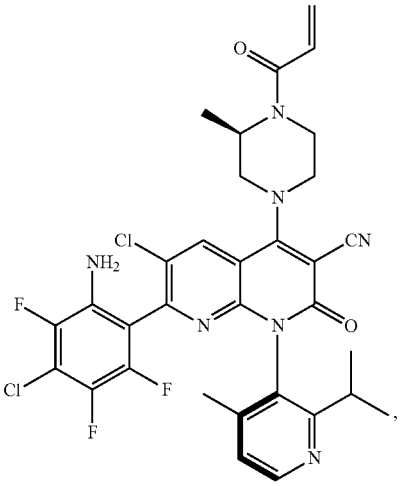

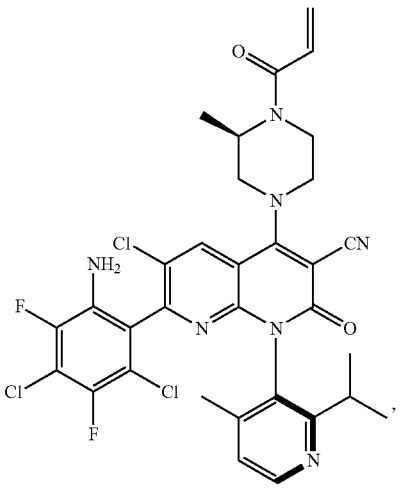

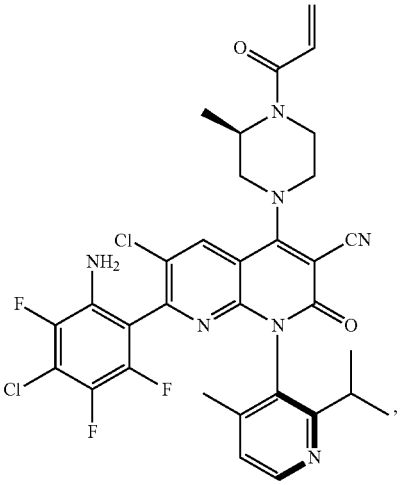

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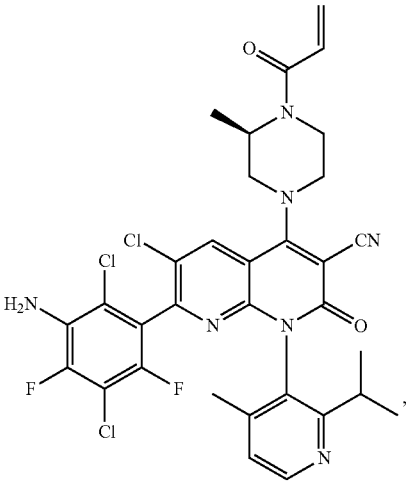

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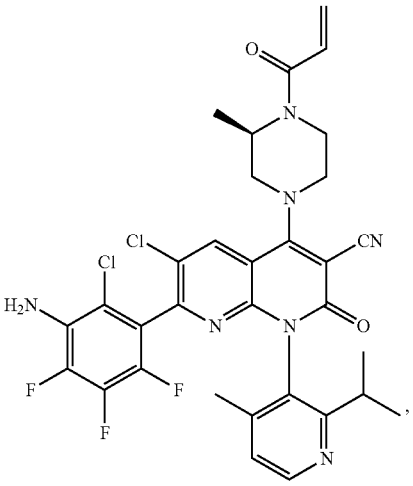

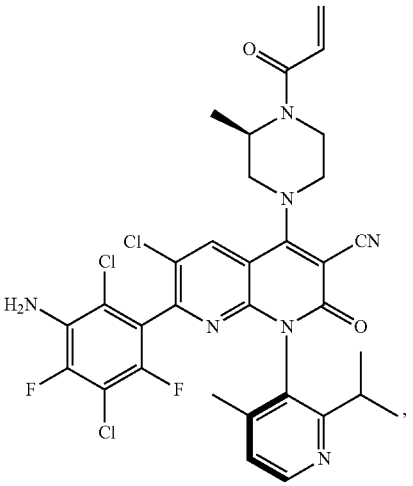

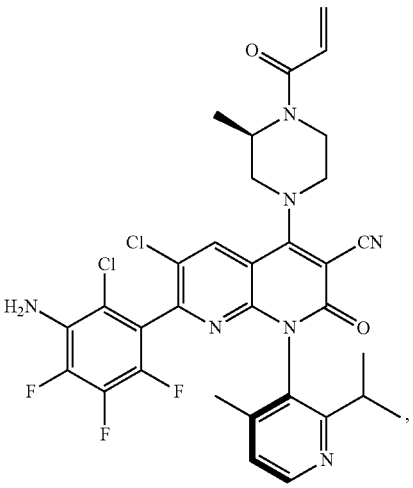

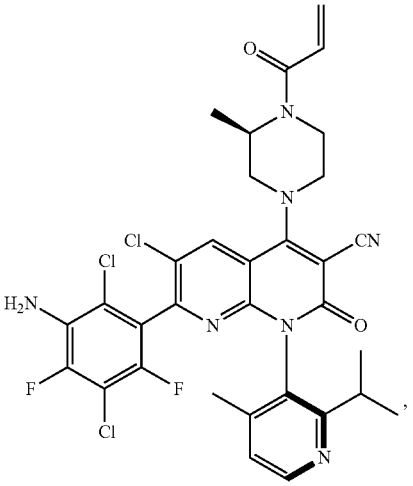

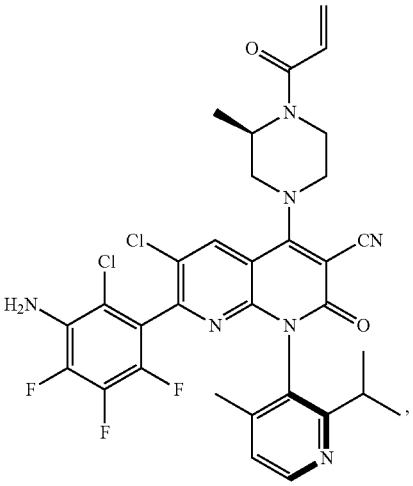

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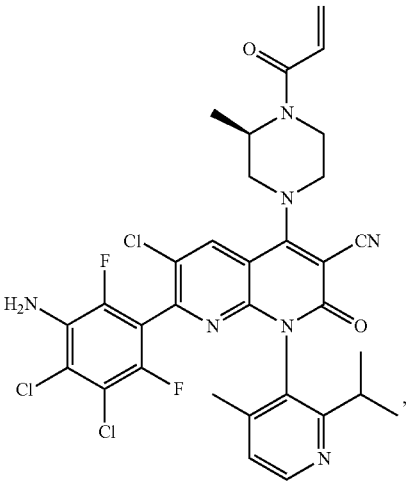

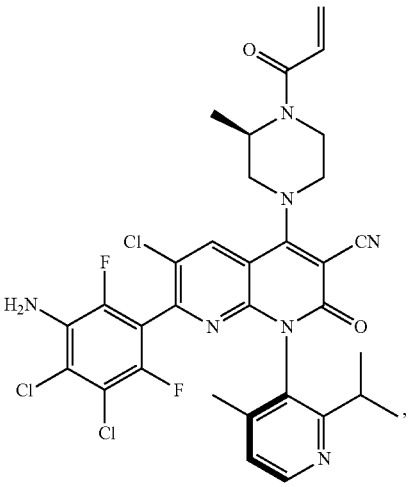

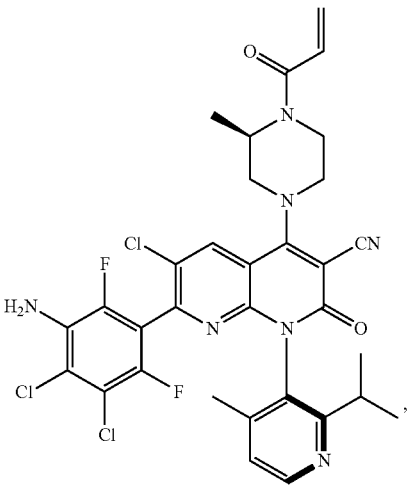

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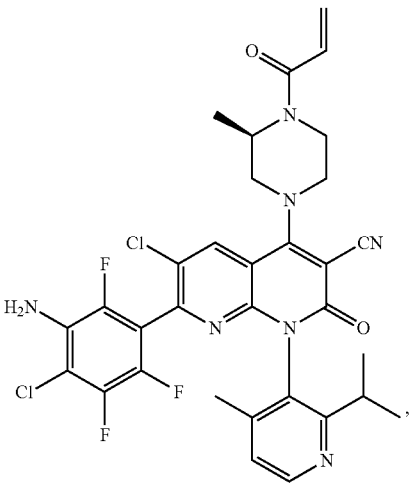

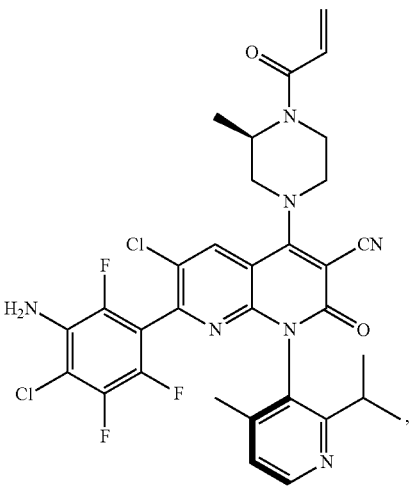

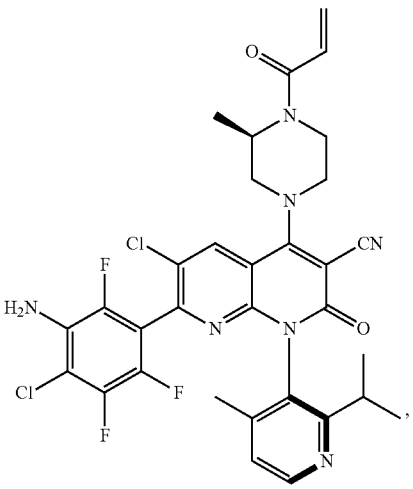

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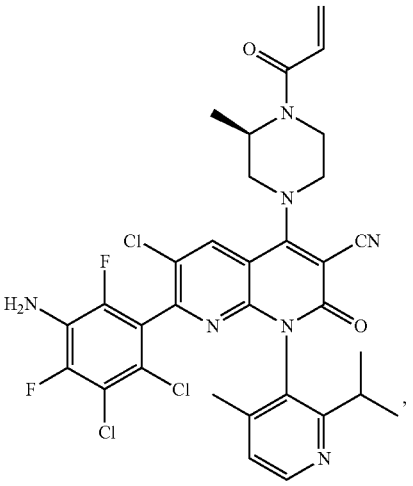

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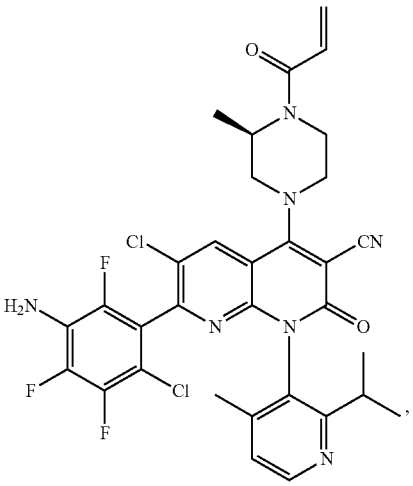

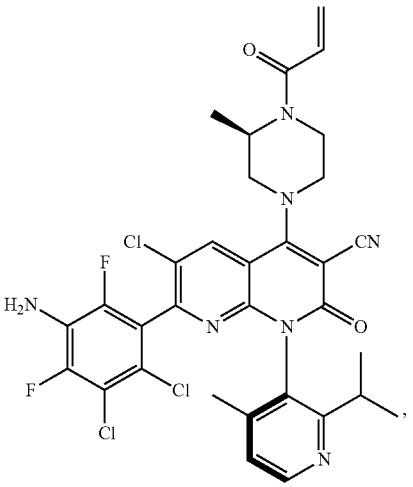

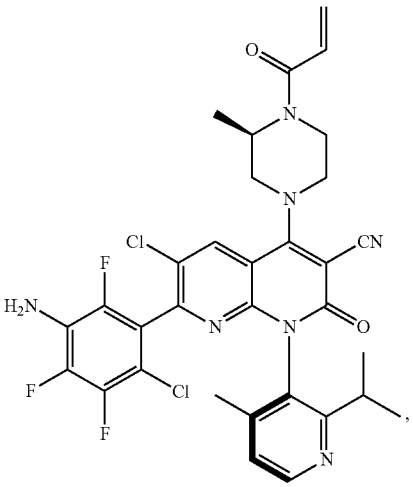

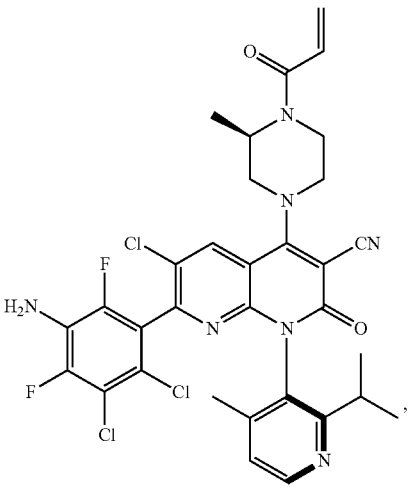

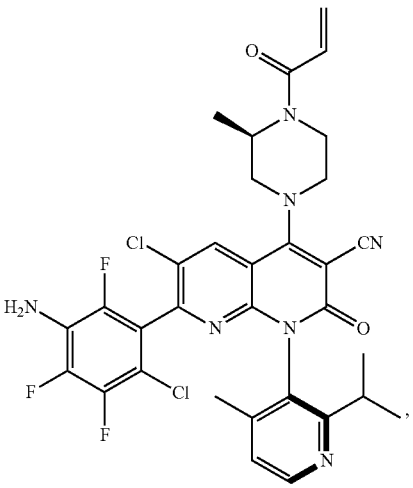

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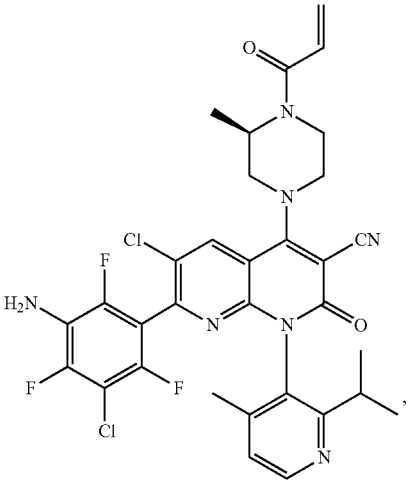

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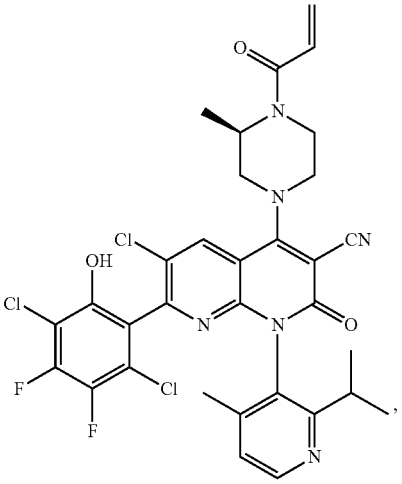

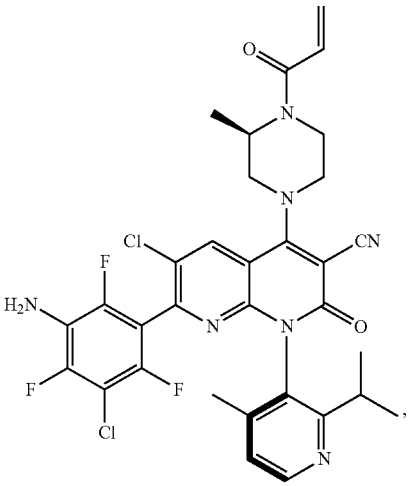

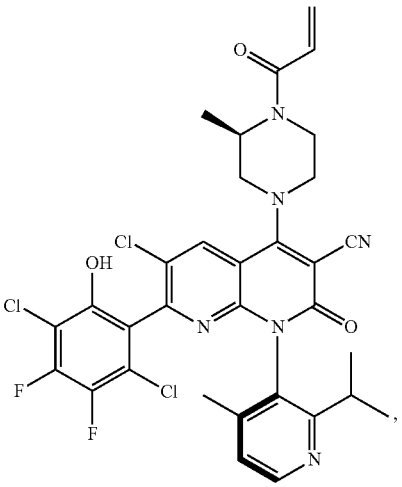

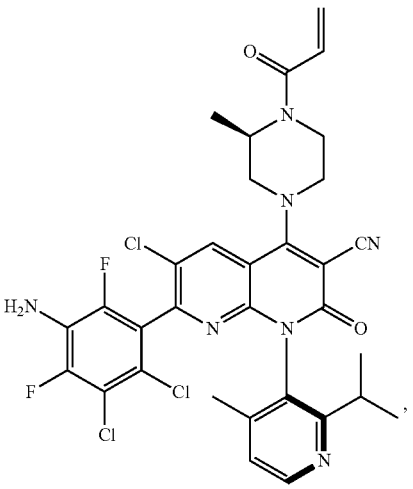

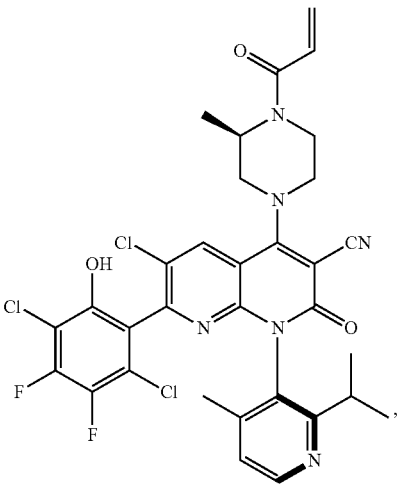

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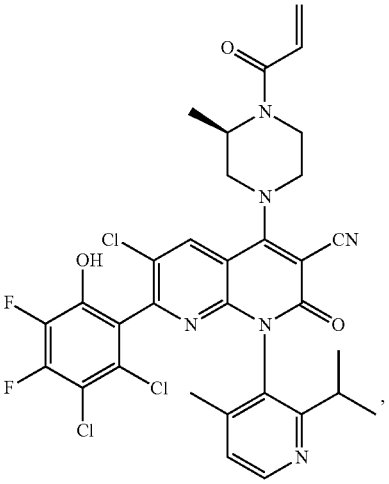

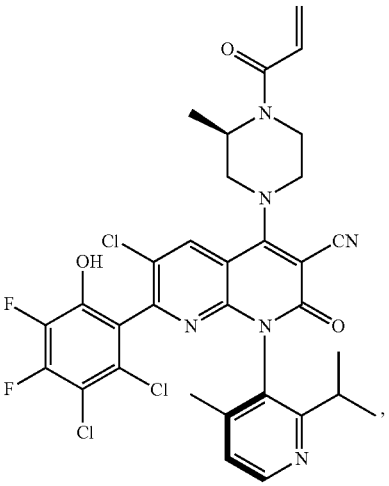

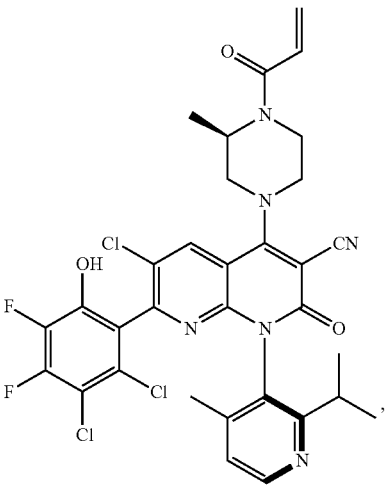

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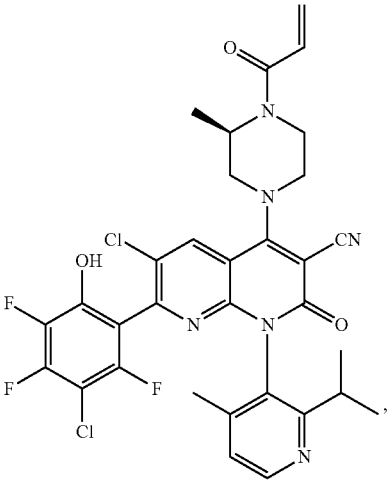

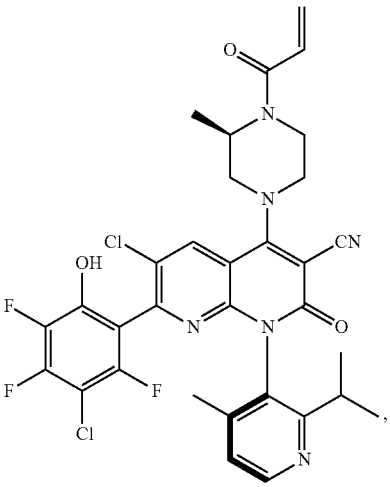

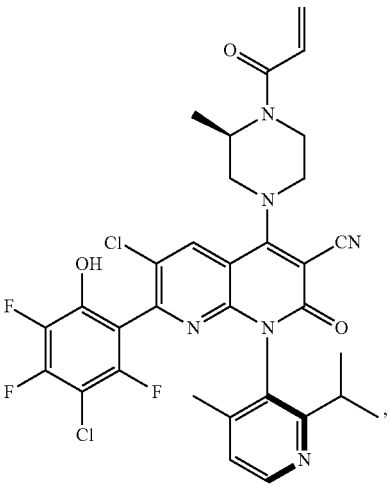

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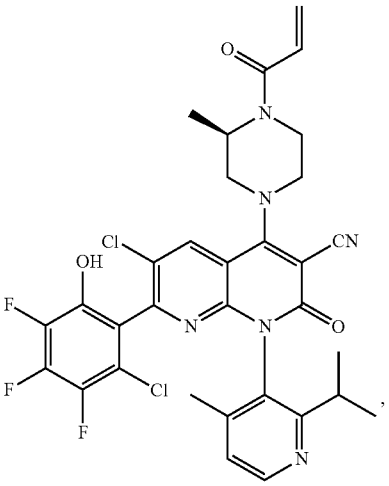

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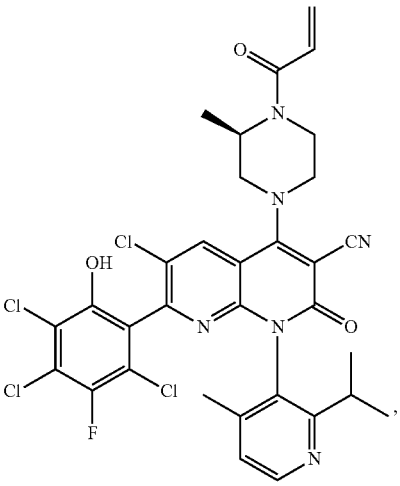

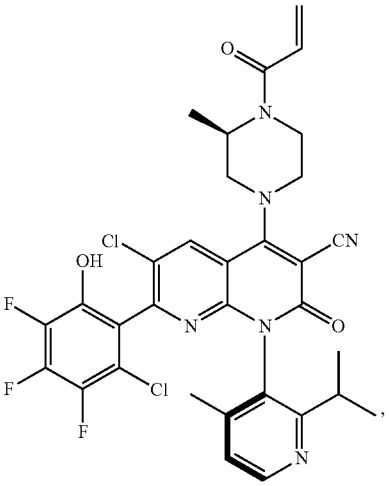

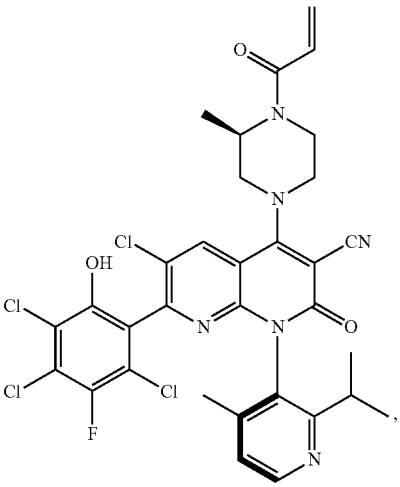

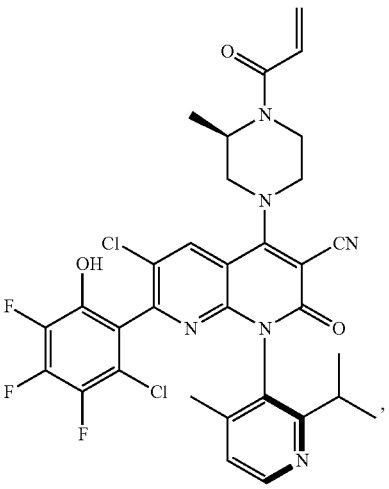

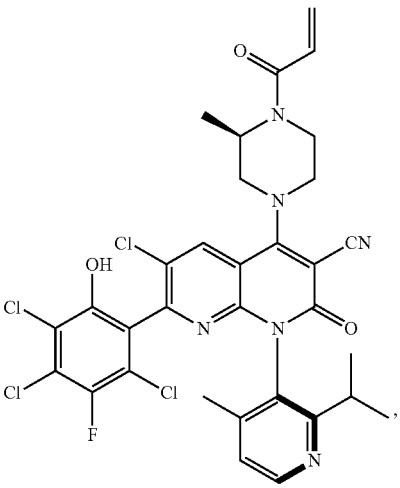

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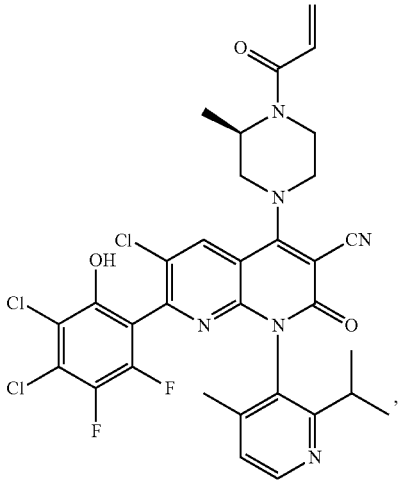

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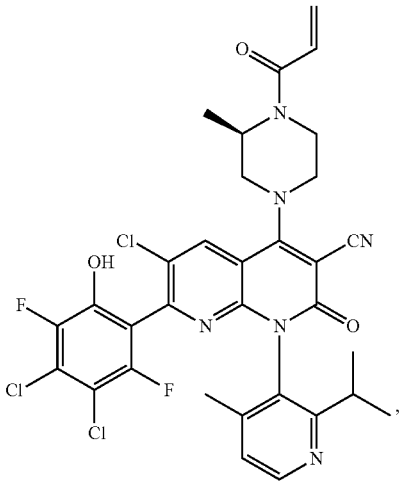

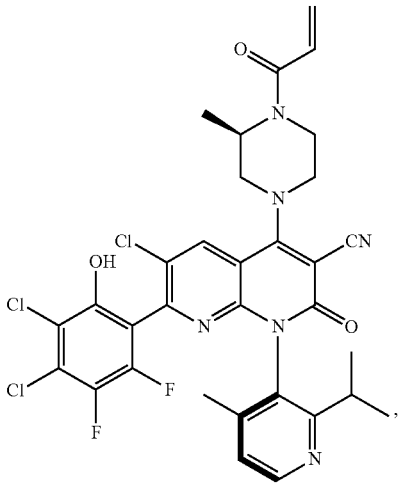

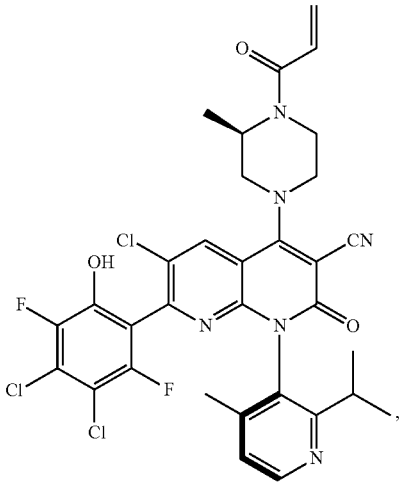

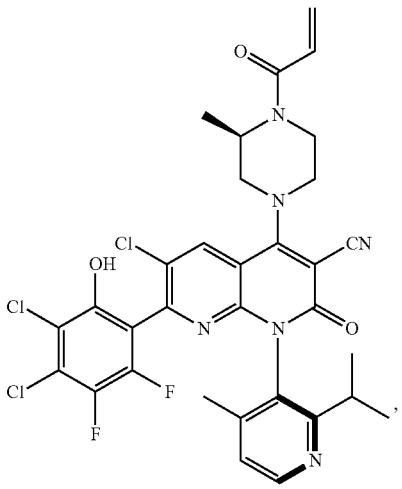

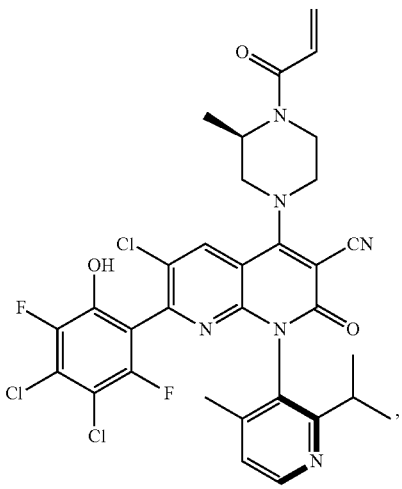

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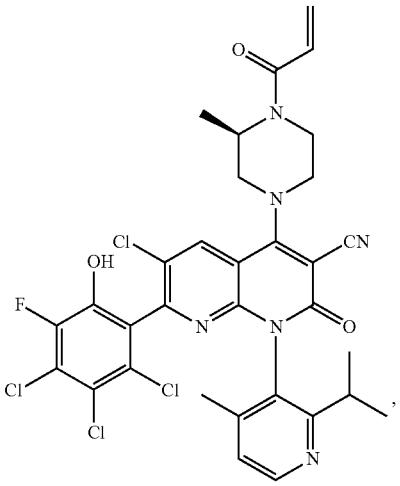

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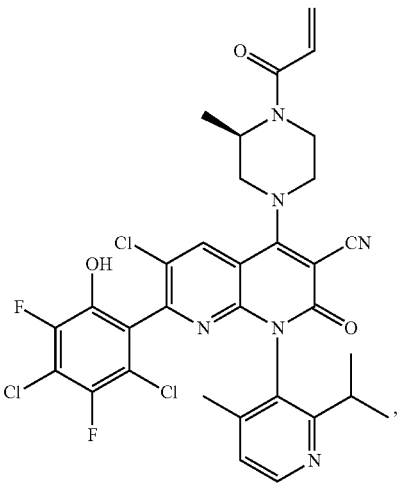

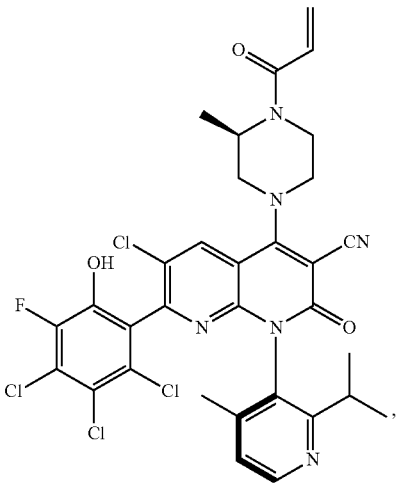

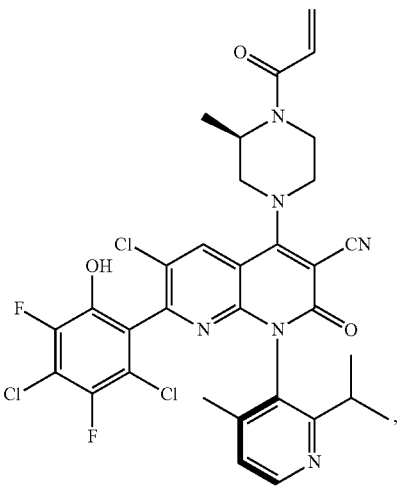

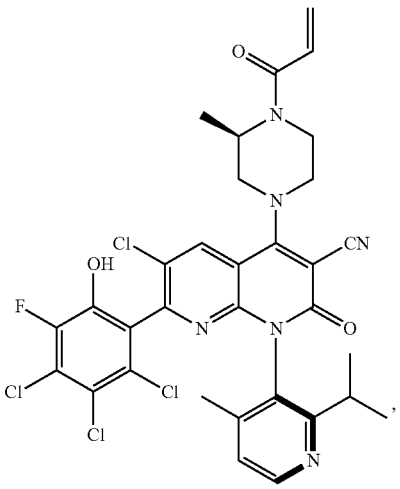

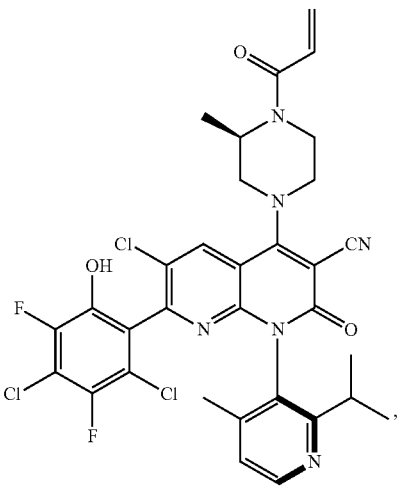

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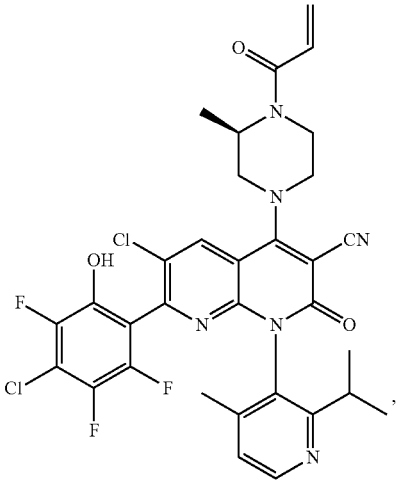

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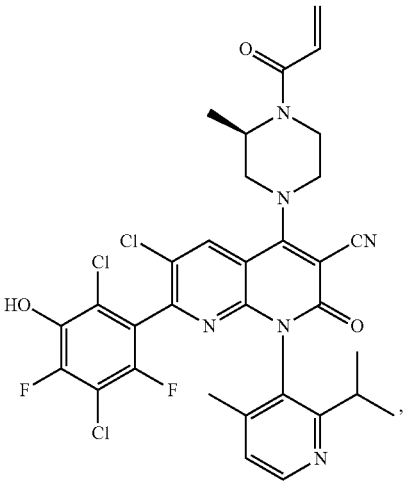

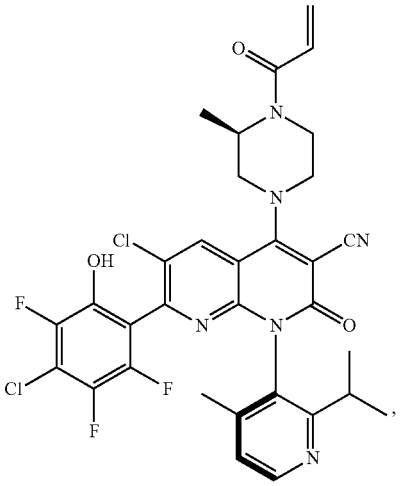

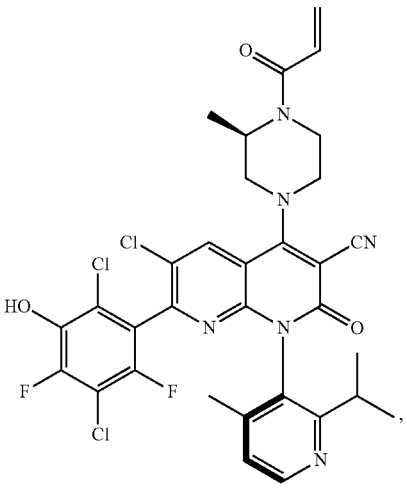

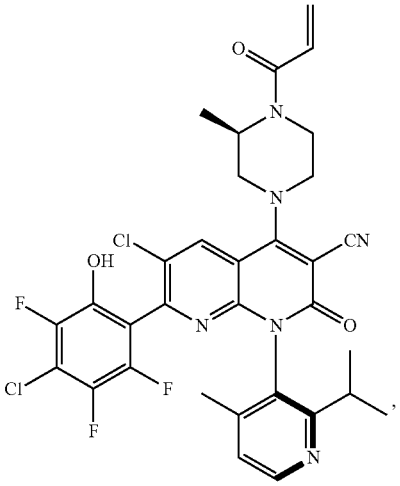

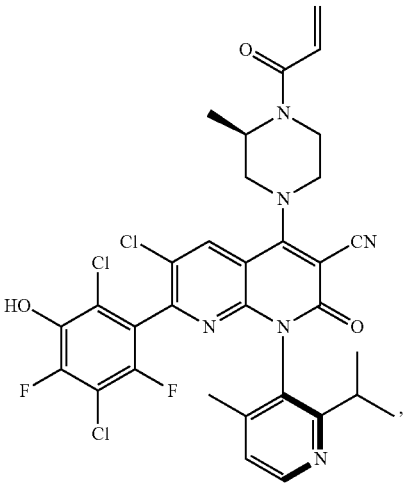

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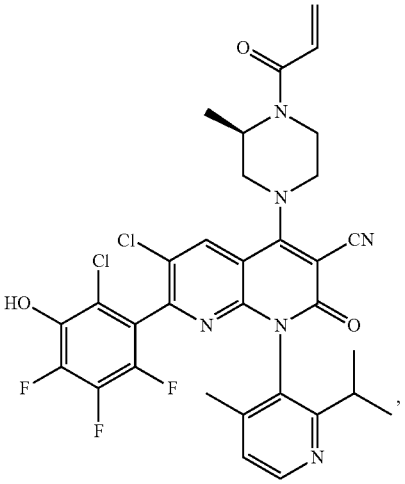

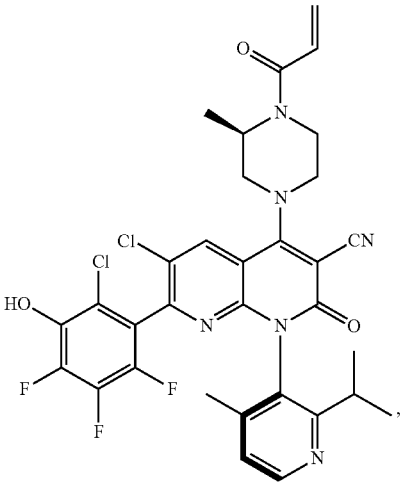

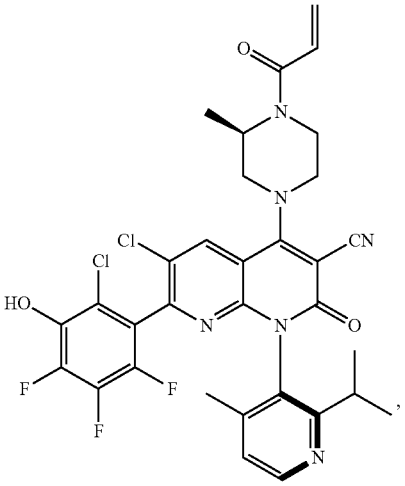

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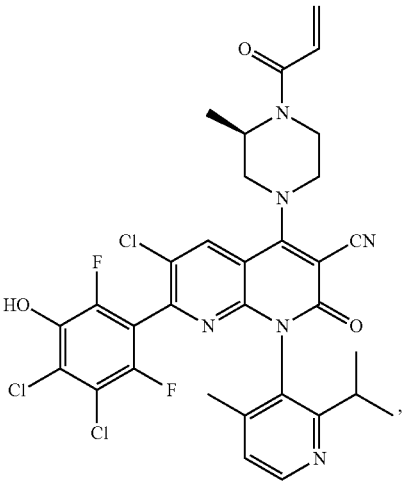

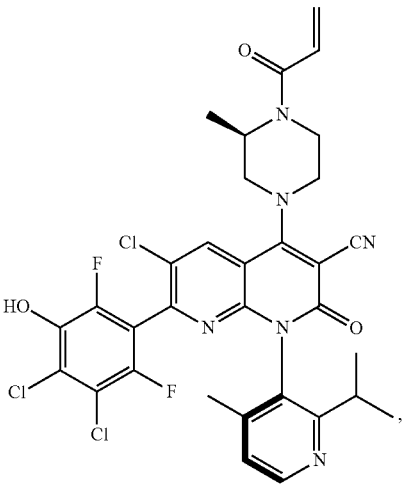

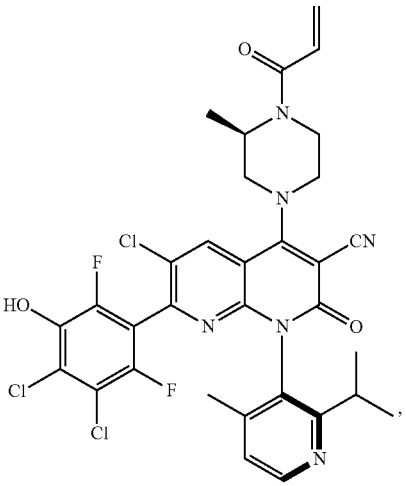

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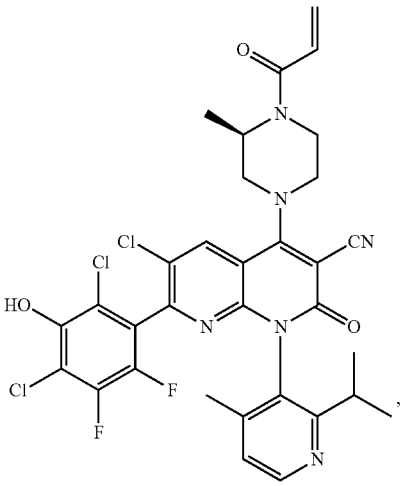

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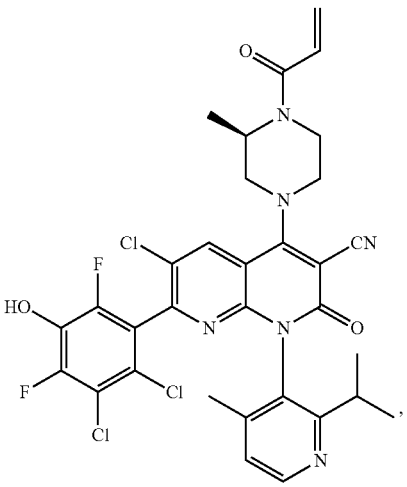

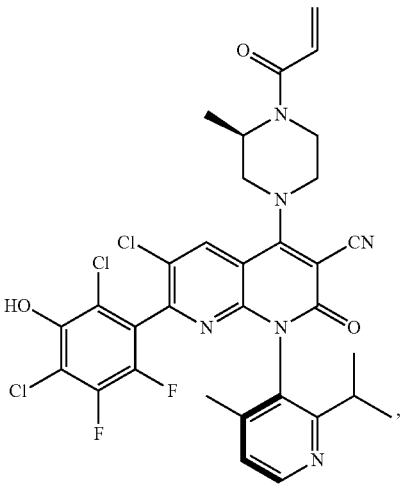

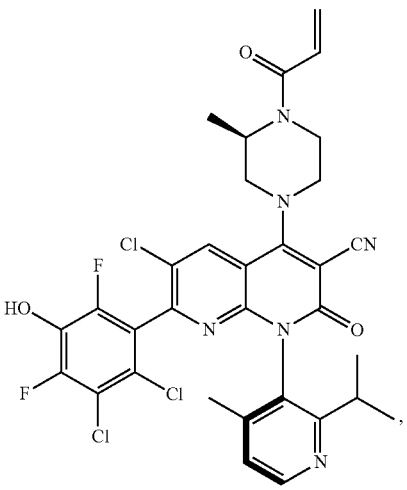

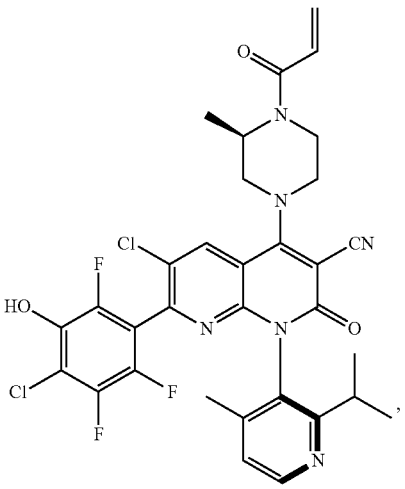

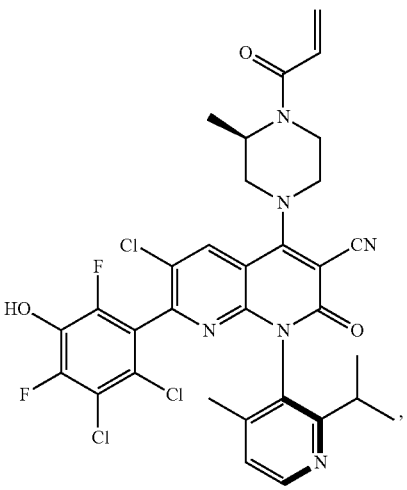

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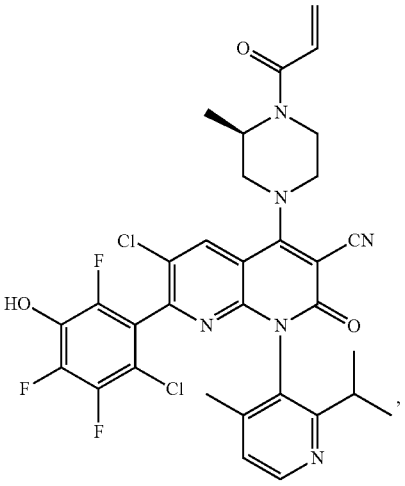

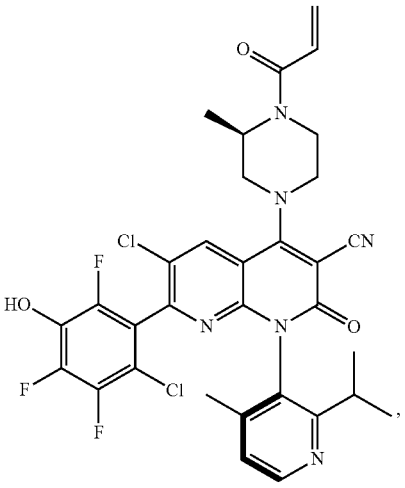

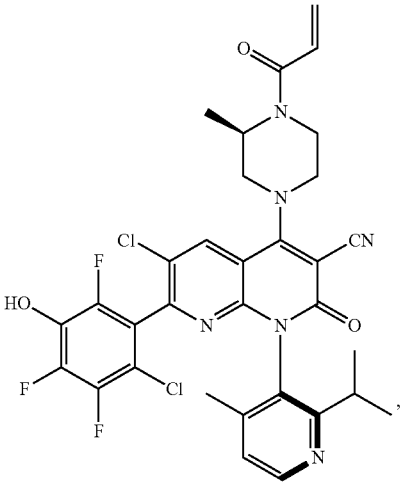

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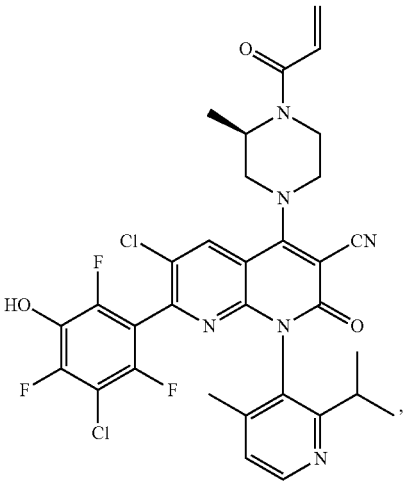

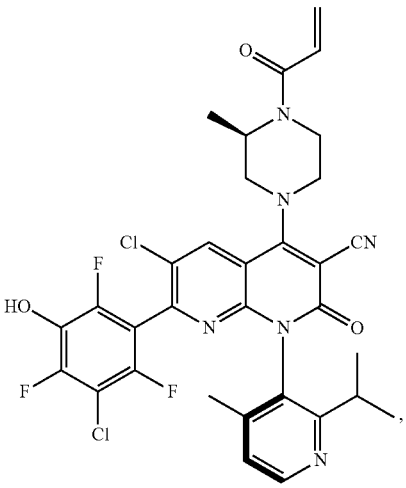

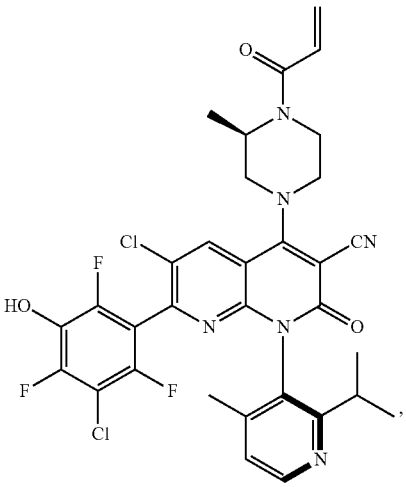

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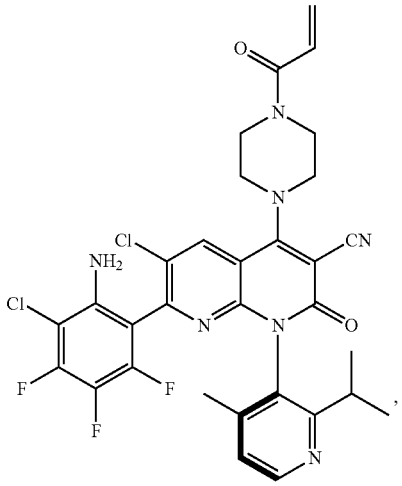

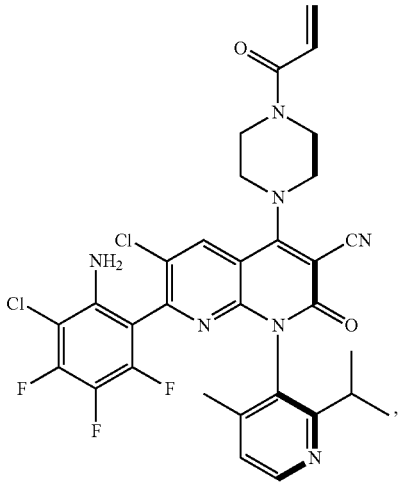

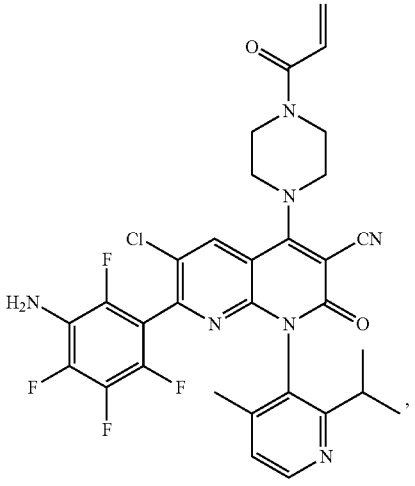

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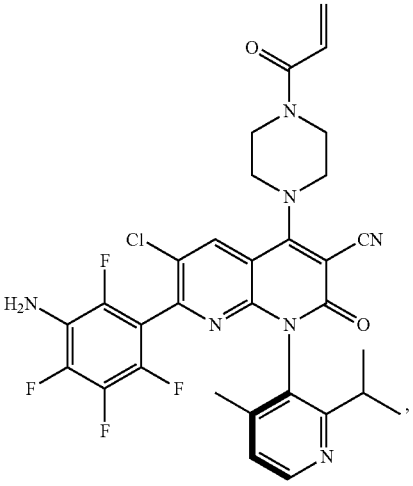

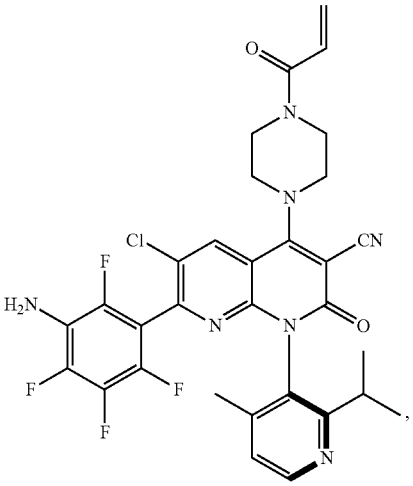

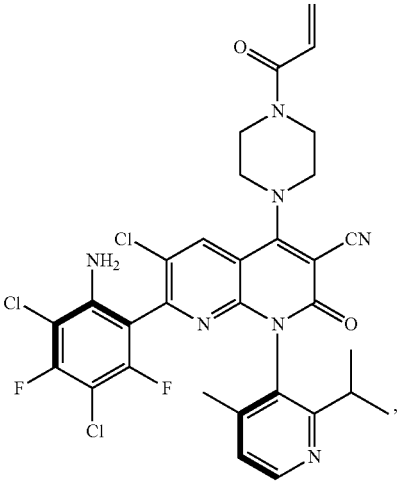

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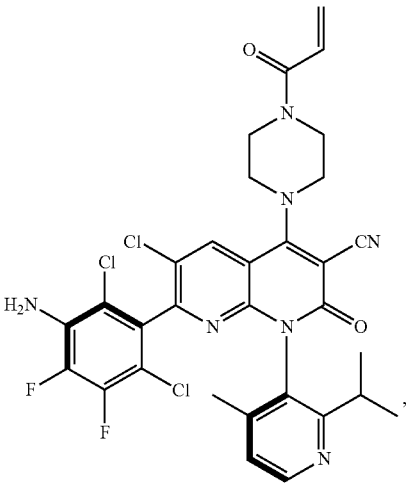

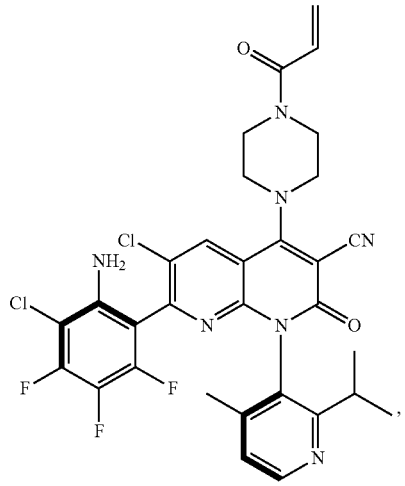

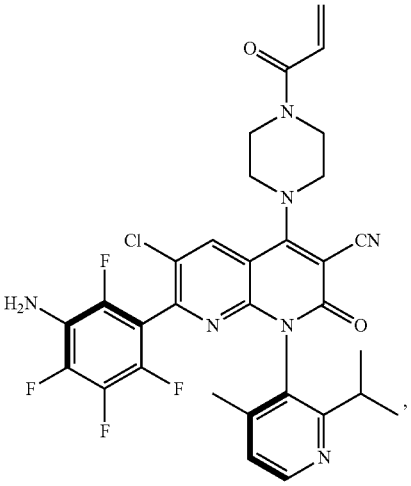

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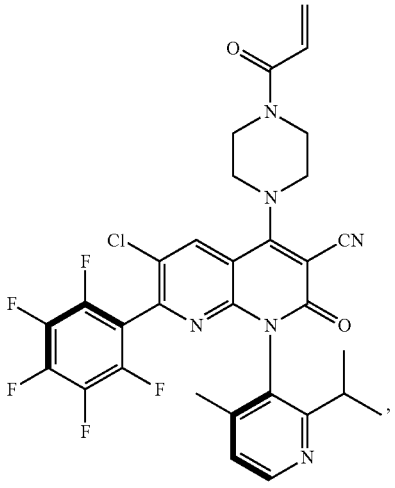

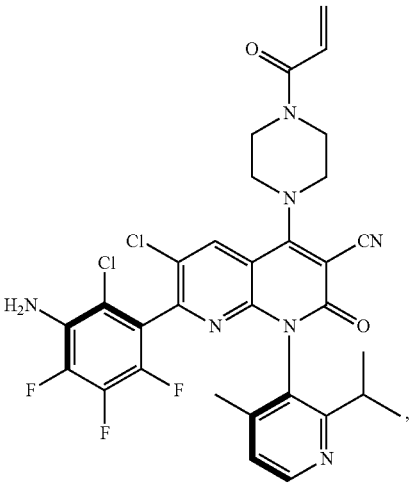

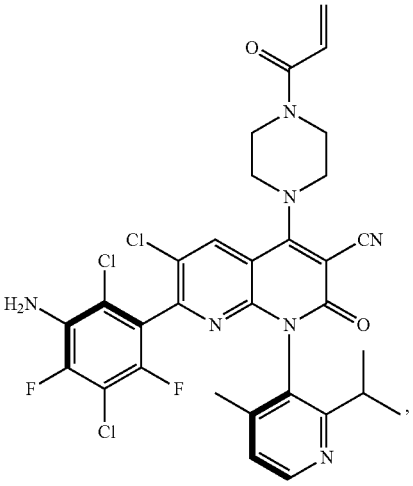

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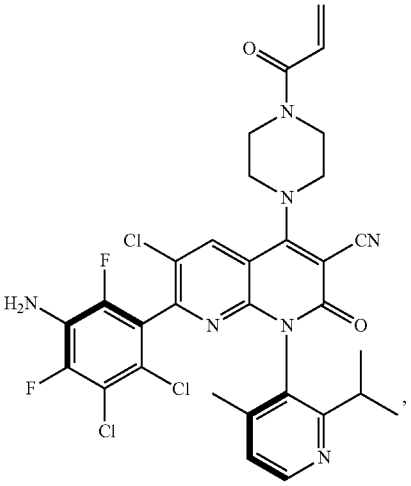

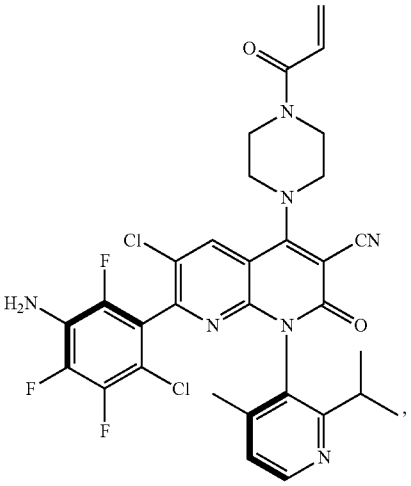

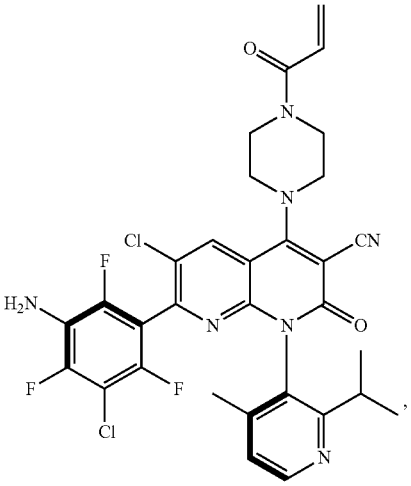

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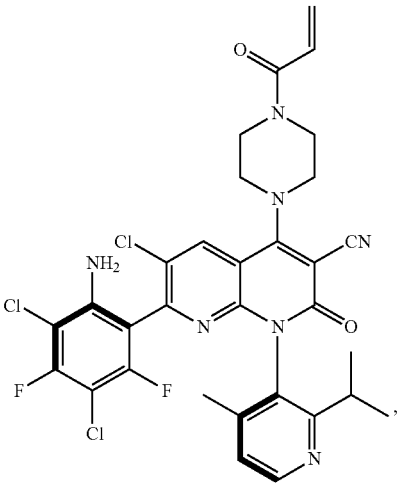

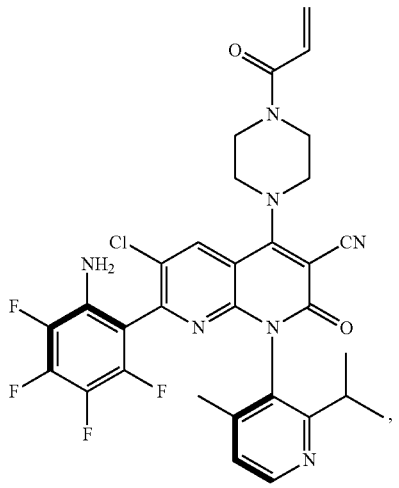

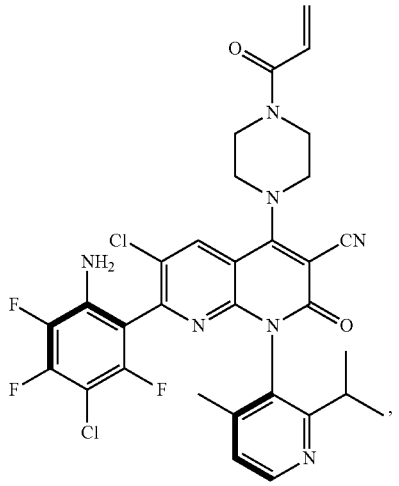

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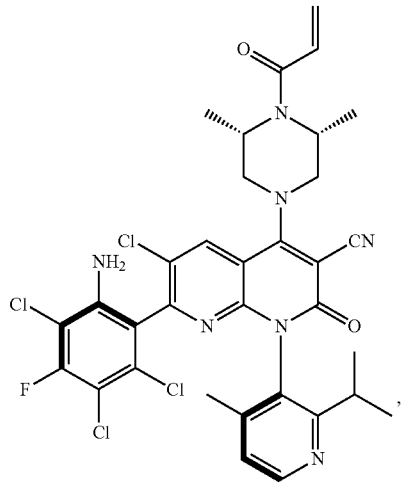

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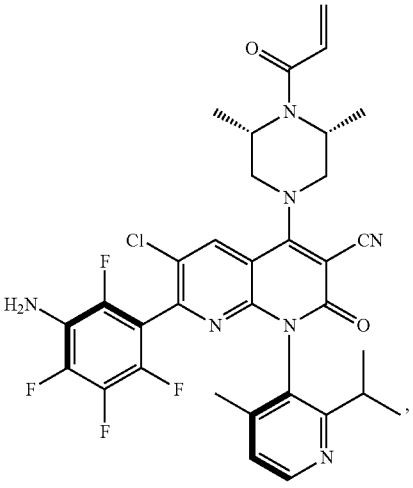

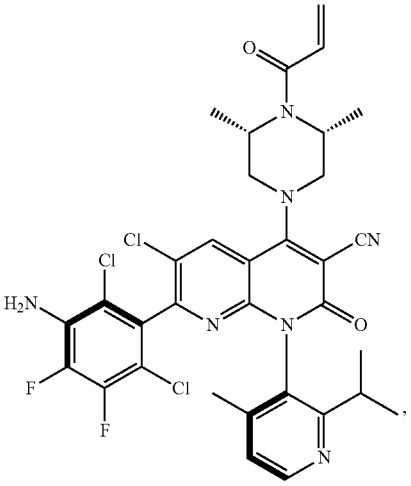

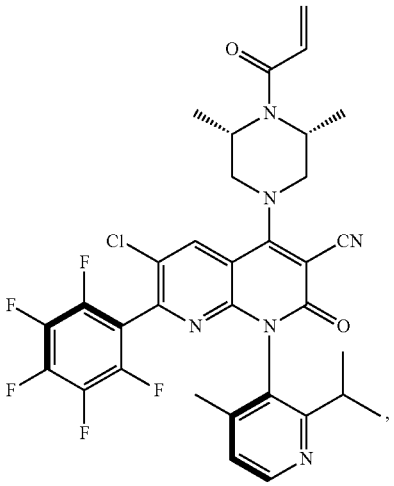

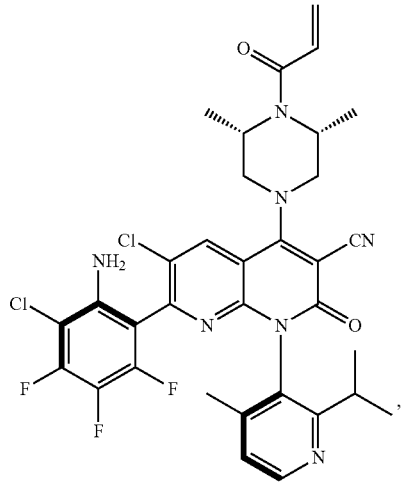

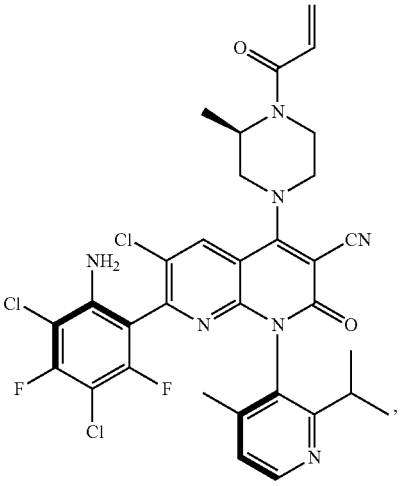

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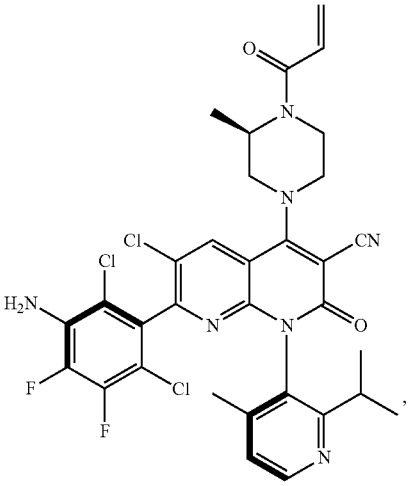

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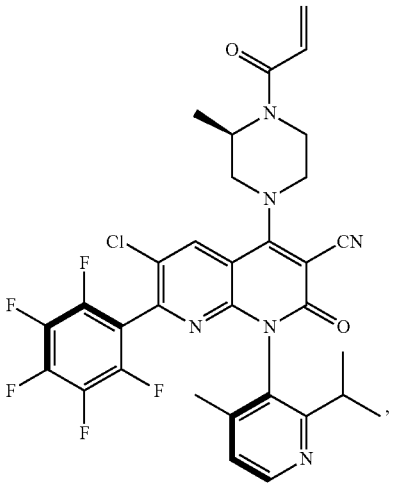

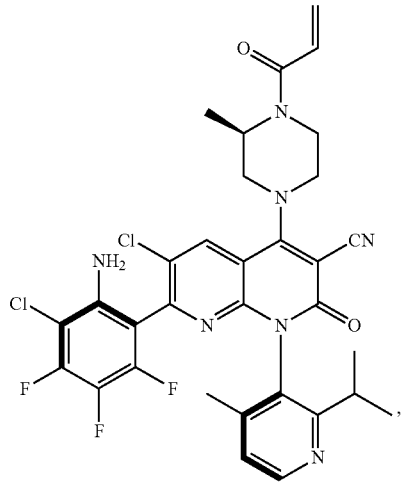

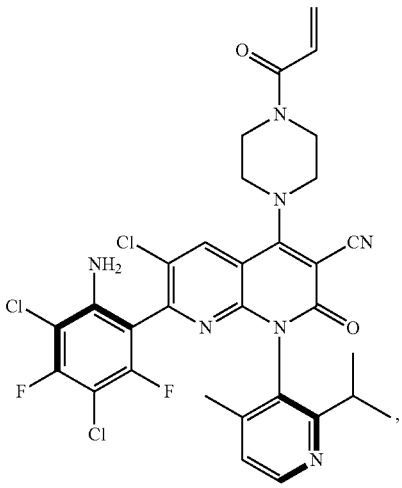

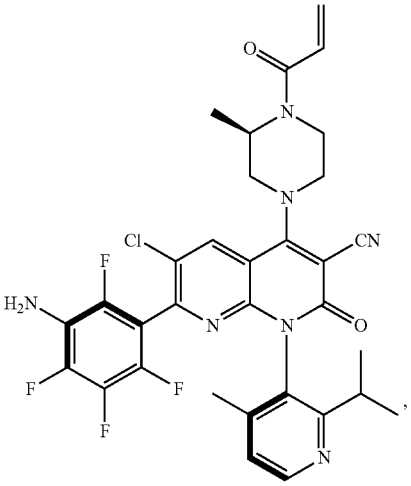

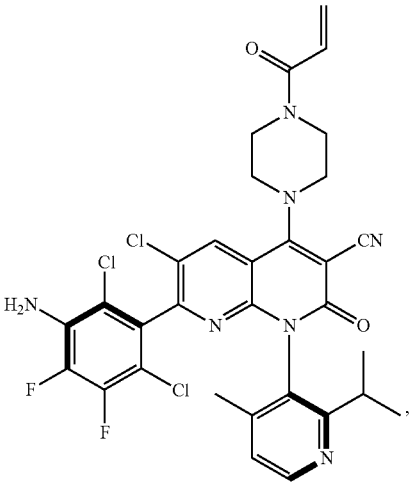

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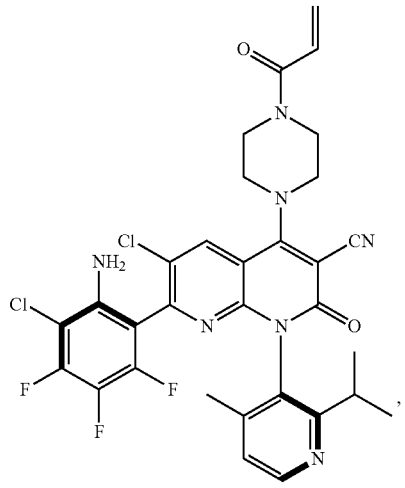

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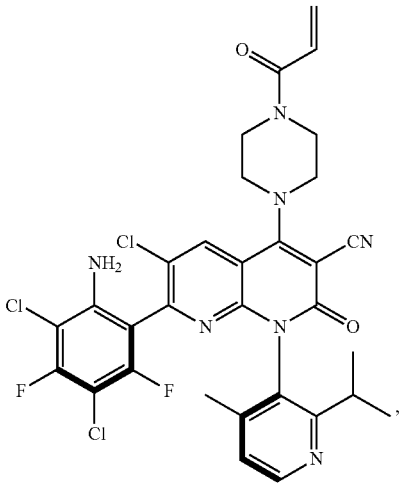

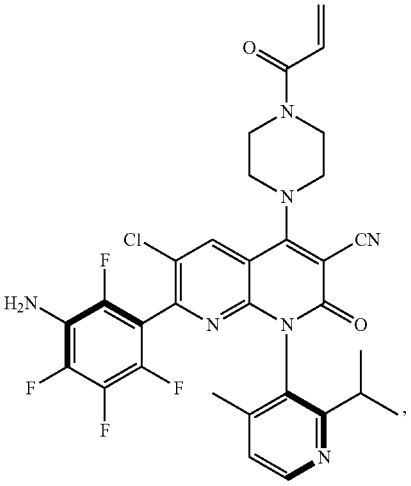

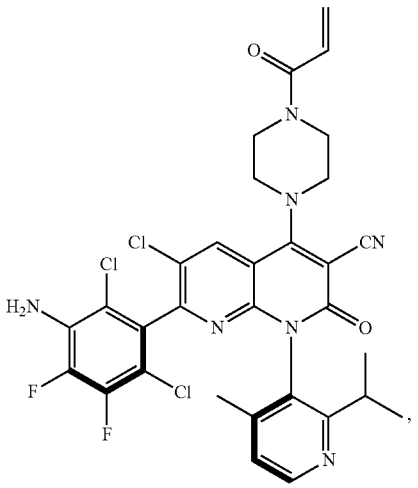

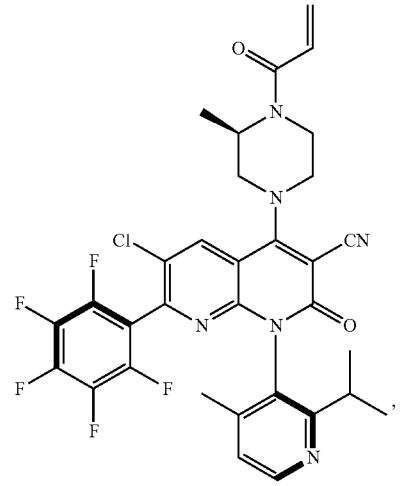

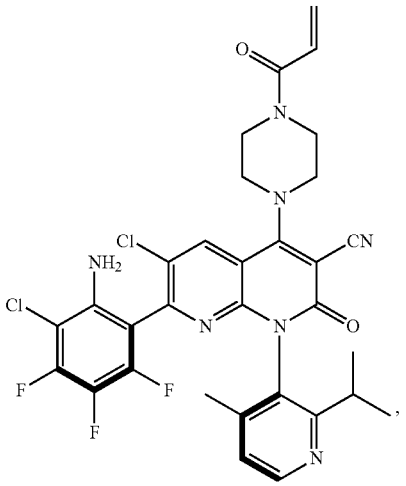

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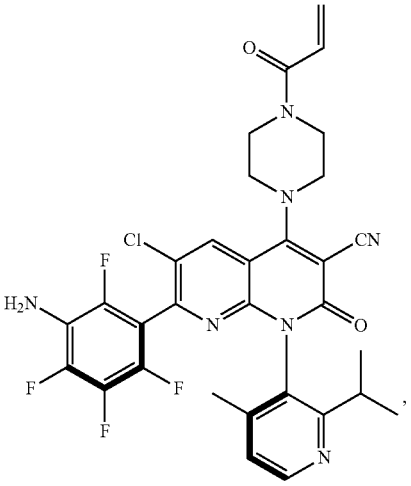

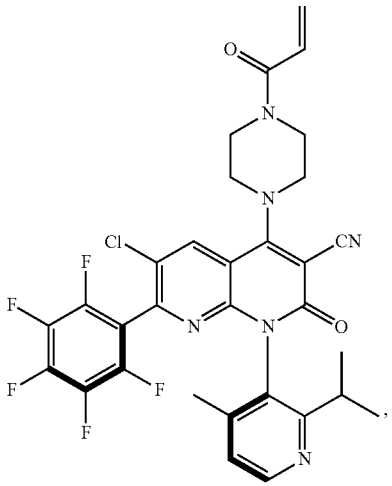

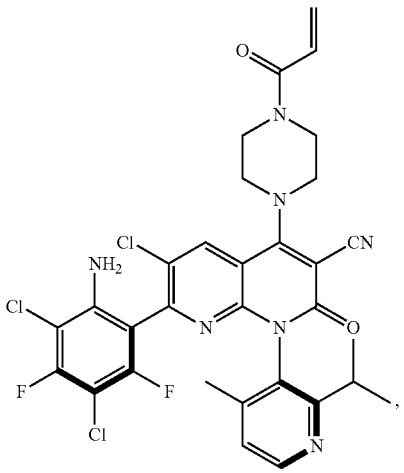

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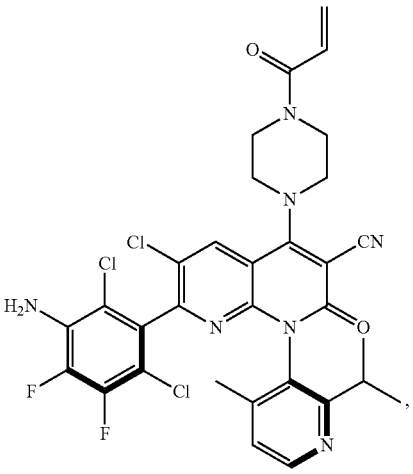

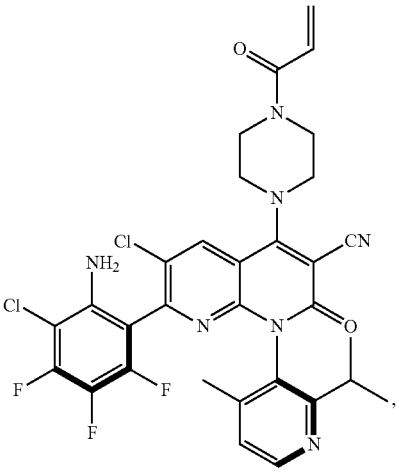

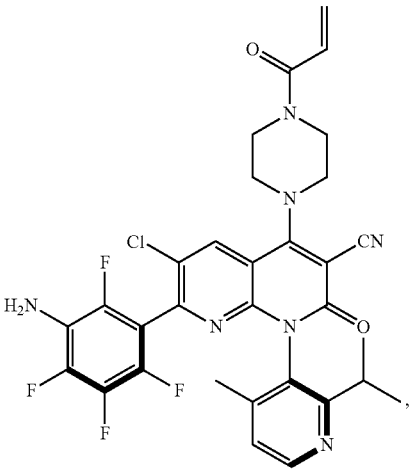

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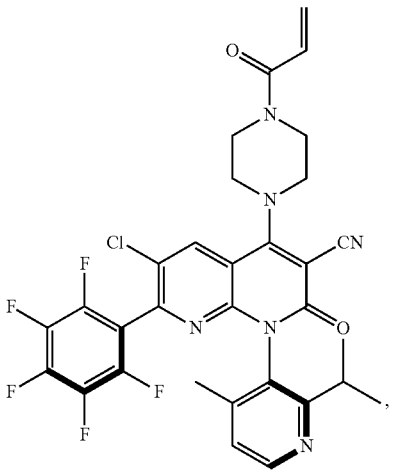

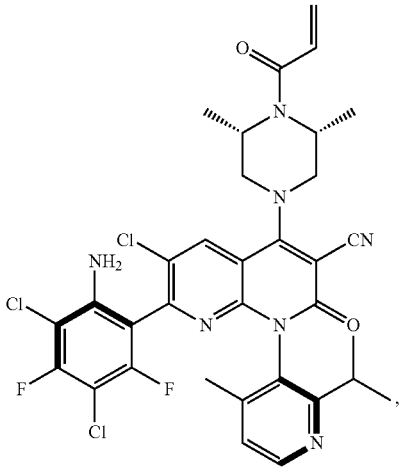

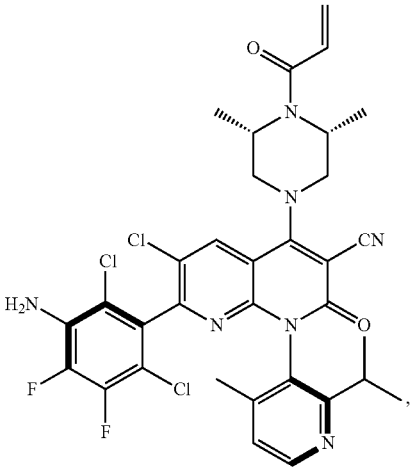

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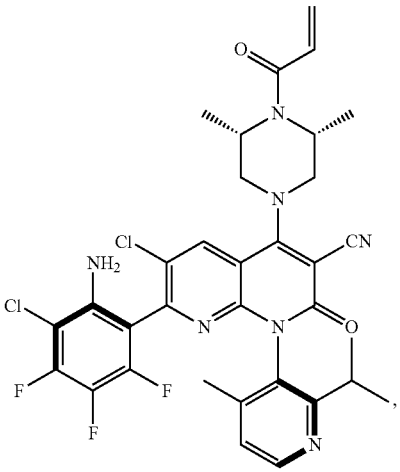

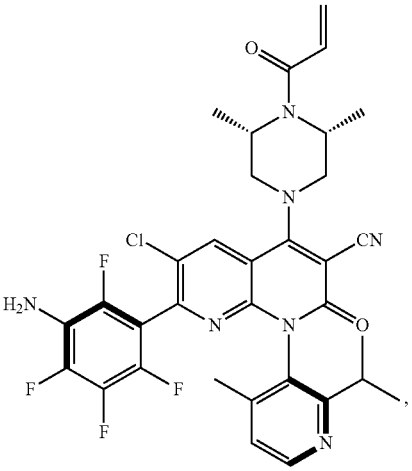

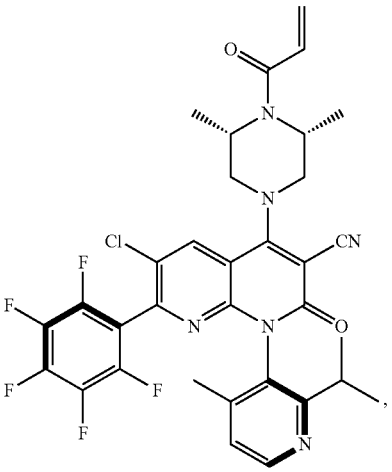

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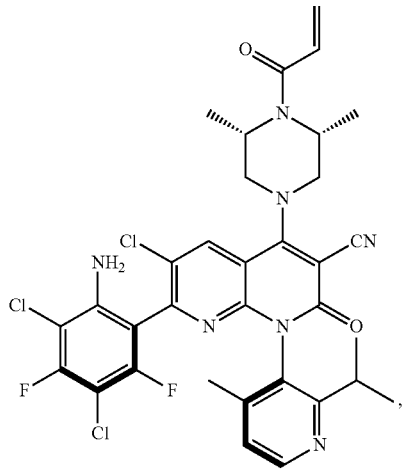

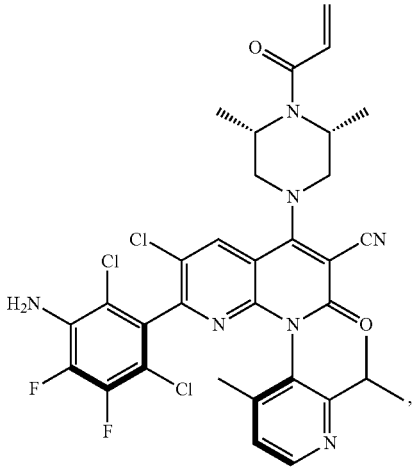

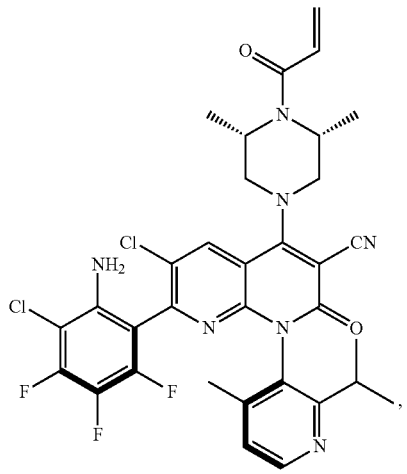

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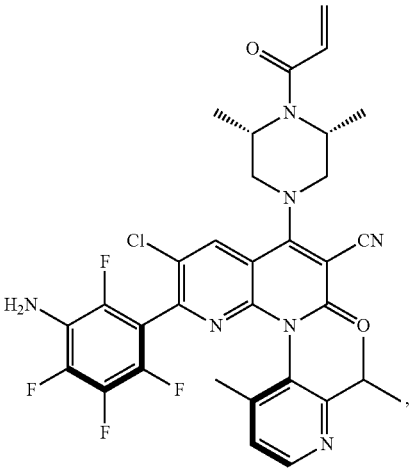

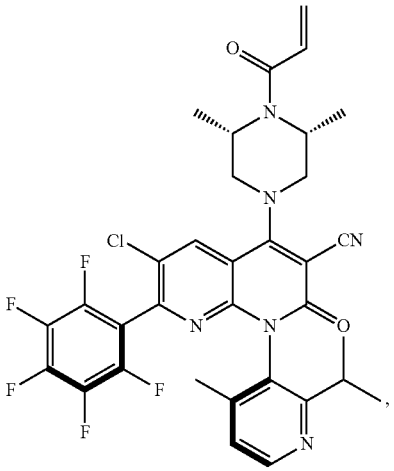

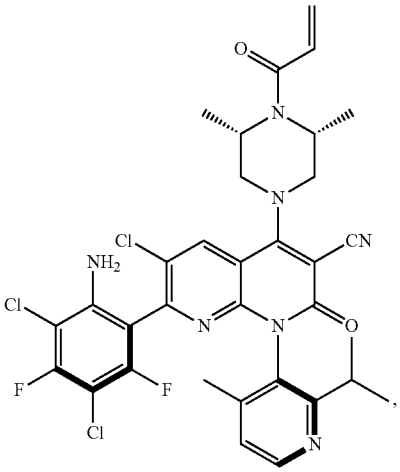

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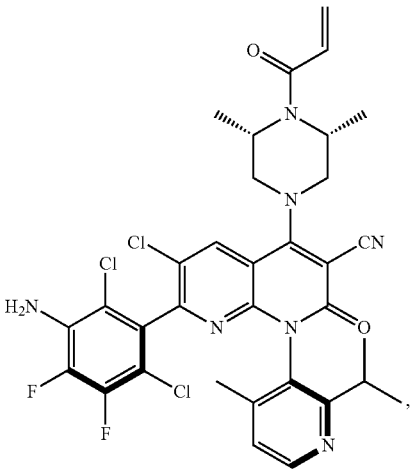

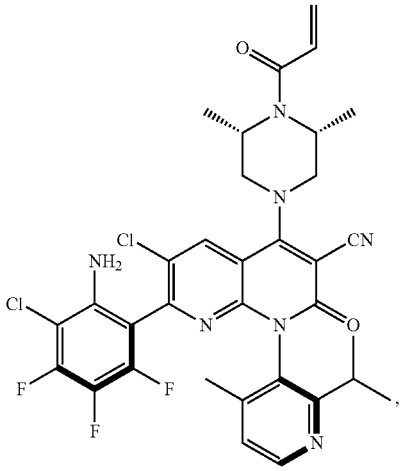

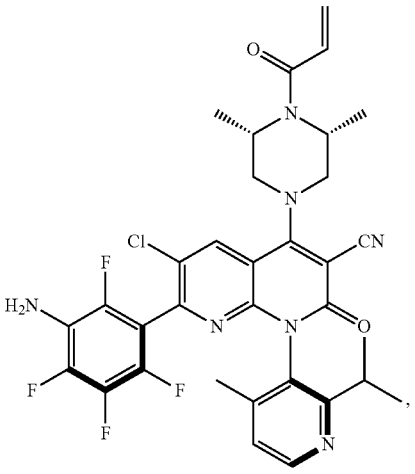

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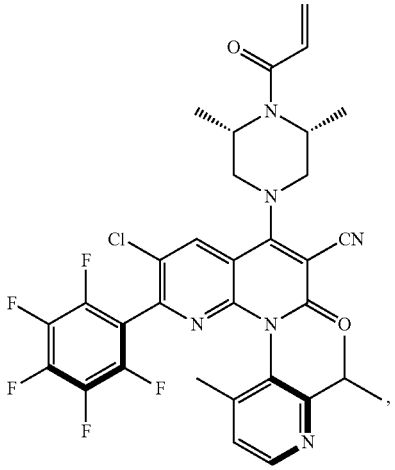

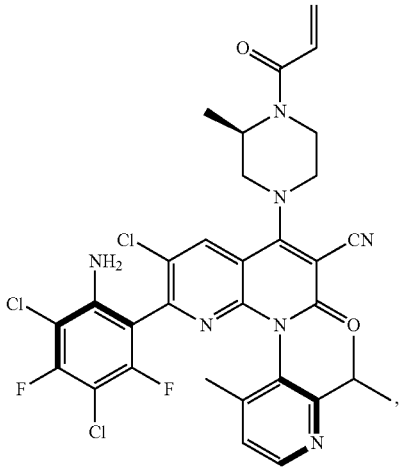

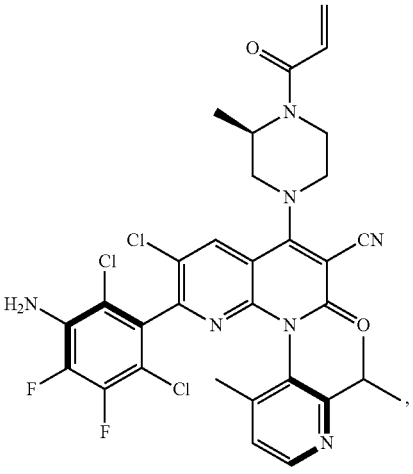

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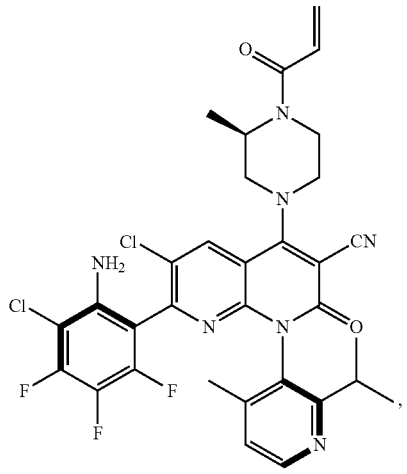

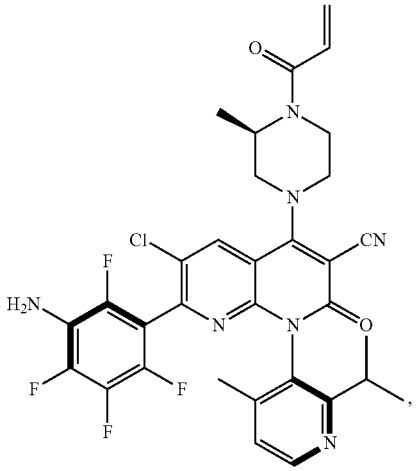

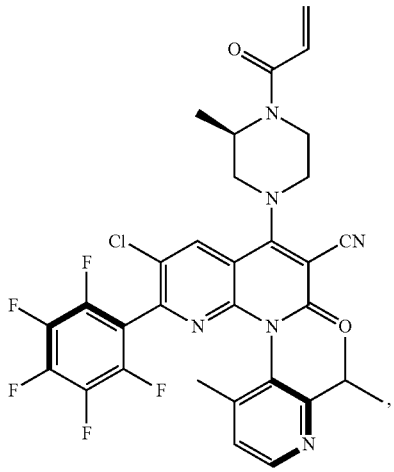

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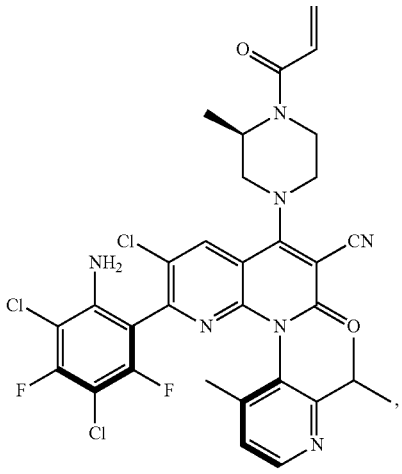

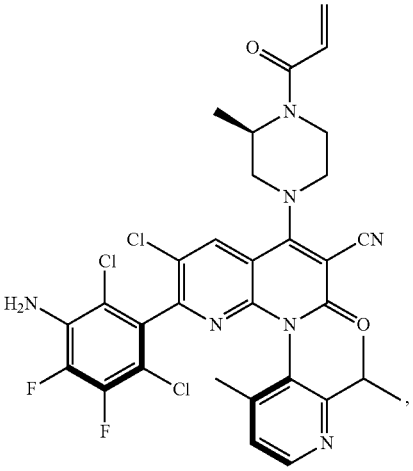

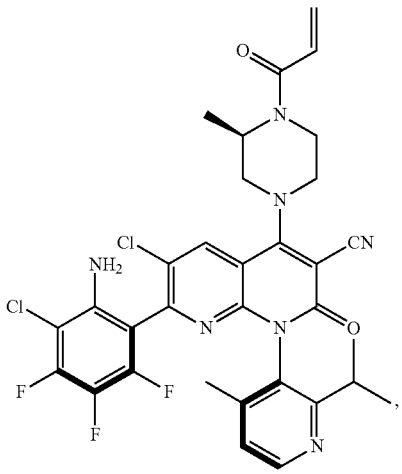

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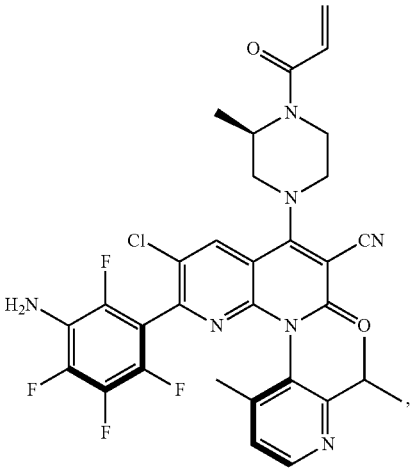

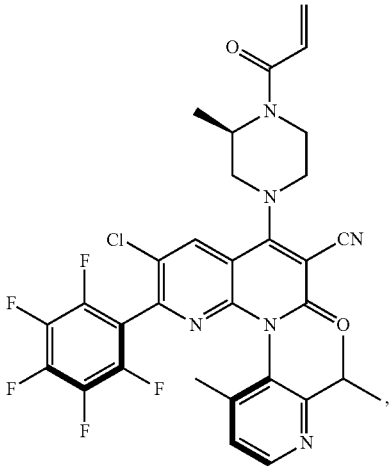

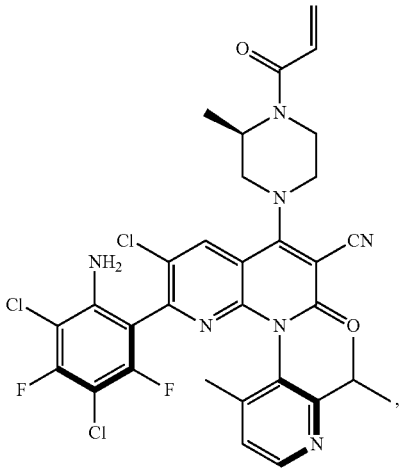

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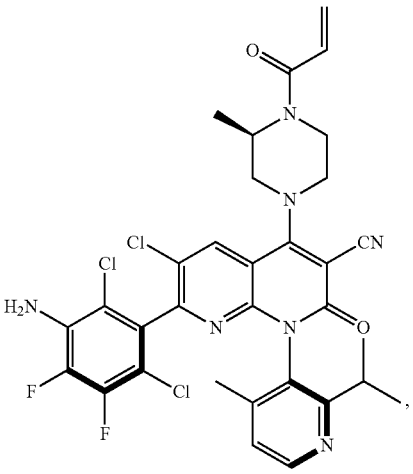

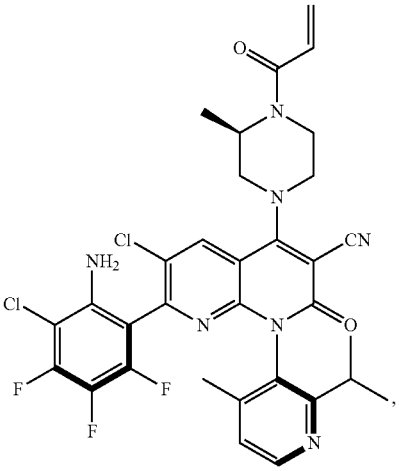

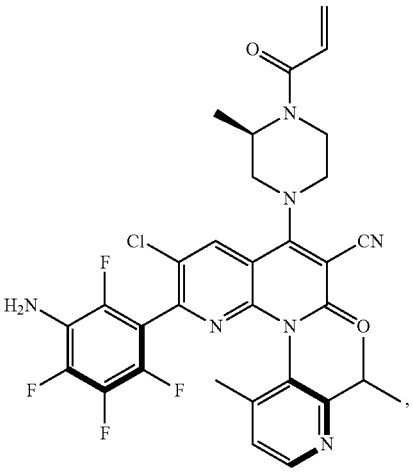

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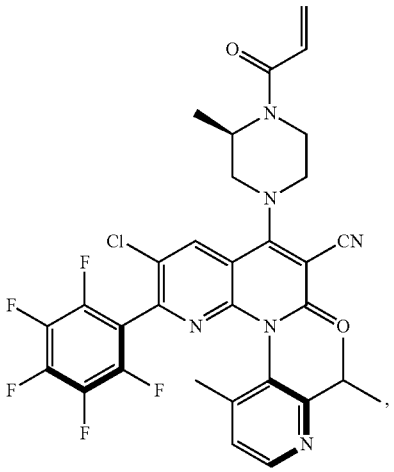

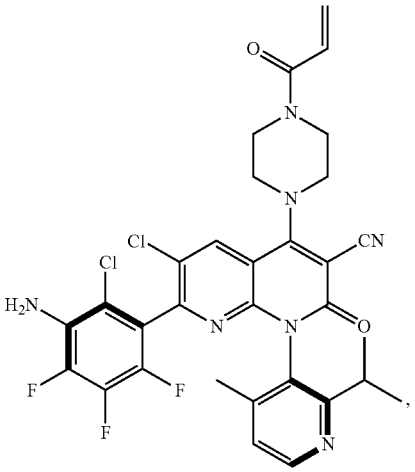

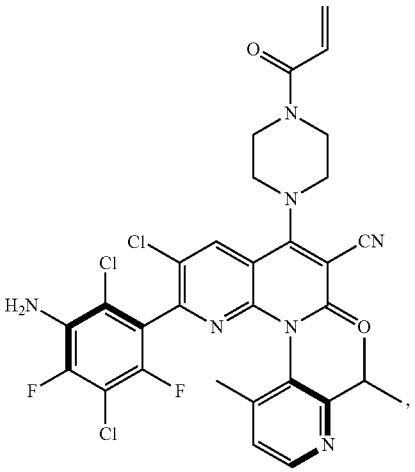

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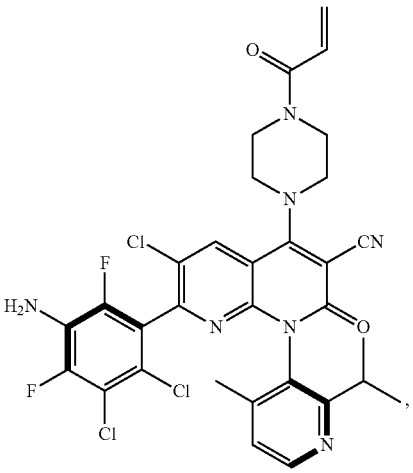

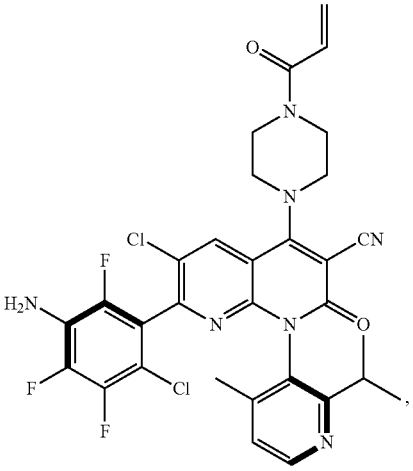

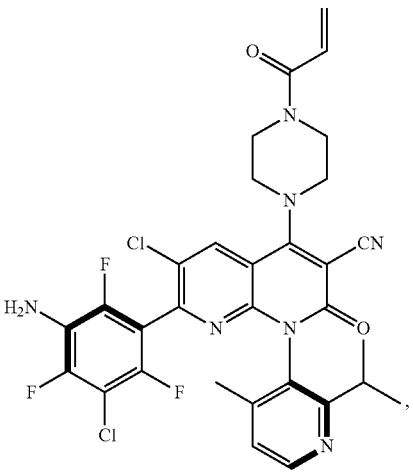

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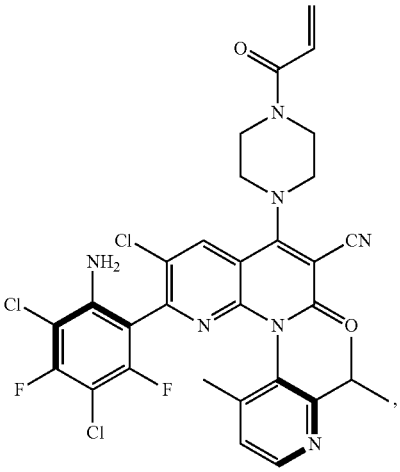

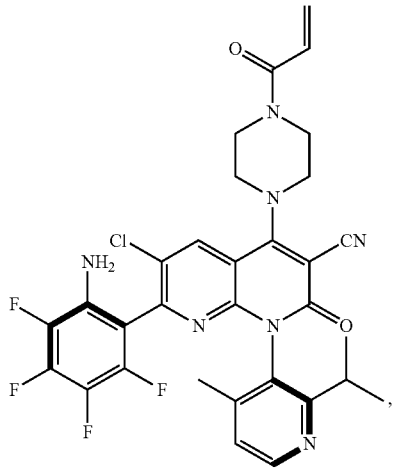

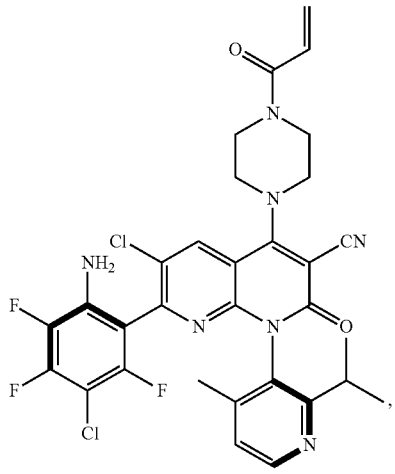

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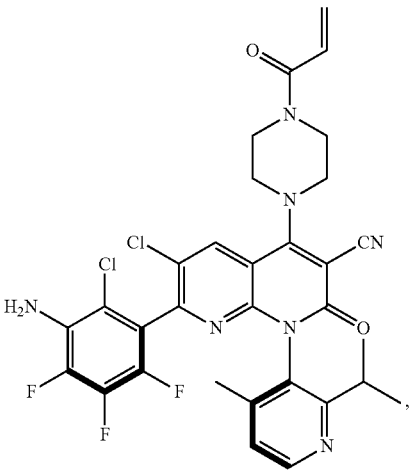

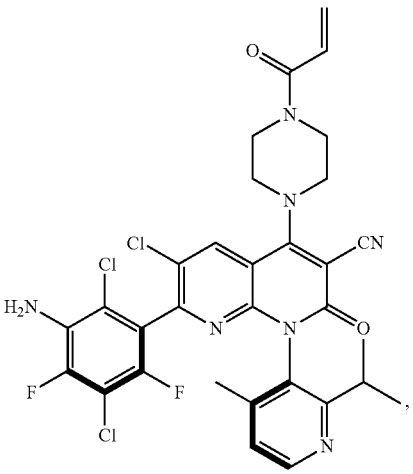

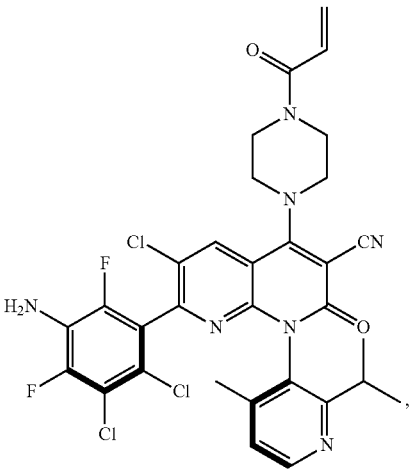

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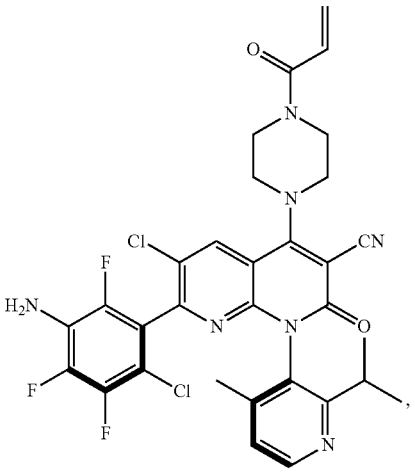

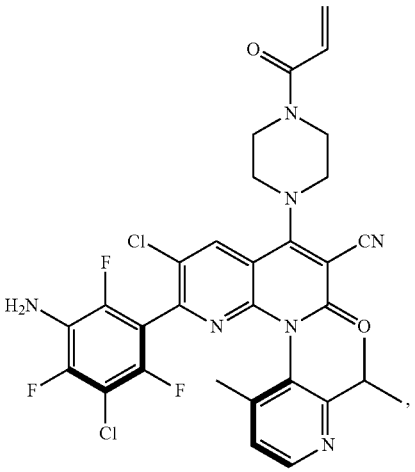

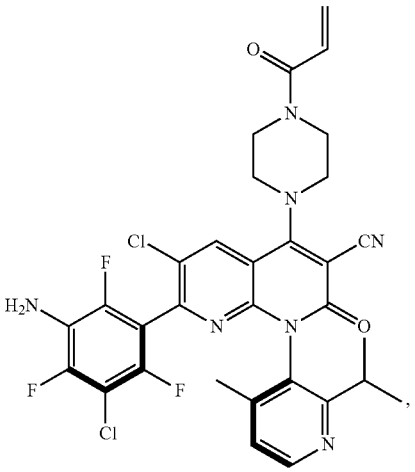

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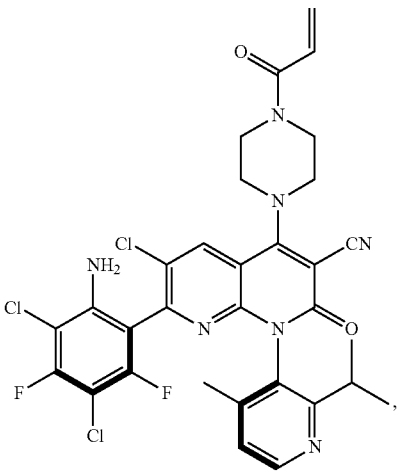

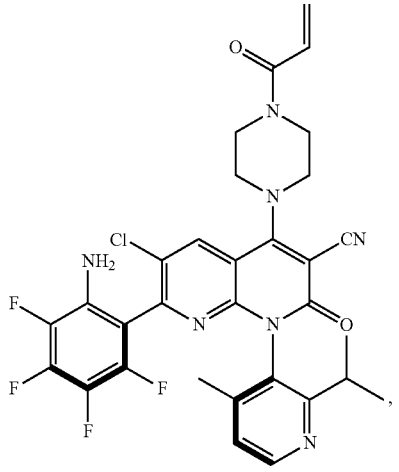

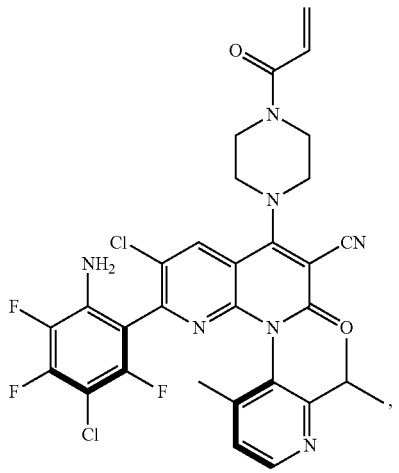

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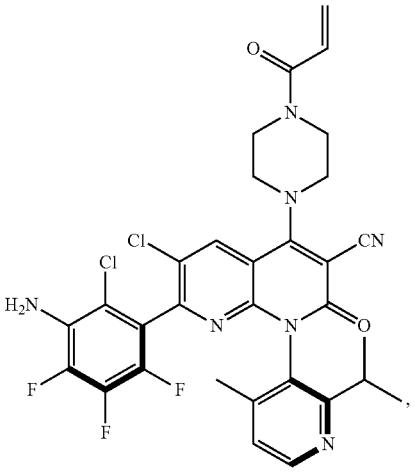

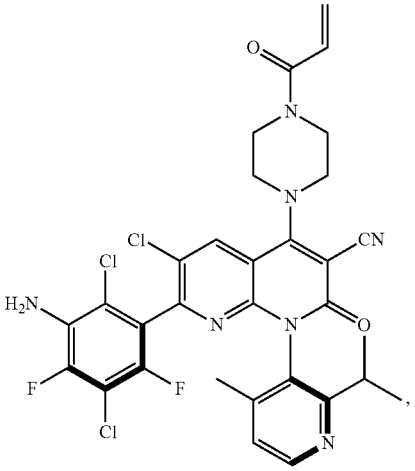

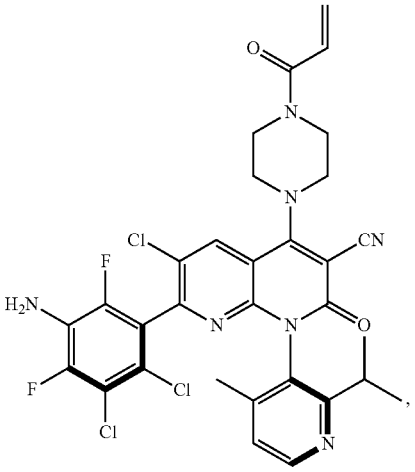

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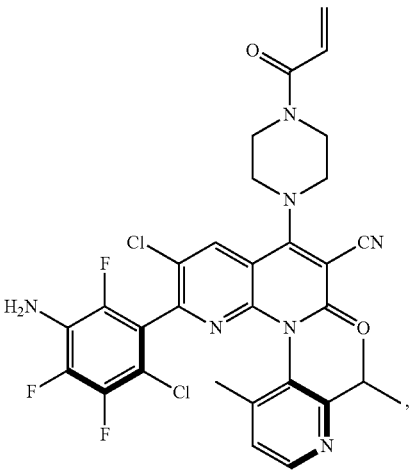

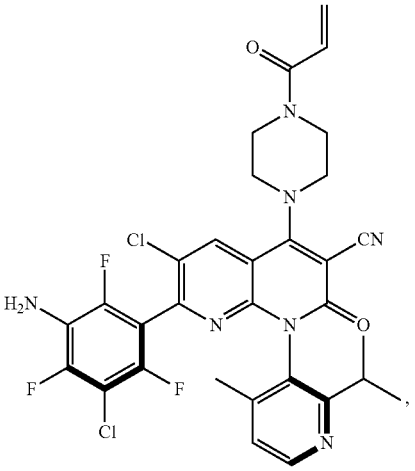

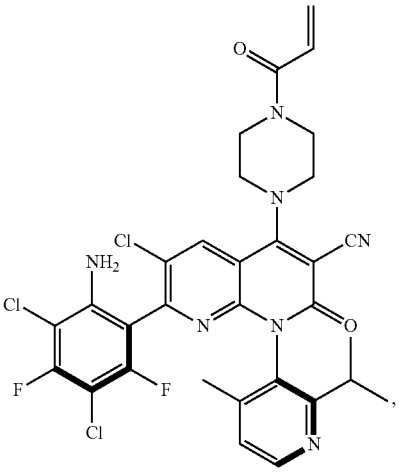

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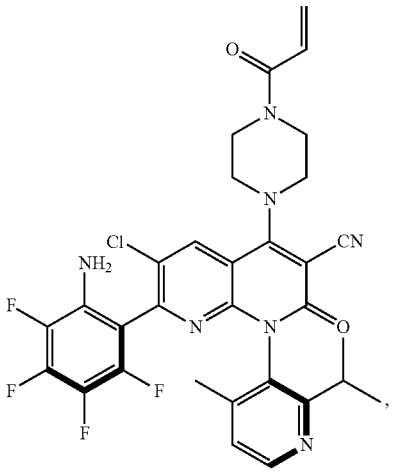

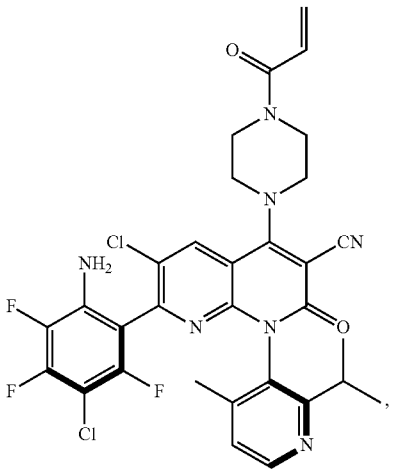

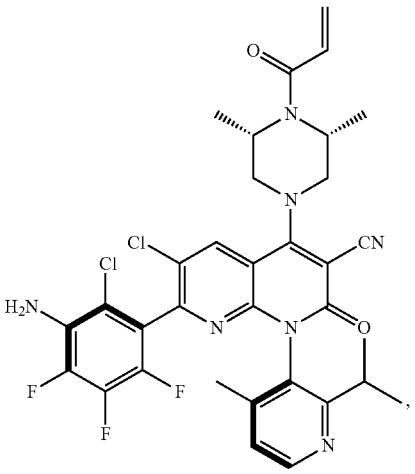

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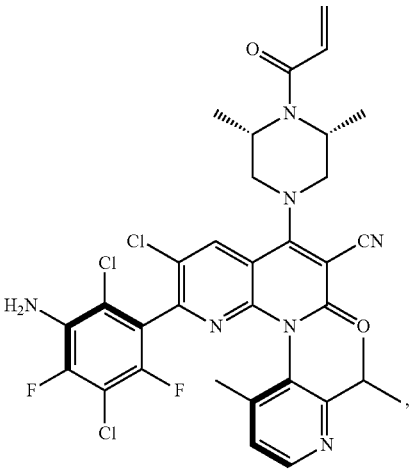

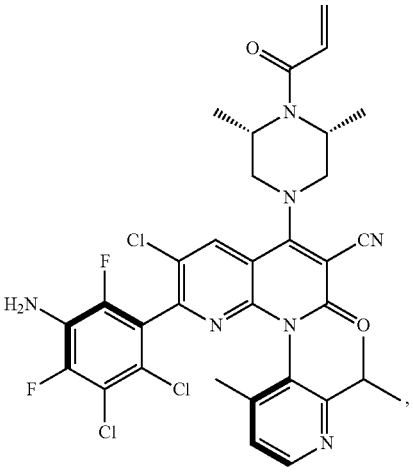

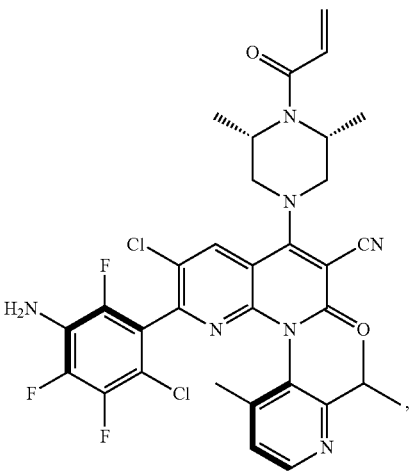

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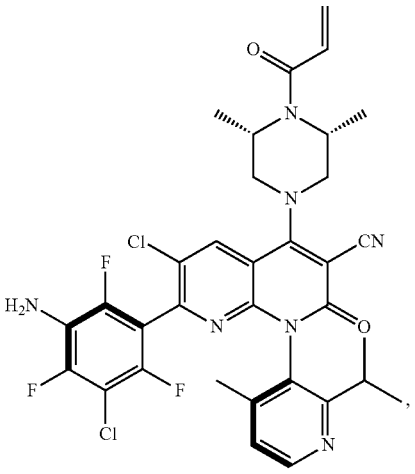

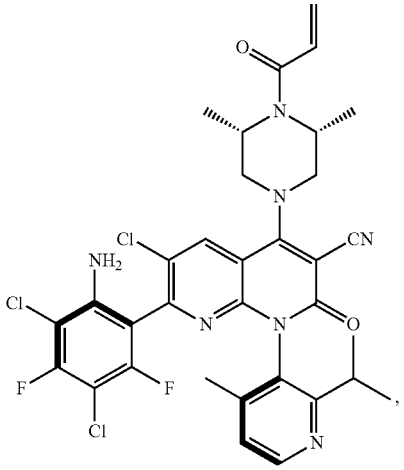

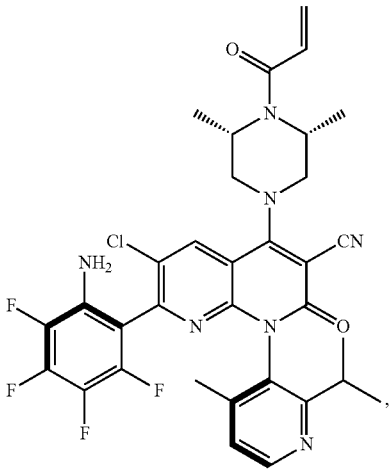

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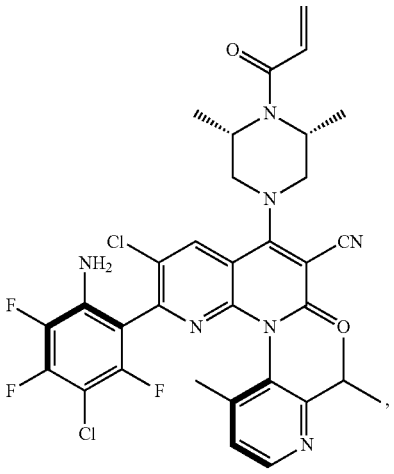

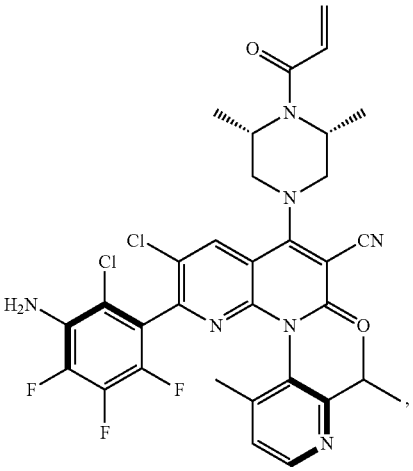

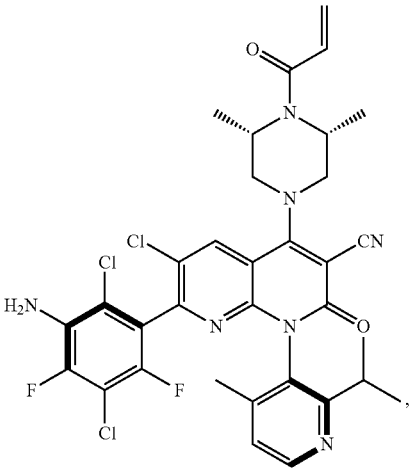

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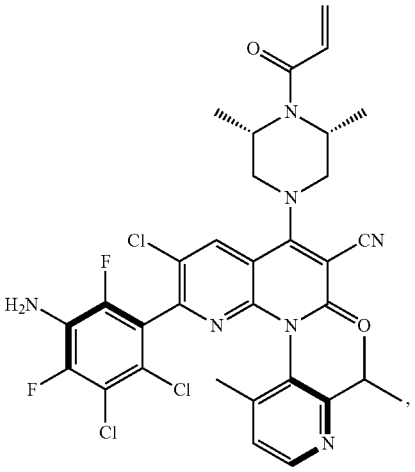

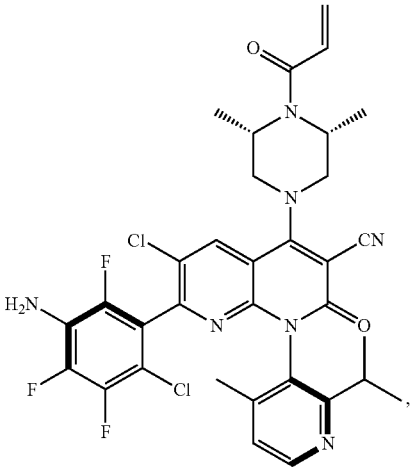

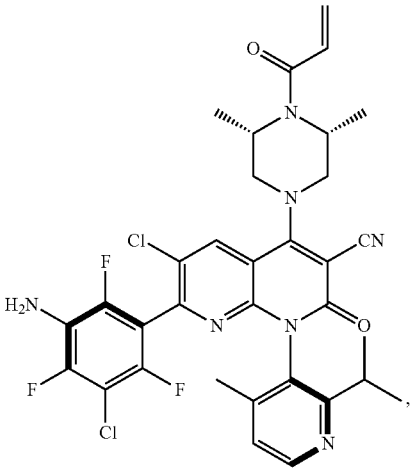

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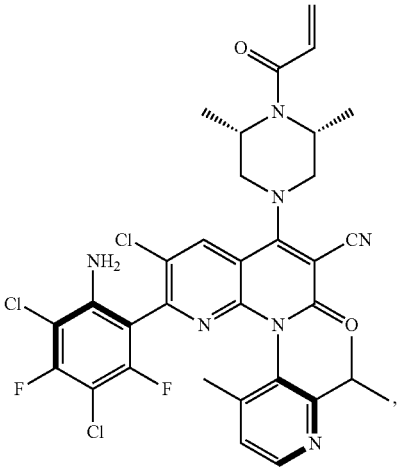

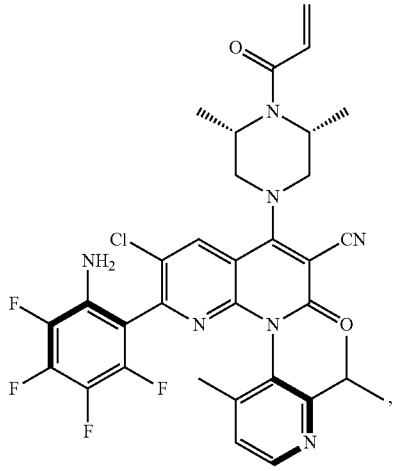

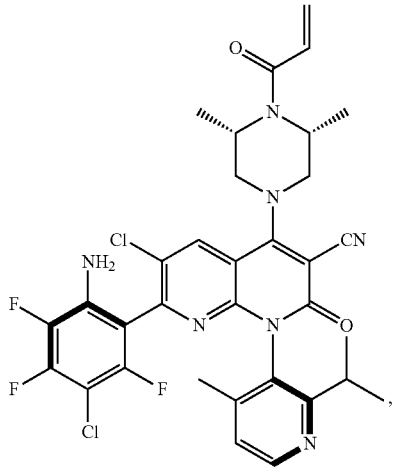

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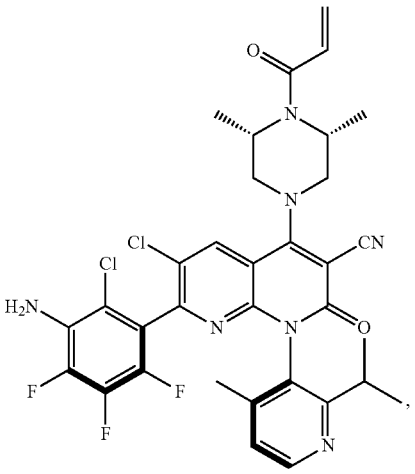

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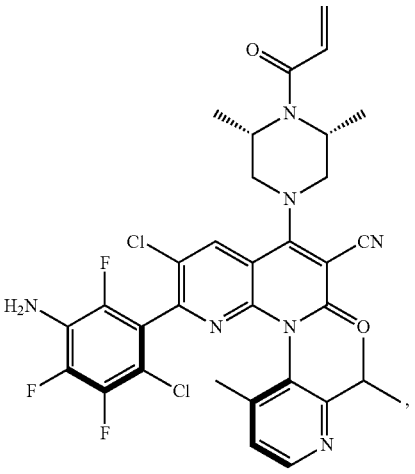

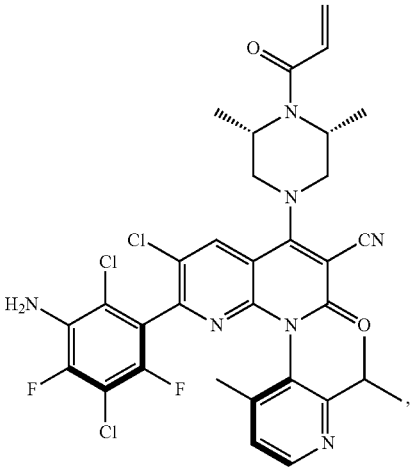

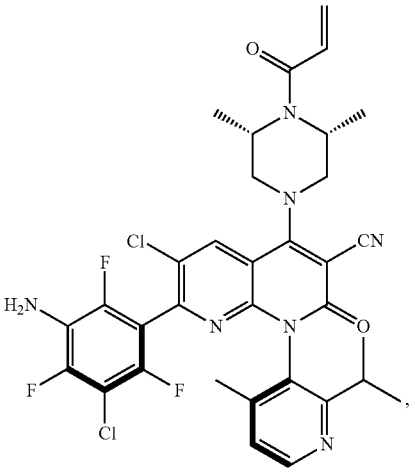

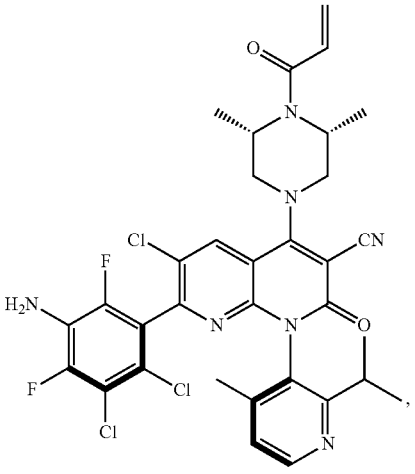

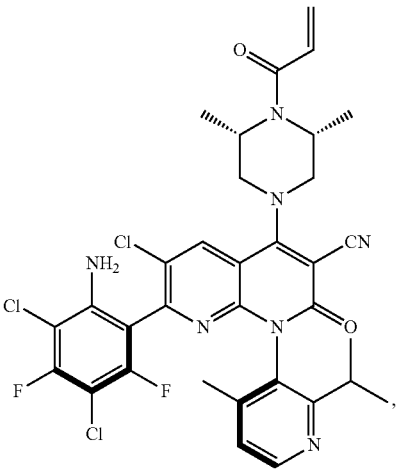

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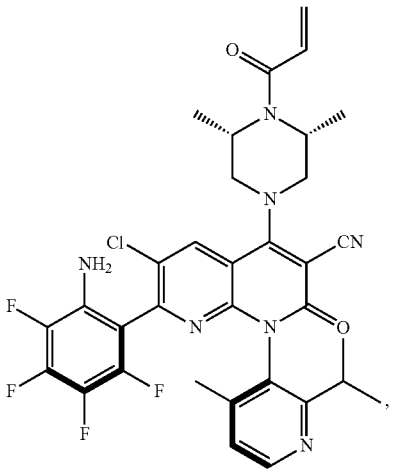

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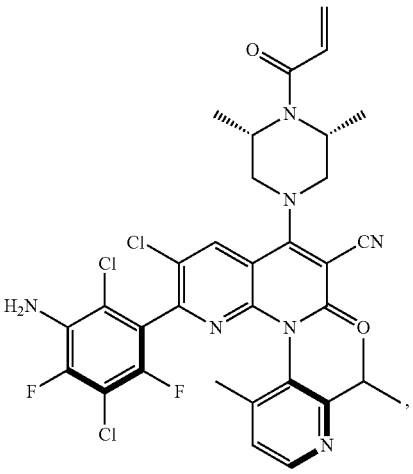

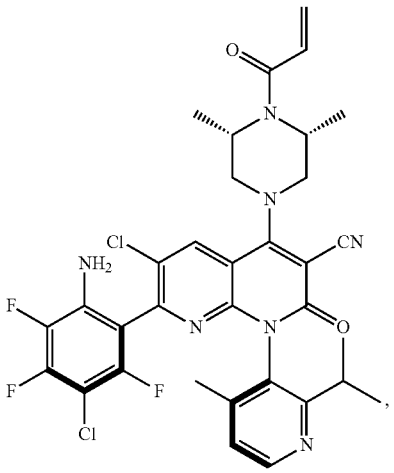

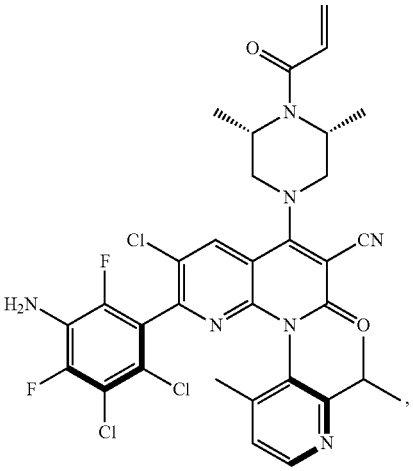

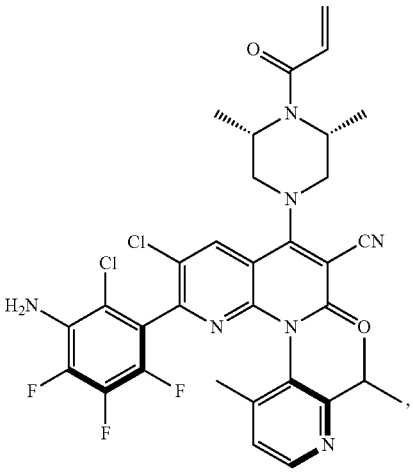

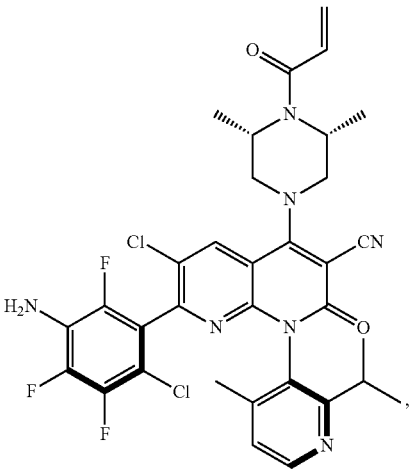

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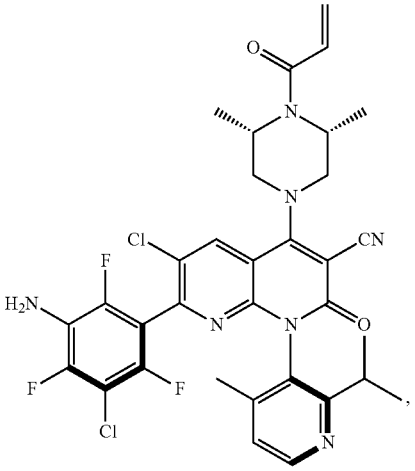

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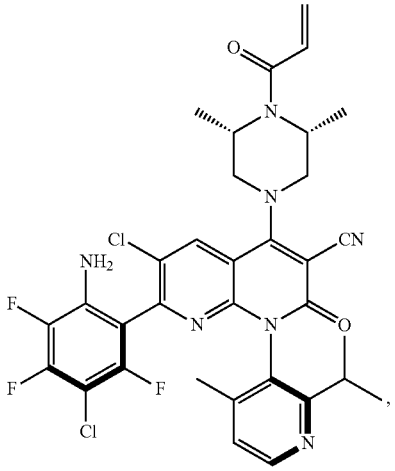

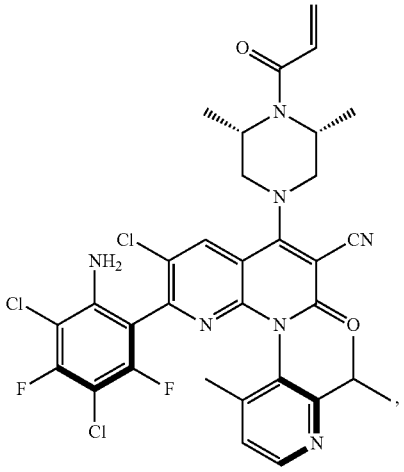

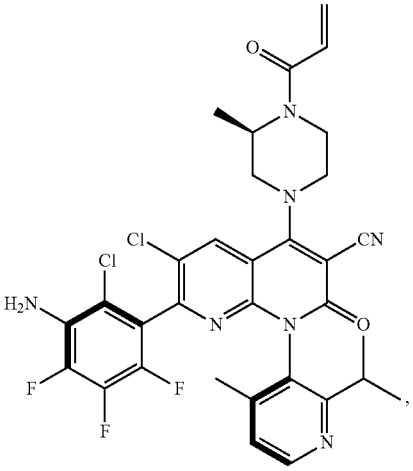

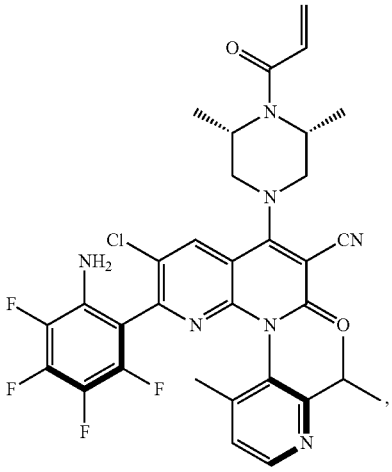

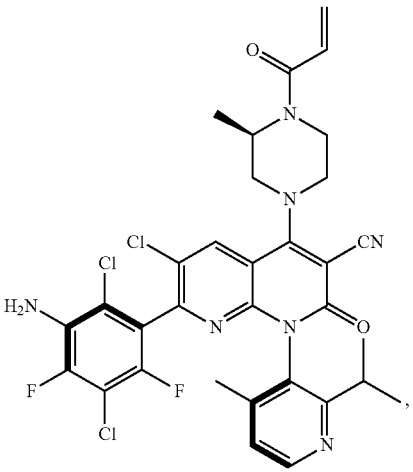

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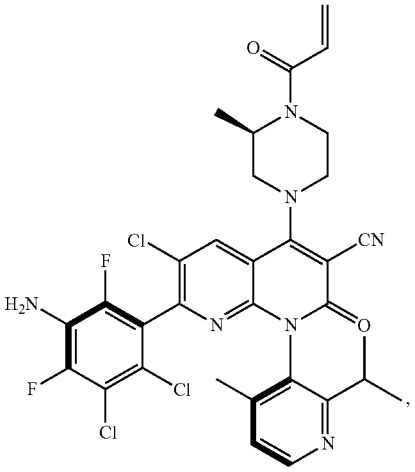

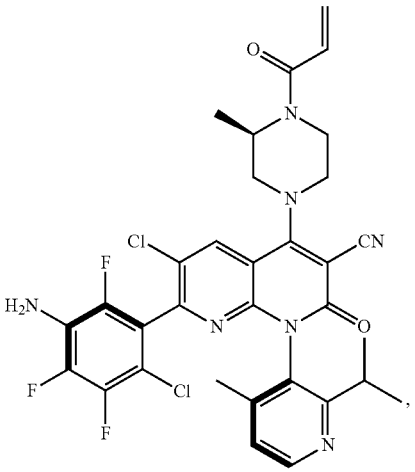

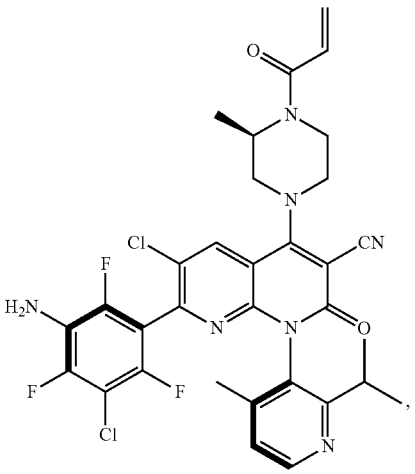

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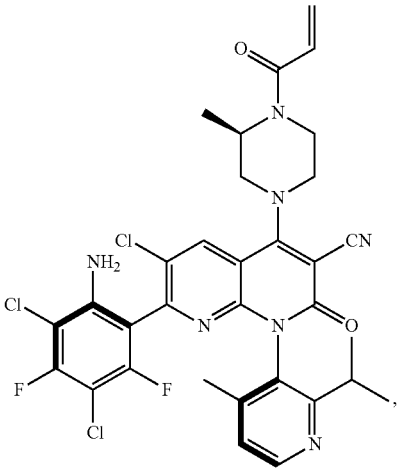

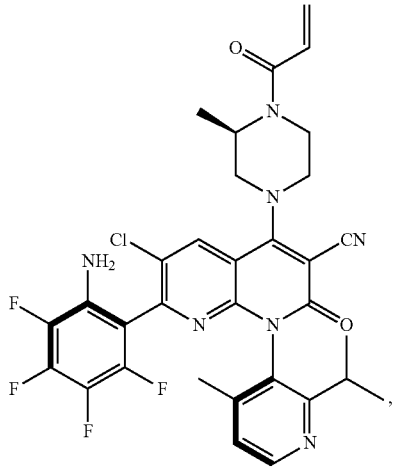

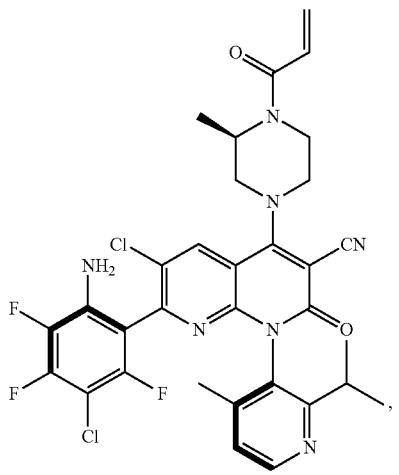

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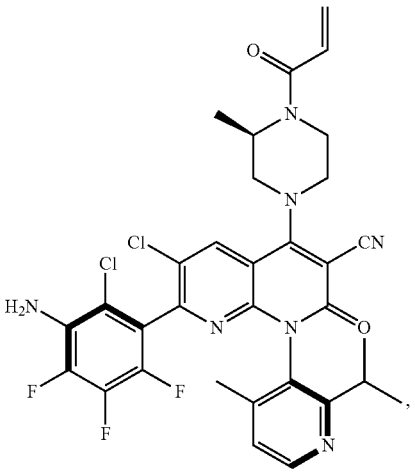

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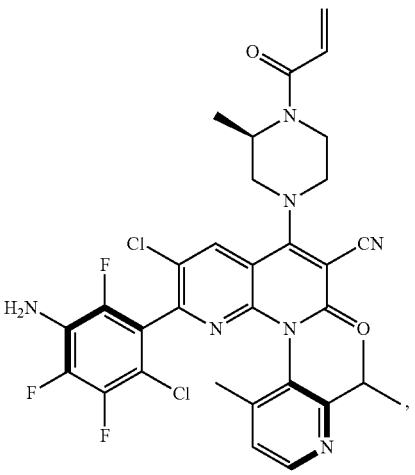

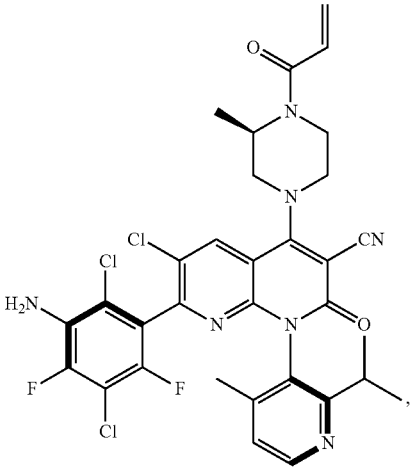

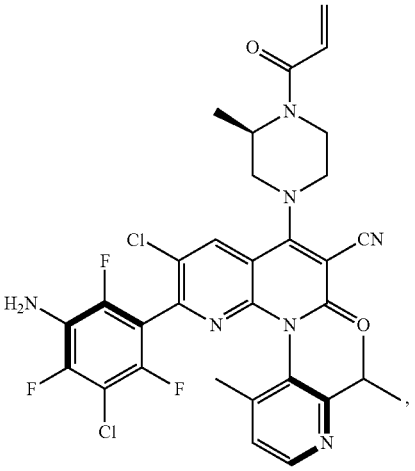

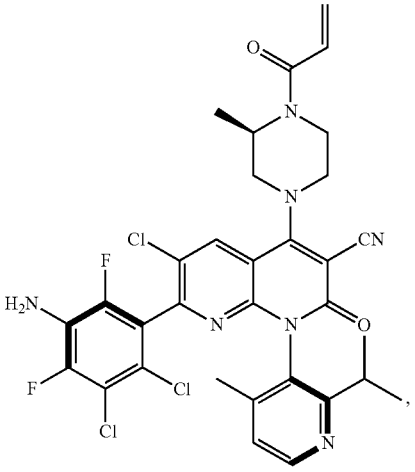

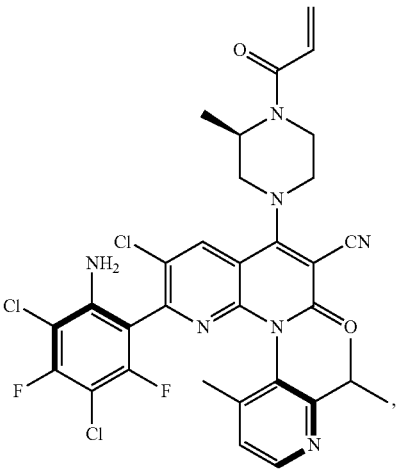

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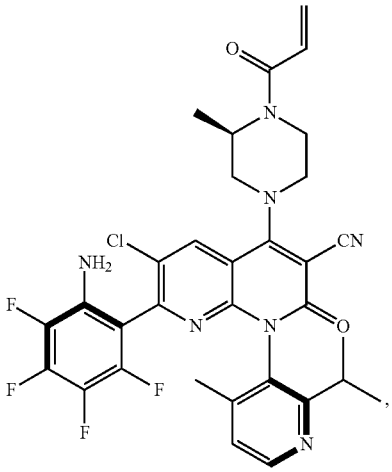

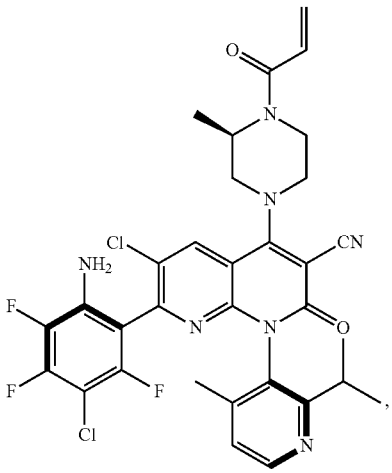

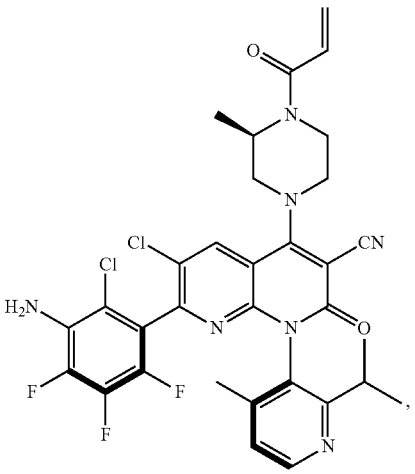

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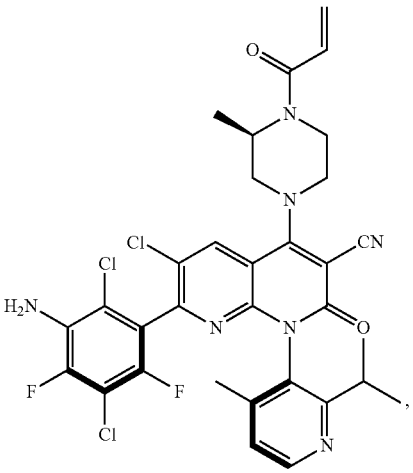

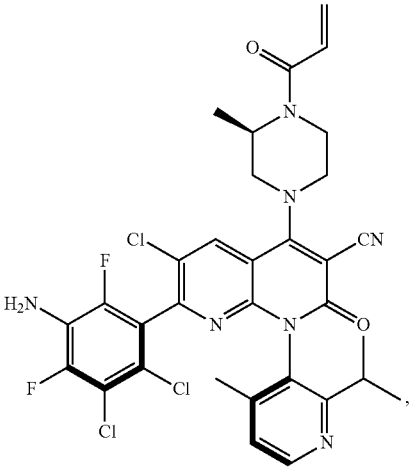

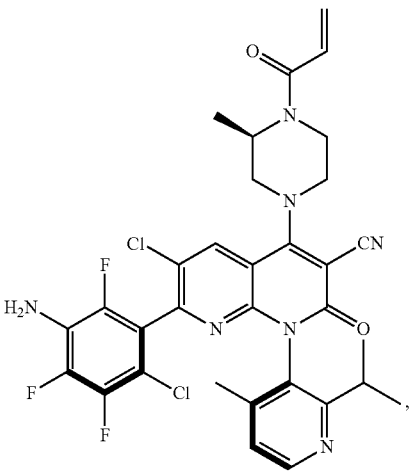

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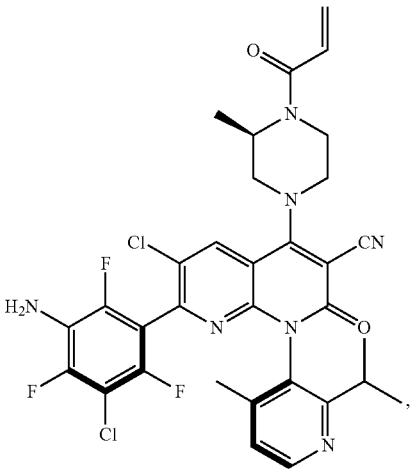

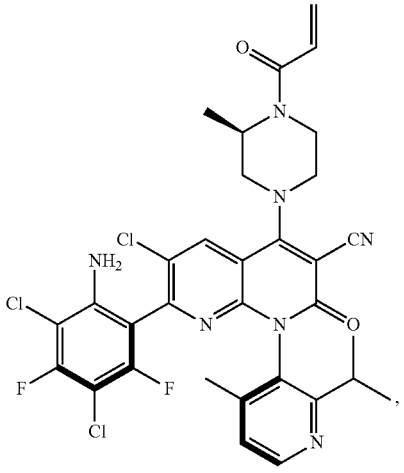

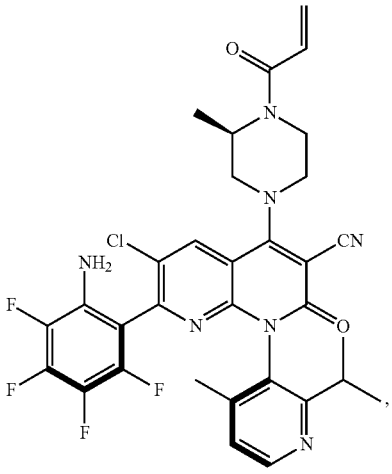

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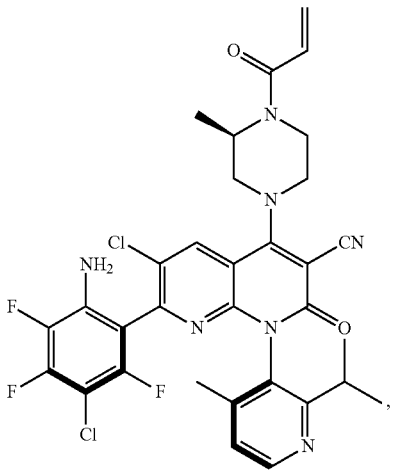

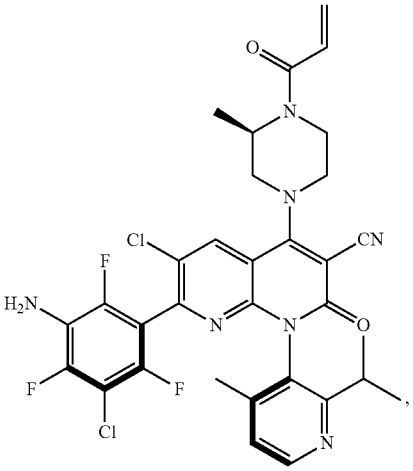

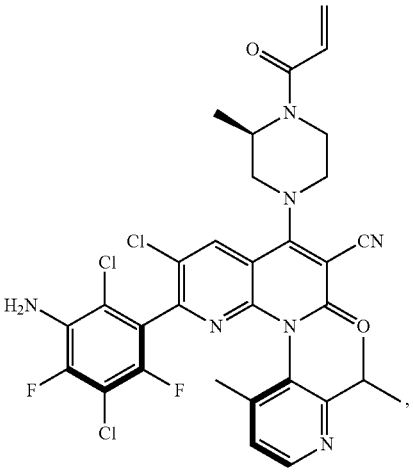

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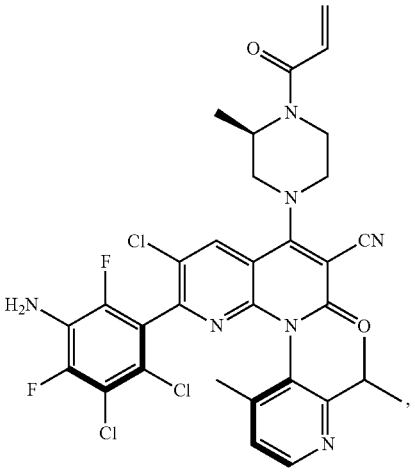

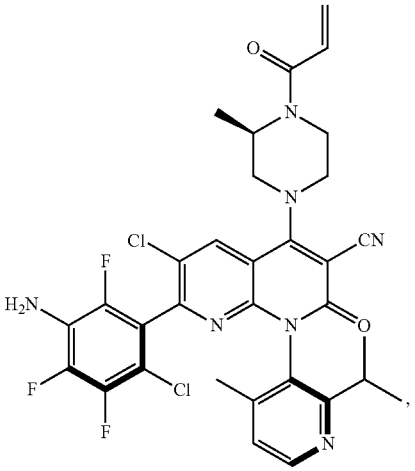

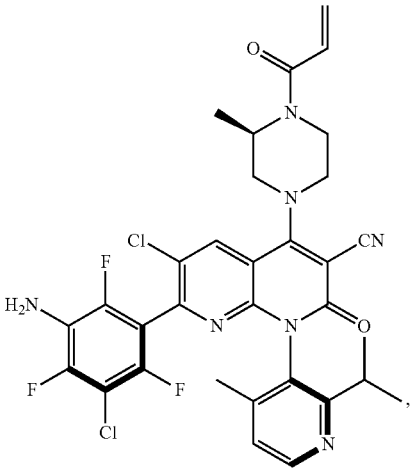

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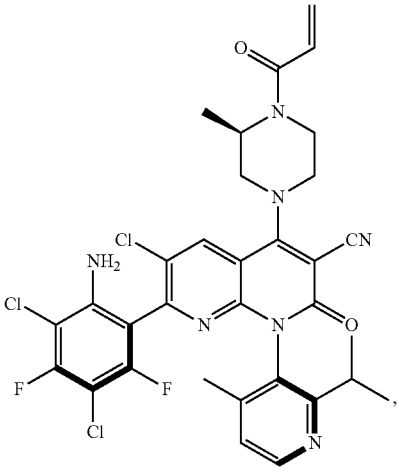

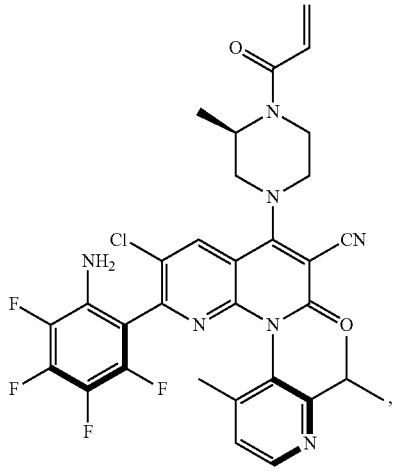

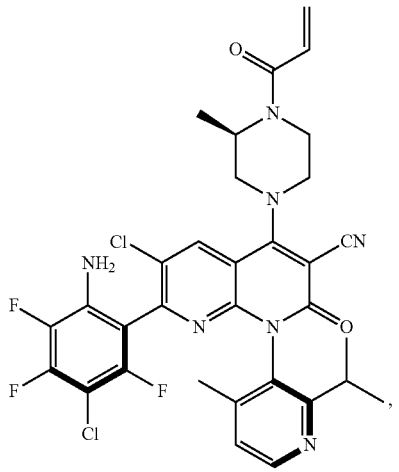

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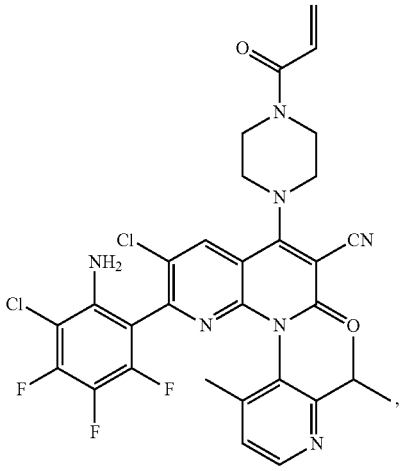

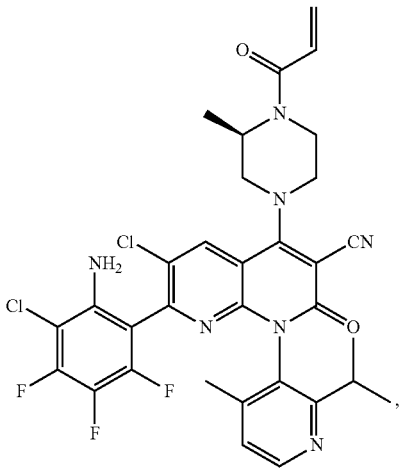

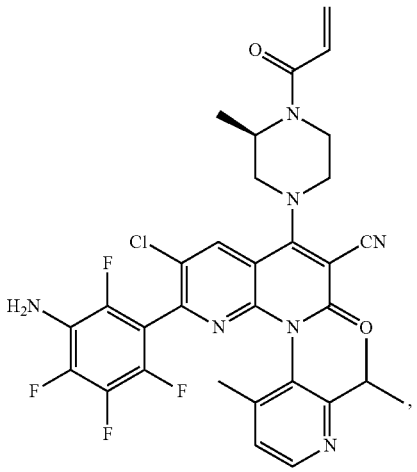

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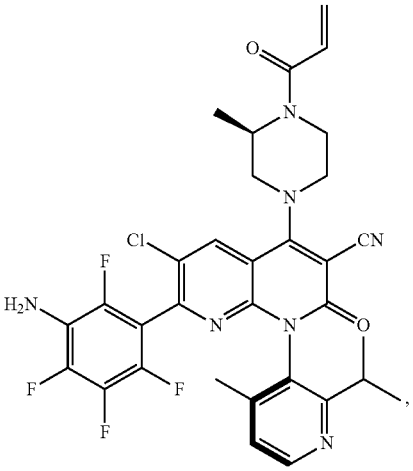

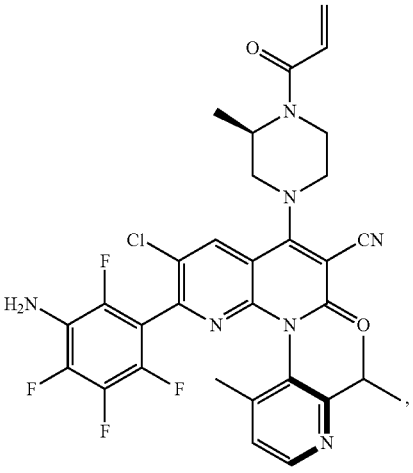

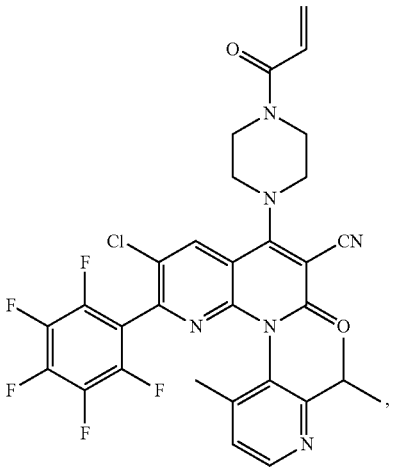

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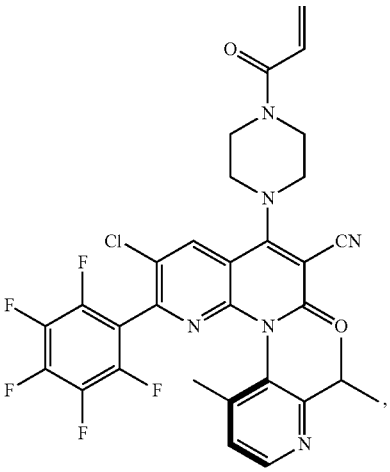

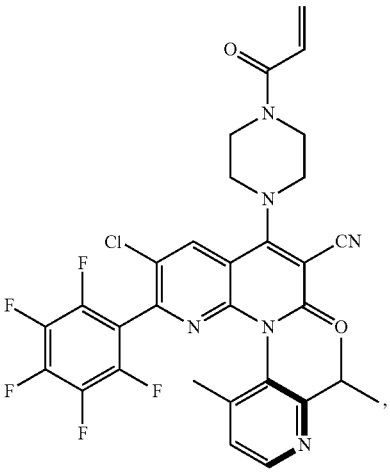

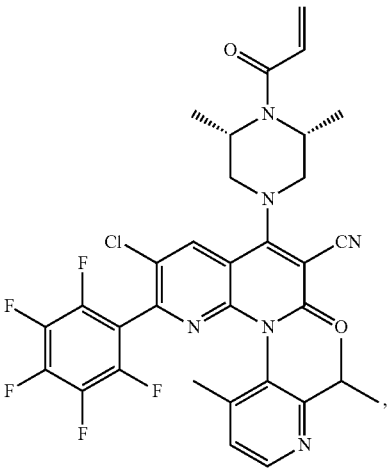

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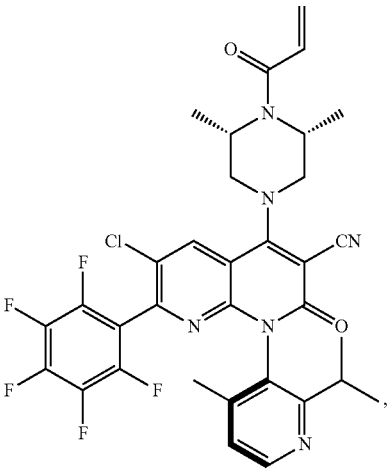

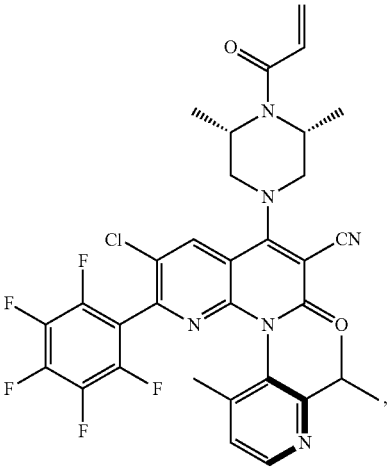

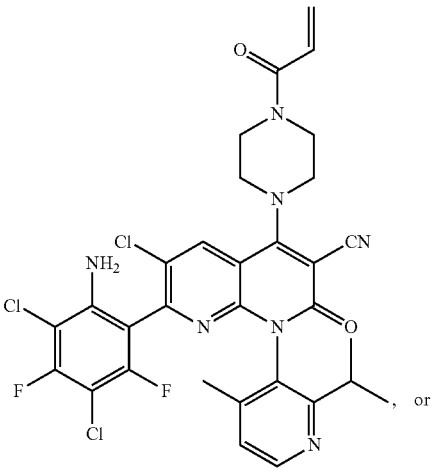

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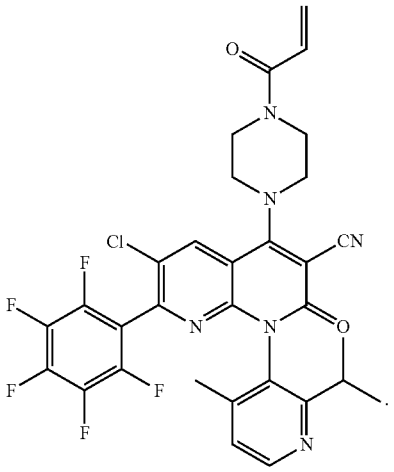
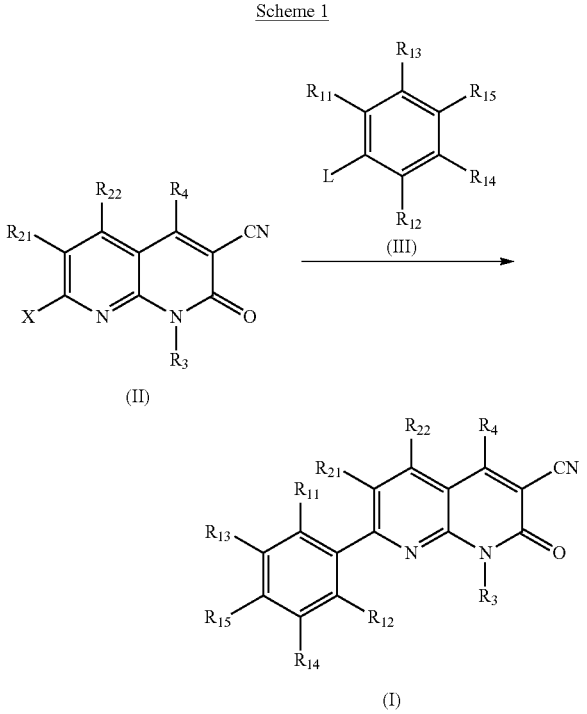
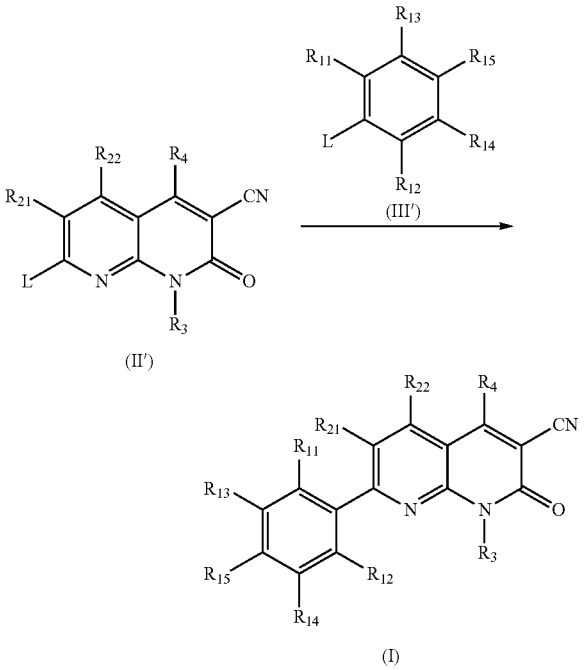


[0085] In another aspect, provided herein is a method for preparing the compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof, the method comprises a coupling reaction between a compound of formula (II) and a compound of formula (III) according to the following reaction Scheme 1 or between a compound of formula (II') and a compound of formula (III') according to the following reaction Scheme 2 catalyzed by a transition metal palladium or nickel reagent:

Scheme 1



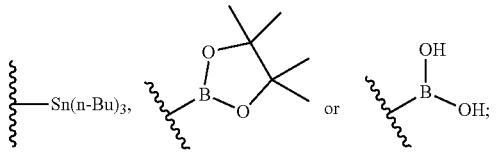
Scheme 2



[0086] Wherein

[0087] the L in the compound of formula (III) or formula (II') is a leaving group; preferably, the leaving group is selected from halogen, —$OS(O)_2CF_3$ or —OTs; more preferably, the halogen is selected from —F, —Cl, —Br, or —I; more preferably, the leaving group is —Cl or —Br;

[0088] the X in the compound of formula (II) or formula (III') is selected from boronic acid, borate ester or organotin; more preferably, the X is selected from



[0089] preferably, the coupling reaction is Suzuki coupling reaction or Stille coupling reaction;

[0090] preferably, the coupling reaction is catalyzed by the transition metal palladium reagent; more preferably, the transition metal palladium reagent is $Pd(PPh_3)_4$.

[0091] In another aspect, provided herein is a pharmaceutical composition comprising the compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof of the present invention, and at least one pharmaceutically acceptable excipient. In some embodiments, the said compound in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

[0092] In another aspect, provided herein is use of the compound of formula (I), a stereoisomer thereof, an atropi-

somer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof of the present invention; or the pharmaceutical composition of the present invention for the manufacture of a medicament for the treatment of diseases or conditions related to KRAS mutant protein. In some embodiments, the diseases or conditions related to KRAS mutant protein is the diseases or conditions related to KRAS G12C mutant protein. In some embodiments, the diseases or conditions related to KRAS G12C mutant protein is cancer related to KRAS G12C mutant protein. In some embodiments, the cancer is selected from blood cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer or lung cancer. In some embodiments, the blood cancer is selected from acute myeloid leukemia or acute lymphocytic leukemia; the lung cancer is selected from non-small cell lung cancer or small cell lung cancer.

[0093] In another aspect, provided herein is a method of treating a subject having a diseases or conditions related to KRAS mutant protein, said method comprising administering to the subject a therapeutically effective amount of the compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof of the present invention; or the pharmaceutical composition of the present invention. In some embodiments, the diseases or conditions related to KRAS mutant protein is the diseases or conditions related to KRAS G12C mutant protein. In some embodiments, the diseases or conditions related to KRAS G12C mutant protein is cancer related to KRAS G12C mutant protein. In some embodiments, the cancer is selected from blood cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer or lung cancer. In some embodiments, the blood cancer is selected from acute myeloid leukemia or acute lymphocytic leukemia; the lung cancer is selected from non-small cell lung cancer or small cell lung cancer.

Definition

[0094] The term "halogen" or "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. The preferred halogen groups include —F, —Cl and —Br. The preferred halogen groups include —F and —Cl.

[0095] The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. Similarly, C_{1-6}, as in C_{1-6} alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement.

[0096] The term "alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. For example, methylene (i.e., —CH_2—), ethylene (i.e., —CH_2—CH_2— or —CH(CH_3)—) and propylene (i.e., —CH_2—CH_2—CH_2—, —CH(—CH_2—CH_3)— or —CH_2—CH(CH_3)—).

[0097] The term "alkenyl" means a straight or branch-chained hydrocarbon radical containing one or more double bonds and typically from 2 to 20 carbon atoms in length. For example, "C_{2-6} alkenyl" contains from 2 to 6 carbon atoms. Alkenyl group include, but are not limited to, for example, ethenyl, propenyl, butenyl, 2-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

[0098] The term "alkynyl" contains a straight or branch-chained hydrocarbon radical containing one or more triple bonds and typically from 2 to 20 carbon atoms in length. For example, "C_{2-6} alkynyl" contains from 2 to 6 carbon atoms. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

[0099] The term "alkoxy" radicals are oxygen ethers formed from the previously described alkyl groups.

[0100] The term "aryl" or "aryl ring", as used herein, unless otherwise indicated, refers to an unsubstituted or substituted mono or polycyclic aromatic ring system only containing carbon ring atoms. The preferred aryls are mono cyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls.

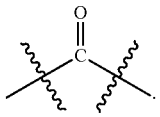
[0101] The term "heterocyclic" or "heterocyclic ring", as used herein, unless otherwise indicated, refers to unsubstituted and substituted mono or polycyclic non-aromatic ring system containing one or more ring heteroatom(s), which comprising moncyclic heterocyclic (ring), bicyclic heterocyclic (ring), bridged heterocyclic (ring), fused heterocyclic (ring) or sipro heterocyclic (ring). Preferred heteroatoms include N, O, and S, including N-oxides, sulfur oxides, and dioxides. Preferably the heterocyclic (ring) is three to ten membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution, preferably one, two or three, are included within the present definition of heterocyclic (ring). Examples of such heterocyclic groups include, but are not limited to azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxoazepinyl, azepinyl, tetrahydrofuranyl, dioxolanyl, tetrahydroimidazolyl, tetrahydrothiazolyl, tetrahydrooxazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and oxadiazolyl.

[0102] The term "heteroaryl" or "heteroaryl ring", as used herein, unless otherwise indicated, represents an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl or heteroaryl ring may be monocyclic or polycyclic, substituted or unsubstituted. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junction, for example, bycyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (cabons and heteroatoms). Examples of heteroaryl groups include, but are not limited to thienyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl adeninyl, quinolinyl or isoquinolinyl.

[0103] The term "carbocyclic" or "carbocyclic ring" refers to a substituted or unsubstituted monocyclic ring, bicyclic ring, bridged ring, fused ring, sipiro ring non-aromatic ring system only containing carbon atoms. The carbocyclic (ring) contain cycloalkyl without substituted degrees and carbocyclic with one or more substituted degrees. Examplary

"cycloalkyl" groups includes but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

[0104] The term "oxo" refers to oxygen atom together with the attached carbon atom forms the group



[0105] The term "—C_{1-6} alkylene-N(C_{1-6} alkyl)$_2$" refers to the —C_{1-6} alkyl as defined above substituted by —N(C_{1-6}alkyl)$_2$.

[0106] The term "—C_{1-6} alkylene-CN" refers to the —C_{1-6} alkyl as defined above substituted by —CN.

[0107] The term "heteroalkyl" refers to the presence of heteroatoms between any two carbon atoms in the alkyl group as defined above, such as N or O atoms. For example, "heteroC_{2-6} alkyl" means that there are N atom or O atom between any two carbon atoms in the C_{2-6} alkyl group, including but not limited to —CH_2OCH_3, —$CH_2CH_2OCH_3$, —CH_2NHCH_3, or —$CH_2N(CH_3)_2$ and the like.

[0108] The term "composition", as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. Accordingly, pharmaceutical compositions containing the compounds of the present invention as the active ingredient as well as methods of preparing the instant compounds are also part of the present invention.

[0109] The compounds of the present invention may also be present in the form of pharmaceutically acceptable salt(s). For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salt(s)". The pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. The pharmaceutically acceptable acidic/anionic salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid.

[0110] The present invention includes within its scope the prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily converted in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0111] It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques know in the art as well as those methods set forth herein.

[0112] The present invention includes compounds described can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof.

[0113] The present invention includes all stereoisomers of the compound and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[0114] The term "stereoisomer" as used in the present invention refers to an isomer in which atoms or groups of atoms in the molecule are connected to each other in the same order but differ in spatial arrangement, including conformational isomers and conformational isomers. The configuration isomers include geometric isomers and optical isomers, and optical isomers mainly include enantiomers and diastereomers. The invention includes all possible stereoisomers of the compound.

[0115] Certain of the compounds provided herein may exist as atropisomers, which are conformational stereoisomers that occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule. The compounds provided herein include all atropisomers, both as pure individual atropisomer preparations, enriched preparations of each, or a non-specific mixture of each. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted.

[0116] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. The isotopes of hydrogen can be denoted as ^{1}H (hydrogen), ^{2}H (deuterium) and ^{3}H (tritium). They are also commonly denoted as D for deuterium and T for tritium. In the application, CD_3 denotes a methyl group wherein all of the hydrogen atoms are deuterium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent.

[0117] When a tautomer of the compound exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically stated otherwise.

[0118] The pharmaceutical compositions of the present invention comprise the compound (or the stereoisomer, the astropisomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the stereoisomer, or the pharmaceutically acceptable salt of the astro-

pisomer) as an active ingredient, and a pharmaceutically acceptable carrier and optionally other adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0119] In practice, the compounds or a prodrug or a metabolite or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[0120] The pharmaceutical carrier employed can be, for example, a solid, liquid or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen. In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[0121] A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05 mg to about 5 g of the active ingredient and each cachet or capsule preferably containing from about 0.05 mg to about 5 g of the active ingredient. For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 0.05 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 0.01 mg to about 2 g of the active ingredient, typically 0.01 mg, 0.02 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1500 mg or 2000 mg.

[0122] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[0123] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[0124] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound of this invention or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 0.05 wt % to about 10 wt % of the compound, to produce a cream or ointment having a desired consistency.

[0125] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[0126] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders,

surface-active agents, thickeners, lubricants, preservatives (including antioxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

[0127] Generally, dosage levels on the order of from about 0.001 mg/kg to about 150 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions or alternatively about 0.05 mg to about 7 g per patient per day. For example, inflammation, cancer, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system (CNS), may be effectively treated by the administration of from about 0.001 to 50 mg of the compound per kilogram of body weight per day or alternatively about 0.05 mg to about 3.5 g per patient per day.

[0128] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0129] FIG. **1** is the ball and stick model of the absolute configuration of Compound 1-2;

[0130] FIG. **2** is the ellipsoid model of the absolute configuration of Compound 1-2;

[0131] FIG. **3** is the graph of unit cell structure of single crystal diffraction for Compound 1-2;

[0132] FIG. **4** is the graph of hydrogen bond of single crystal diffraction for Compound 1-2;

[0133] FIG. **5** is the graph of 3D structure-a direction of single crystal diffraction for Compound 1-2;

[0134] FIG. **6** is the graph of 3D structure-b direction of single crystal diffraction for Compound 1-2;

[0135] FIG. **7** is the graph of 3D structure-c direction of single crystal diffraction for Compound 1-2.

[0136] FIG. **8** shows the efficacy of Compound 1-2 and Compound 12-2 in NCI-H1373 xenograft model.

[0137] FIG. **9** shows the safety of Compound 1-2 in MIA-PaCa-2 model.

METHODS OF PREPRATION

[0138] Compounds of the present invention can be synthesized from commercially available reagents using the synthetic methods described herein. The examples which outline specific synthetic route below are meant to provide guidance to the ordinarily skilled synthetic chemist, who will readily appreciate that the solvent, concentration, reagent, protecting group, order of synthetic steps, time, temperature, and the like can be modified as necessary, well within the skill and judgment of the ordinarily skilled artisan.

[0139] The following Examples are provided to better illustrate the present invention. All parts and percentages are by weight and all temperatures are degrees Celsius, unless explicitly stated otherwise. The following abbreviations in Table 1 have been used in the examples:

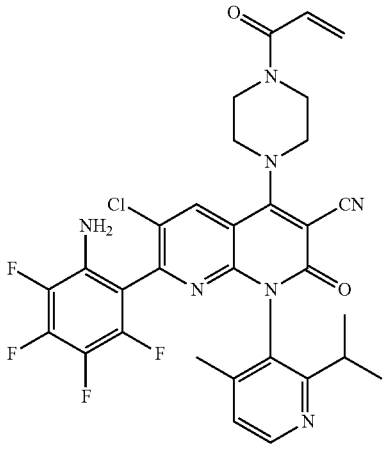
TABLE 1

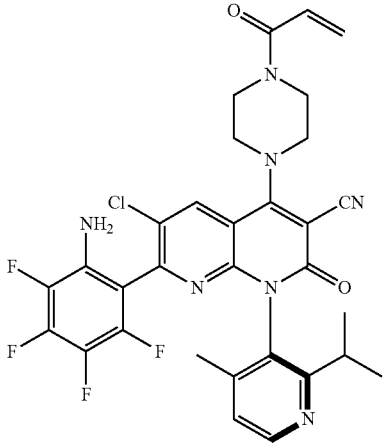
MeOH	Methanol
EtOH	Ethanol
DCM	Dichloromethane
TEA	Triethylamine
TFA	Trifluoroacetic acid
DMF	N,N-Dimethylformamide
DMA	N,N-dimethylacetamide
THF	Tetrahydrofuran
MeCN/ACN	Acetonitrile
HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
HOBT	1-Hydroxybenzotriazole
LiHMDS	Lithium Hexamethyldisilazide
Hunig's base/DIEA/DIPEA	N,N-Diisopropylethylamine
EA	Ethyl acetate
min	Minute(s)
h	Hour(s)
Pre-TLC	Preparative thin layer chromatography
prep-HPLC	Preparative High Performance Liquid Chromatography
SFC	Supercritical fluid chromatography
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
R.T./r.t.	Room temperature(20° C.~30° C.)
AcOH	Acetic acid
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
NCS	N-Chlorosuccinimide
Hex	n-Hexane
PPTS	Pyridinium 4-toluenesulfonate
IPA	Isopropanol
DHP	3,4-Dihydro-2H-pyran
a.q./aq	Aqueous
AcOK/KOAc	Potassium acetate
NMP	Methyl-2-pyrrolidinone

Example 1

4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 1"); (P)-4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 1-1"); and (M)-4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 1-2")

[0140]





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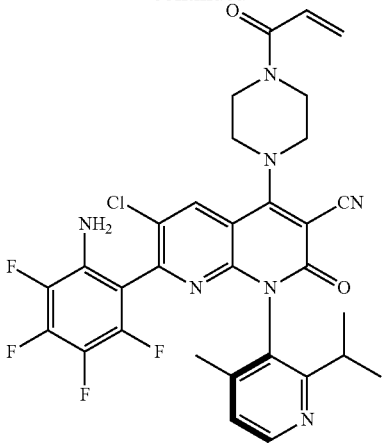


Step 1. 4-methyl-2-(prop-1-en-2-yl)pyridin-3-amine

[0141] Into a 350-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2-bromo-4-methylpyridin-3-amine (BD, APL099) (15.01 g, 80.25 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (BD, AQA827) (13.62 g, 81.05 mmol), Pd(dppf)Cl_2 (5.95 g, 8.03 mmol), K_2CO_3 (33.52 g, 240 mmol), dioxane (150 mL) and water (20 mL). The reaction mixture was stirred at 100° C. for 8 h. The reaction mixture was filtered and concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v:v=2:3). This resulted in 11.2 g (94%) of 4-methyl-2-(prop-1-en-2-yl)pyridin-3-amine as yellow oil. LCMS: m/z=149 $[M+1]^+$.

Step 2. 2-isopropyl-4-methylpyridin-3-amine (Intermediate A)

[0142] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-methyl-2-(prop-1-en-2-yl)pyridin-3-amine (11.2 g, 75.67 mmol) and MeOH (100 mL). Palladium on carbon (2.81 g) was added in three portions. The mixture was degassed under vacuum and then purged with H_2 (gas) for three cycles. The mixture was stirred for 3 h at 25° C. The resulting mixture was filtered, the filtrate was concentrated under vacuum. This resulted in 11 g (crude) of 2-isopropyl-4-methylpyridin-3-amine which was used directly in the next step. LCMS: m/z=151 $[M+1]^+$.

Step 3. 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)acetamide

[0143] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-cyanoacetic acid (3 g, 35.27 mmol) and DCM (40 mL). Oxalyl chloride (6.2 g, 48.85 mmol) was added in dropwise. After the addition, DMF (0.1 mL) was added. The mixture was stirred for 3 h at 25° C. The resulting solution was concentrated under vacuum. This resulted in 3.10 g (crude) of 2-cyanoacetylchloride which was used directly in the next step.

[0144] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-isopropyl-4-methylpyridin-3-amine (2.00 g, 13.31 mmol),

TEA (5.40 g, 53.36 mmol) and DCM (40 mL) and stirred. The mixture was cooled to 0° C. and then 2-cyanoacetyl-chloride (3.10 g, crude) was added in dropwise. The resulting solution was stirred for further 2 h at room temperature. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with dichloromethane (3×50 mL), the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered, the filtrate was concentrated under vacuum and applied onto a silica gel column eluted with EA/hexane (v:v=3:2). This resulted in 1.00 g (34%) of 2-cyano-N-(2-isopropyl-4-methyl pyridin-3-yl)acetamide as yellow solid. LCMS: m/z=218 $[M+1]^+$.

Step 4. 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)-3-oxo-3-(2,5,6-trichloropyridin-3-yl) propanamide

[0145] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2,5,6-trichloronicotinic acid (5.01 g, 22.12 mmol) and $SOCl_2$ (30 mL). The mixture was heated to 80° C. and stirred for 2 h. The solution was concentrated under vacuum. This resulted in 5.10 g (crude) of 2,5,6-trichloronicotinoyl chloride which was used directly in the next step.

[0146] Into a 250-mL round-bottom flask, was placed 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)acetamide (3.01 g, 13.85 mmol) and THF (40 mL). The mixture was stirred at 0° C. NaH (1.16 g, 28.99 mmol) was added in three batches. The mixture was stirred at 0° C. for further 40 min. Then 2,5,6-trichloronicotinoyl chloride (3.19 g, 13.03 mmol) in THF (10 mL) was added in dropwise. The reaction mixture was stirred at 25° C. for 2 h. The reaction mixture was concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with ACN/H_2O (v/v=1/3). This resulted in 5.89 g (crude) of 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)-3-oxo-3-(2,5,6-trichloropyridin-3-yl)propanamide as yellow solid. LCMS: m/z=425 $[M+1]^+$.

Step 5. 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate B)

[0147] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)-3-oxo-3-(2,5,6-trichloropyridin-3-yl)propanamide (5.89 g, 13.83 mmol) and THF (70 mL) and stirred at room temperature. NaH (2.73 g, 68.25 mmol) was added in batch-wise. The mixture was stirred at 50° C. for 2 h. The reaction mixture was concentrated under vacuum. The residue was dissolved in 100 mL water and adjusted pH to 7 with AcOH. The resulting solid was filtered and dried under vacuum to provide 5.85 g (108% in two steps) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=389 $[M+1]^+$.

[0148] ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J=5.7 Hz, 1H), 8.38 (s, 1H), 7.89 (d, J=5.4 Hz, 1H), 3.01-2.88 (m, 1H), 2.19 (s, 3H), 1.21 (d, J=6.9 Hz, 3H), 1.14 (d, J=6.9 Hz, 3H).

[0149] The mixture of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (10.59 g, "Intermediate B") was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IC, 3.0×100 mm, 3 μm; mobile phase, IPA/ACN=(v/v=1/1); detection wavelength, UV 210 nm. This resulted in 4.99 g (47%) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Intermediate B-1", M or P atropisomer) as a brown solid; ^1H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.33-7.22 (m, 1H), 2.76-2.61 (m, 1H), 2.03 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H).

[0150] And 4.60 g (43%) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Intermediate B-2", P or M atropisomer) as a brown solid;

[0151] ^1H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.28 (d, J=5.0 Hz, 1H), 2.76-2.63 (m, 1H), 2.03 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.08-1.00 (m, 3H).

Step 6. 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0152] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate B, 980 mg, 2.51 mmol), $POCl_3$ (1150 mg, 7.50 mmol), DIEA (1.32 g, 10.21 mmol) and acetonitrile (12 mL). The mixture was stirred at 80° C. for 2 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. This resulted in crude 4,6,7-trichloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile which was used directly in the next step.

Step 7. tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate

[0153] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.20 g, crude) and acetonitrile (20 mL). DIEA (660 mg, 5.10 mmol) and tert-butyl piperazine-1-carboxylate (0.57 g, 3.06 mmol) were added. The reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (3×50 mL), the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=30%-70%). This resulted in 0.92 g (65% in two steps) of tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as yellow solid. LCMS: m/z=557 $[M+1]^+$.

Step 8. 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate C)

[0154] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl

4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (920 mg, 1.65 mmol), TFA (4 ml) and DCM (15 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The residue was dissolved by DCM (15 mL) in 50-mL round-bottom flask. DIEA (1.02 g, 10.08 mmol) was added. The reaction mixture was cooled to 0° C. and acryloyl chloride (190 mg, 2.09 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction was then quenched by the addition of water (30 mL). The resulting solution was extracted with ethyl acetate (3×50 mL), the organic layers were combined and washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=40%-80%). This resulted in 0.86 g (crude) of 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=511 $[M+1]^+$.

Step 9. 2-bromo-3,4,5,6-tetrafluoroaniline

[0155] Into a 50-mL round-bottom flask was placed 2,3,4,5-tetrafluoroaniline (1.99 g, 12.05 mmol), Sodium acetate (1.32 g, 16.09 mmol), iron (0.10 g, 1.79 mmol) and AcOH (7 mL). The reaction mixture was heated to 45° C. This was followed by the added of bromine (3.02 g, 18.90 mmol) in AcOH (7 mL). The reaction mixture was heated to 60° C. and stirred for 1.5 h. The reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (30 mL). The resulting solution was extracted with ethyl acetate (2×50 mL), the organic layers were combined and washed with saturated aqueous Na_2CO_3 (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. This resulted in 2.28 g (77%) of 2-bromo-3,4,5,6-tetrafluoroaniline as yellow solid. LCMS: m/z=244,246 $[M+1]^+$.

Step 10. 2,3,4,5-tetrafluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0156] Into a 150-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2-bromo-3,4,5,6-tetrafluoroaniline (2.28 g, 9.35 mmol), bis(pinacolato)diboron (3.96 g, 15.59 mmol), $Pd(dppf)Cl_2$ (1.21 g, 1.65 mmol), AcOK (1.84 g, 18.75 mmol) and dioxane (20 mL). The reaction mixture was stirred at 100° C. for 2 h. The reaction mixture was filtered and concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v/v=0%-20%). This resulted in 2.28 g (81% yield) of 2,3,4,5-tetrafluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as white solid. LCMS: m/z=210 $[M+1]^+$.

Step 11. 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 1")

[0157] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (221 mg, 0.43 mmol), 2,3,4,5-tetrafluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (513 mg, 1.76 mmol), $Pd(PPh_3)_4$ (151 mg, 0.13 mmol), Na_2CO_3 (161 mg, 1.52 mmol), dioxane (5 mL) and water (0.5 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with CH_3CN/H_2O (v/v=40° A-80%). This resulted in 7 mg (2% yield) of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 1") as yellow solid. LCMS: m/z=640 $[M+1]^+$.

[0158] ^1H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.43 (d, J=5.0 Hz, 1H), 7.33-7.20 (m, 1H), 6.87 (dd, J=16.7, 10.6 Hz, 1H), 6.31 (d, J=16.9 Hz, 1H), 5.84 (d, J=10.6 Hz, 1H), 3.98 (d, J=23.5 Hz, 8H), 2.73 (d, J=28.0 Hz, 1H), 2.00 (d, J=31.9 Hz, 3H), 1.32-1.10 (m, 3H), 1.00 (dd, J=40.7, 6.8 Hz, 3H).

[0159] The mixture of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (356 mg, several batches) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IG, 3 cm×25 cm, Sum; mobile phase, CO_2:EtOH=55:45; Detection wavelength, UV 220 nm. This resulted in 175 mg (49.16%) of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Compound 1-1") as a yellow solid. LCMS: m/z=640 $[M+1]^+$.

[0160] ^1H NMR (400 MHz, CD_3OD) δ 8.45 (d, J=1.9 Hz, 1H), 8.34 (d, J=5.0 Hz, 1H), 7.17 (d, J=5.0 Hz, 1H), 6.78 (dd, J=16.8, 10.6 Hz, 1H), 6.21 (dd, J=16.8, 2.0 Hz, 1H), 5.74 (dd, J=10.6, 2.0 Hz, 1H), 4.02-3.72 (m, 8H), 2.70-2.58 (m, 1H), 1.97-1.88 (m, 3H), 1.07 (dd, J=8.2, 6.7 Hz, 3H), 0.97-0.88 (m, 3H).

[0161] And 184 mg (51.69%) of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 1-2") as a yellow solid. LCMS: m/z=640 $[M+1]^+$.

[0162] ^1H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.45 (d, J=5.0 Hz, 1H), 7.31 (d, J=4.7 Hz, 1H), 6.88 (dd, J=16.7, 10.7 Hz, 1H), 6.32 (d, J=16.8 Hz, 1H), 5.88 (d, J=10.5 Hz, 1H), 4.08-3.92 (m, 8H), 2.81-2.66 (m, 1H), 2.06-1.98 (m, 3H), 1.18 (t, J=7.4 Hz, 3H), 1.06-0.96 (m, 3H).

[0163] About 10 mg Compound 1-2 was taken into a glass vial and dissolved with 0.8 mL ethanol and 0.4 mL n-heptane. The clear solution was evaporated to dryness at room temperature through a small hole to obtain the bulk-like crystals as the sample of the testing of single crystal diffraction using the following instrument and parameters in Table 2:

TABLE 2

Instrument and Parameters		
Instrument	Single Crystal Diffractometer	
Model	Bruker SMART APEX II	
Detector Model	4K CCD	
Sources	Enhance Cu radiation	
Lens	Temperature	293.44 K
	Wavelength	1.54 Å

[0164] The results are shown in Table 3, Table 4, Table 5, Table 6 and Table 7.

Crystallographic Data

[0165]

TABLE 3

Crystallographic Data and Structure Refinement for Compound 1-2 Phase Data

Formula	$C_{31}H_{26}ClF_4N_7O_2$
Formula Weight	640.04
Crystal System	Monoclinic
Space group	C2
Cell Parameters	a = 20.6796 (7) Å; b = 11.2352 (4) Å; c = 14.0148 (5) Å; $\alpha = \gamma = 90.00°$; $\beta = 91.971$ (2)
Cell Ratio	a/b = 1.8406; b/c = 0.8017; c/a = 0.6777
Z	4
Cell Volume	3254.3 (2) $Å^3$
Calc. density	1.306 g/cm^3
Flack	0.07 (3)
R-indices R_1	0.0962
R-indices WR_2	0.1665
Goodness-of-Fit, S	1.015
R_{sigma}	0.0799
R_{int}	0.0923

Molecular Structure of Compound 1-2

[0166]

TABLE 4

Molecular Structure of Compound 1-2 Results

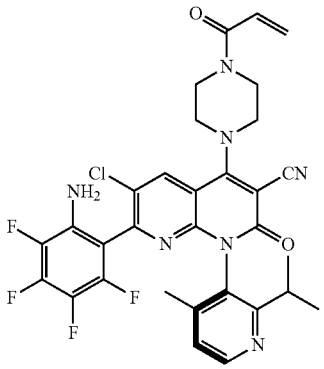
Molecular Absolute Configuration in single crystal	Planar chirality (Axis chirality)	M
Molecular Ball and Stick Model in single crystal	FIG. 1	
Molecular Ellipsoid Model in single crystal	FIG. 2	
Structure of Absolute Configuration		
Unit cell Structure	FIG. 3	
Main Hydrogen Bond In single crystal	FIG. 4	
Proton Transfer in Single crystal	—	

TABLE 4-continued

Molecular Structure of Compound 1-2 Results

Molecular Absolute Configuration in single crystal	Planar chirality (Axis chirality)	M
3D Structure-a Direction Looking From a Direction	Network FIG. 5	
3D Structure-b Direction Looking From b	Chained and Laminated FIG. 6	
3D Structure-c Direction Looking From c Direction	Chained and Laminated FIG. 7	

Crystal Structure Solution Data

[0167]

TABLE 5

Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Compound 1-2. U(eq) is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor.

Atom	x	y	z	U(eq)
C11	6246.0(6)	1711.4(11)	4631.9(9)	90.2(4)
F1	4785.8(15)	2906(3)	3954(3)	117.0(11)
F2	4111.9(15)	1499(4)	2704(3)	136.7(14)
F3	4659(2)	862(4)	1040(3)	148.9(16)
F4	5807(2)	1798(5)	582(2)	153.1(16)
O1	6947.1(19)	8554(3)	4282(3)	103.3(12)
O2	6947(2)	3659(5)	9789(3)	127.4(16)
N1	6087.9(17)	4937(3)	3501(3)	68.6(9)
N2	6491.6(17)	6770(4)	3932(2)	72.5(9)
N3	7296(3)	8781(6)	6695(4)	133(2)
N4	6971.7(18)	5546(4)	6708(3)	76.7(10)
N6	6493(2)	3262(5)	1777(3)	105.7(15)
N7	5536(3)	8178(6)	1965(5)	148(2)
C1	5043(3)	2606(5)	3116(4)	84.7(13)
C2	4701(3)	1929(5)	2488(5)	93.3(16)
C3	4966(3)	1641(6)	1637(4)	100.9(17)
C4	5555(3)	2081(5)	1423(4)	97.7(17)
C5	5901(2)	2829(4)	2034(3)	79.3(13)
C6	5646(2)	3082(4)	2919(3)	71.5(11)
C7	6001(2)	3774(4)	3662(3)	70.8(12)
C8	6264(2)	3232(4)	4494(3)	69.3(11)
C9	6532(2)	3936(4)	5196(3)	70.3(11)
C10	6571(2)	5161(4)	5077(3)	64.6(10)
C11	6846(2)	5977(5)	5801(3)	75.2(13)
C12	6960(2)	7121(4)	5505(3)	73.5(12)
C13	6820(2)	7551(5)	4547(4)	79.2(13)
C14	6379(2)	5597(4)	4184(3)	68.9(11)
C15	7166(3)	8039(6)	6156(4)	94.6(16)
C16	6309(3)	7206(4)	2980(4)	86.0(15)
C17	6749(4)	7054(5)	2262(4)	110(2)
C18	6535(6)	7460(8)	1367(5)	146(3)
C19	5946(6)	8011(11)	1271(7)	166(4)
C20	5716(3)	7763(6)	2858(4)	98.4(17)
C21	5247(3)	7954(6)	3613(5)	114(2)
C23	4722(4)	7012(9)	3532(8)	173(4)
C22	4967(6)	9207(9)	3602(9)	199(4)
C24	7389(4)	6458(7)	2421(6)	142(3)
C25	6453(5)	5039(9)	7253(8)	79(2)
C26	6758(4)	4128(9)	7917(7)	85(2)
N5	7274(4)	4605(7)	8506(6)	85.7(18)
C27	7753(4)	5199(8)	7924(6)	83.4(19)
C28	7476(6)	6148(10)	7310(8)	84(2)
C25'	6610(9)	4538(16)	7194(14)	85(3)
C26'	6480(7)	4955(14)	8202(9)	87(2)
N5'	7092(6)	5244(12)	8726(9)	88.7(18)
C27'	7501(7)	6051(13)	8300(9)	88(2)
C28'	7620(9)	5650(16)	7238(14)	87(3)
C29	7324(3)	4417(7)	9488(4)	109.7(19)
C30	7861(3)	4907(7)	10040(4)	112(2)
C31	8076(4)	4358(8)	10783(5)	128(2)

TABLE 6

Hydrogen Coordinates ($\times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Compound 1-2.

Atom	x	y	z	U(eq)
H6A	6646	3067	1236	127
H6B	6709	3728	2156	127
H9	6691	3591	5761	84
H18	6790	7358	839	175
H19	5823	8293	668	199
H21	5478	7841	4229	137
H23A	4551	6982	2887	259
H23B	4381	7207	3953	259
H23C	4901	6250	3705	259
H22A	4702	9317	3034	299
H22B	5314	9777	3614	299
H22C	4710	9319	4153	299
H24A	7549	6613	3059	214
H24B	7689	6762	1973	214
H24C	7339	5615	2331	214
H25A	6133	4666	6828	95
H25B	6242	5654	7614	95
H26A	6429	3808	8321	102

TABLE 6-continued

Hydrogen Coordinates ($\times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Compound 1-2.

Atom	x	y	z	U(eq)
H26B	6924	3477	7542	102
H27A	7955	4610	7525	100
H27B	8088	5538	8342	100
H28A	7804	6496	6919	101
H28B	7288	6770	7692	101
H25C	6206	4369	6849	102
H25D	6870	3820	7212	102
H26C	6205	5655	8174	104
H26D	6255	4335	8539	104
H27C	7910	6088	8659	106
H27D	7307	6838	8301	106
H28C	7888	6231	6926	104
H28D	7842	4889	7236	104
H30	8050	5618	9856	135
H31A	7886	3647	10965	153
H31B	8423	4669	11143	153

TABLE 7

Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Compound 1-2. The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2 a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C11	104.2(9)	71.6(7)	94.8(9)	11.9(6)	4.1(7)	−1.6(7)
F1	91(2)	142(3)	120(3)	−12(2)	35.8(19)	−15.5(19)
F2	93(2)	156(3)	159(3)	23(3)	−15(2)	−45(2)
F3	178(3)	164(3)	101(3)	13(2)	−45(2)	−73(3)
F4	175(3)	205(4)	80(2)	−41(3)	9(2)	−65(3)
O1	116(3)	81(2)	113(3)	11(2)	−1(2)	−27(2)
O2	126(3)	181(5)	76(3)	27(3)	11(2)	−32(3)
N1	72(2)	63(2)	71(2)	3.0(17)	4.7(19)	−2.8(17)
N2	83(2)	75(2)	60(2)	12.0(19)	3.0(18)	−11(2)
N3	137(5)	136(5)	125(5)	−46(4)	7(4)	−27(4)
N4	75(2)	96(3)	59(2)	2.3(18)	5.7(19)	−17(2)
N6	97(3)	155(4)	66(3)	−17(3)	19(2)	−41(3)
N7	140(5)	166(6)	137(5)	70(5)	−27(4)	−38(4)
C1	80(3)	90(3)	85(4)	2(3)	12(3)	−4(3)
C2	72(3)	93(4)	113(4)	19(3)	−14(3)	−25(3)
C3	107(4)	109(4)	85(4)	15(3)	−33(3)	−27(4)
C4	109(4)	128(5)	55(3)	−7(3)	−6(3)	−19(3)
C5	89(3)	87(3)	62(3)	5(2)	0(3)	−11(3)
C6	75(3)	73(3)	66(3)	−1(2)	5(2)	−12(2)
C7	68(3)	76(3)	70(3)	2(2)	21(2)	0(2)
C8	77(3)	60(3)	71(3)	15(2)	7(2)	−1(2)
C9	68(3)	80(3)	62(3)	2(2)	9(2)	−2(2)
C10	68(3)	68(3)	58(2)	9.1(18)	5(2)	−3(2)
C11	64(3)	98(4)	64(3)	−4(2)	11(2)	−12(2)
C12	68(3)	84(3)	70(3)	−9(2)	9(2)	−18(2)
C13	73(3)	83(3)	82(3)	3(3)	6(2)	−15(3)
C14	69(3)	65(3)	73(3)	2(2)	20(2)	−10(2)
C15	95(4)	102(4)	88(4)	−12(3)	15(3)	−10(3)
C16	111(4)	78(3)	69(3)	15(2)	1(3)	−22(3)
C17	155(6)	101(4)	76(4)	20(3)	29(4)	−26(4)
C18	219(10)	138(6)	82(5)	28(4)	21(6)	−29(6)
C19	186(9)	200(10)	111(7)	70(6)	−19(7)	−54(8)
C20	95(4)	110(4)	90(4)	35(3)	−6(3)	−22(3)
C21	85(4)	111(5)	145(6)	29(4)	2(4)	1(3)
C23	101(5)	180(9)	239(10)	−11(7)	35(6)	−29(5)
C22	213(10)	132(7)	252(12)	30(7)	−6(9)	37(7)
C24	162(6)	114(6)	156(7)	6(4)	67(5)	10(5)
C25	72(5)	94(5)	71(5)	14(4)	9(4)	−14(4)
C26	79(5)	95(5)	81(5)	13(4)	7(4)	−16(4)
N5	92(4)	91(5)	74(4)	12(3)	8(3)	−7(4)
C27	88(5)	97(5)	65(4)	0(4)	0(4)	−16(4)
C28	87(5)	97(6)	67(5)	−2(4)	0(4)	−15(4)
C25'	90(6)	93(6)	72(6)	7(5)	12(5)	−12(5)

TABLE 7-continued

Anisotropic Displacement Parameters ($Å^2$ × 10^3) for Compound 1-2. The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2 a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C26'	92(5)	95(5)	74(5)	7(4)	11(4)	−8(4)
N5'	97(4)	95(5)	75(4)	8(4)	7(3)	−9(4)
C27'	97(5)	93(5)	75(5)	8(4)	5(4)	−12(4)
C28'	95(6)	91(6)	75(6)	7(5)	3(5)	−16(5)
C29	107(5)	150(6)	72(4)	10(3)	11(3)	−23(4)
C30	138(6)	131(5)	68(4)	3(3)	−1(4)	−18(4)
C31	129(6)	164(6)	90(5)	−6(4)	9(4)	−4(5)

[0168] The following conclusions were obtained by crystal structure analysis:

[0169] The crystal system of Compound 1-2 is monoclinic and has two symmetries and one centering vector, space group is C_2.

[0170] The single crystal of Compound 1-2 have four molecules in a unit cell.

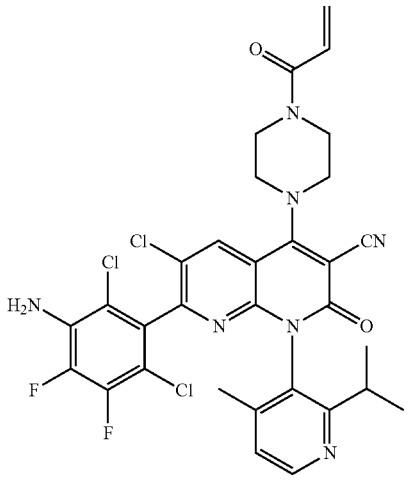
[0171] Compound 1-2 has one planar chirality (axis chirality). Absolute configuration is M.

[0172] Unit cell has two kinds of hydrogen bonds, they are respectively O2-H6A-N6, N3-H6B—N6. The three-dimensional structure of the chain, laminate and network is formed through hydrogen bond and van der Waals force in the crystal.

Example 2

4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,6-dichloro-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 2")

[0173]



Step 1. 2-(3,4-difluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0174] Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 5-bromo-1,2-difluoro-3-nitrobenzene (207 mg, 0.38 mmol), bis(pinacolato)diboron (2.16 g, 8.51 mmol), $Pd(dppf)Cl_2$ (0.322 g, 0.44 mmol), KOAc (1.199 g, 12.22 mmol) and dioxane (10 mL). The reaction mixture was stirred at 100° C. for 2 h. The reaction mixture was filtered and concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v/v=0%-5%). This resulted in 1.528 g (crude) of 2-(3,4-difluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as off-white solid.

Step 2. 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0175] Into a 40-mL round-bottom flask was placed 2-(3,4-difluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.489 g, 5.22 mmol), iron (1.546 g, 27.68 mmol), NH_4Cl (2.654 g, 49.62 mmol), EtOH (15 mL) and H_2O (5 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was washed with DCM (20 mL), filtered and concentrated under vacuum. This resulted in 0.957 g of 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as off-white solid. LCMS: m/z=256 $[M+1]^+$.

Step 3. 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0176] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.21 g, 0.41 mmol), 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.279 g, 1.09 mmol), $Pd(PPh_3)_4$ (57 mg, 0.05 mmol), Na_2CO_3 (206 mg, 1.94 mmol), dioxane (5 mL) and water (1 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v/v=50%-100%). This resulted in 125 mg of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=604 $[M+1]^+$.

Step 4. 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,6-dichloro-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 2")

[0177] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed

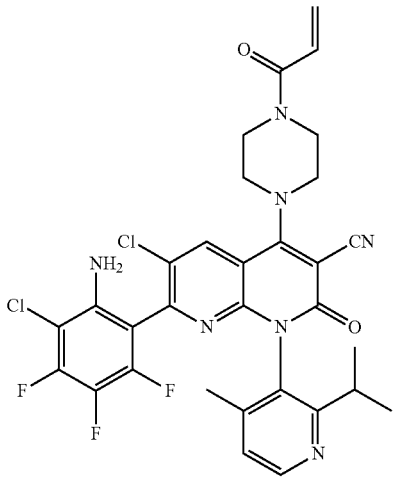
4-(4-acryloylpiperazin-1-yl)-7-(3-amino-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (103 mg, 170.52 μmop, NCS (51 mg, 381.93 μmop and DMA (1.5 mL). The reaction mixture was stirred for 15 h at room temperature. The reaction was then quenched by the addition of H_2O (20 mL). The resulting solution was extracted with ethyl acetate (3×20 mL), the organic layers were combined and concentrated under vacuum. The residues was purified by prep-HPLC eluted with CH_3CN/H_2O (v/v=7/1). This resulted in 30 mg (26%) of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,6-dichloro-4,5-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 2"). LCMS: m/z=672 $[M+1]^+$.

[0178] ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.40 (d, J=5.0 Hz, 1H), 7.29-7.15 (m, 1H), 6.87 (dd, J=16.8, 10.6 Hz, 1H), 6.30 (d, J=16.8 Hz, 1H), 5.83 (d, J=10.7 Hz, 1H), 4.30-3.77 (m, 8H), 2.85-2.66 (m, 1H), 1.99 (s, 3H), 1.18 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H).

Example 3

4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 3")

[0179]



Step 1. 2-bromo-3,4,5-trifluoroaniline

[0180] Into a 100-mL round-bottom flask was placed 2-bromo-3,4,5-trifluoro-1-nitrobenzene (2.64 g, 10.31 mmol), iron (5.71 g, 102.25 mmol), ammonium chloride (5.67 g, 106.00 mmol), ethanol (25 mL) and water (25 mL). The reaction mixture was heated to 55° C. and stirred for 1.5 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residues was dissolved in ethanol (30 mL) and applied onto a C_{18} column eluted with CH_3CN/H_2O (v:v=9:1). This resulted in 1.33 g (57%) of 2-bromo-3,4,5-trifluoroaniline LCMS: m/z=226, 228 $[M+1]^+$.

Step 2. 3,4,5-trifluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0181] Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2-bromo-3,4,5-trifluoroaniline (2.99 g, 13.23 mmol), bis(pinacolato) diboron (10.20 g, 40.17 mmol), $Pd(dppf)Cl_2$ (0.98 g, 1.34 mmol), KOAc (4.18 g, 42.59 mmol) and dioxane (40 mL). The reaction mixture was stirred at 100° C. for 5 h. The reaction mixture was concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v/v=0%-10%). This resulted in 5.34 g (crude) of 3,4,5-trifluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline.

Step 3. 4-(4-acryloylpiperazin-1-yl)-7-(6-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0182] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.547 g, 1.08 mmol), 3,4,5-trifluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.279 g, 1.09 mmol), $Pd(PPh_3)_4$ (1.376 g, 5.04 mmol), Na_2CO_3 (0.347 g, 3.27 mmol), dioxane (5 mL) and water (1 mL). The reaction mixture was stirred at 80° C. for 4 h. The reaction mixture was filtered and concentrated under vacuum. The residue was applied onto a silica gel column eluted with EA/hexane (v/v=50%-100%). This resulted in 115 mg of 4-(4-acryloylpiperazin-1-yl)-7-(6-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=622 $[M+1]^+$.

Step 4. 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 3")

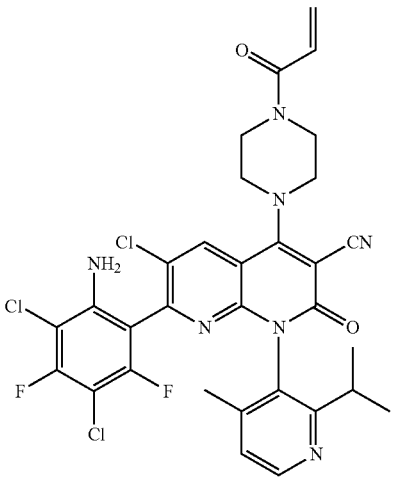
[0183] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-7-(6-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (100 mg, 160.76 μmol), NCS (0.035 g, 262.11 μmol) and AcOH (1 mL). The reaction mixture was stirred for 7 h at 35° C. and 15 h at room temperature. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The resulting solution was extracted with ethyl acetate (2×10 mL), the organic layers were combined and concentrated under vacuum. The residues was purified by prep-HPLC eluted with CH_3CN/H_2O (v/v=6/1). This resulted in 6 mg (5%) of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 3") as yellow solid. LCMS: m/z=656 $[M+1]^+$.

[0184] ^1H NMR (400 MHz, CD_3OD) δ 8.66-8.51 (m, 1H), 8.43 (d, J=5.1 Hz, 1H), 7.26 (d, J=5.1 Hz, 1H), 6.88 (dd, J=16.8, 10.7 Hz, 1H), 6.31 (d, J=16.7 Hz, 1H), 5.84 (d, J=10.7 Hz, 1H), 4.06-3.92 (m, 8H), 2.84-2.62 (m, 1H), 2.06-1.92 (m, 3H), 1.17 (dd, J=9.6, 7.0 Hz, 3H), 1.06-0.94 (m, 3H).

Example 4

4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 4")

[0185]



Step 1. 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0186] Into a 100-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2-bromo-3,5-difluoroaniline (3.01 g, 14.47 mmol), bis(pinacolato) diboron (6.46 g, 25.43 mmol), $Pd(dppf)Cl_2$ (1.03 g, 1.41 mmol), KOAc (4.20 g, 42.83 mmol), dioxane (20 mL). The reaction mixture was stirred at 80° C. for 12 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=1/19). This resulted in 6.01 g (crude) of 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as yellow oil. LCMS: m/z=256 $[M+1]^+$.

Step 2. tert-butyl 4-(7-(2-amino-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl) piperazine-1-carboxylate

[0187] Into a 100-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (5.86 g, 23.00 mmol), tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (1.29 g, 2.31 mmol), $Pd(PPh_3)_4$ (0.73 g, 0.63 mmol), Na_2CO_3 (0.84 g, 7.89 mmol), dioxane (15 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 2 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=1/1). This resulted in 1.42 g (crude) of tert-butyl 4-(7-(2-amino-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as yellow solid. LCMS: m/z=650 $[M+1]^+$.

Step 3. tert-butyl 4-(7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate

[0188] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl 4-(7-(2-amino-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (1.21 g, 1.87 mmol), NCS (0.49 g, 3.73 mmol) and AcOH (30 mL). The reaction mixture was stirred for 48 h at room temperature. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (2×100 mL), the organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=1/1). This resulted in 0.53 g (crude) of tert-butyl 4-(7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate as yellow solid. LCMS: m/z=718[M+1]$^+$.

Step 4. 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 4")

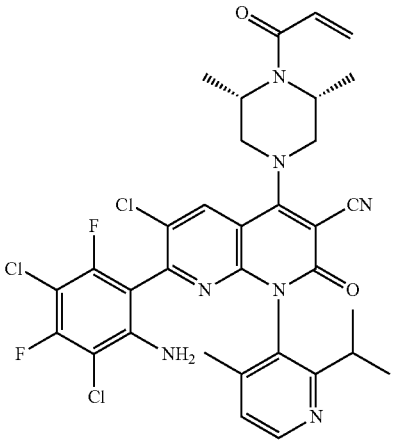
[0189] Into a 20-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl 4-(7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-3-cyano-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate (0.53 g, 0.73 mmol), TFA (5 ml) and DCM (20 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The residue was dissolved by DCM (10 mL) in 25-mL round-bottom flask. DIEA (1.22 g, 9.48 mmol) was added. The reaction mixture was cooled to 0° C. and acryloyl chloride (0.08 g, 0.88 mmol) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC (CH_3CN/H_2O (v/v=7/3)). This resulted in 239 mg (50% in two steps) of 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 4") as yellow solid. LCMS: m/z=672 $[M+1]^+$.

[0190] ^1H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.43 (s, 1H), 7.26 (s, 1H), 6.87 (dd, J=16.1, 11.1 Hz, 1H), 6.31 (d, J=16.3 Hz, 1H), 5.84 (d, J=10.1 Hz, 1H), 4.25-3.75 (m, 8H), 2.85-2.60 (m, 1H), 2.14-1.88 (m, 3H), 1.25-0.87 (m, 6H).

Example 5

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 5")

[0191]



Step 1. 4-((3R,5S)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (Intermediate D)

[0192] Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (6.21 g, 15.95 mmol), $POCl_3$ (6.88 g, 48.87 mmol), DIEA (6.80 g, 52.61 mmol) and acetonitrile (100 mL). The mixture was stirred for 2 h at 80° C. The reaction was cooled to room temperature and concentrated under vacuum. This resulted in 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile which was used directly in the next step.

[0193] Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (crude), DIEA (6.80 g, 52.61 mmol) and acetonitrile (100 mL), (2S,6R)-2,6-dimethylpiperazine (2.17 g, 19.00 mmol) was added. The mixture was stirred for 1 h at room temperature. The resulting solution was concentrated under vacuum and applied onto a silica gel column eluted with EA/hexane (v/v=2/1). This resulted in 4.30 g (50% yield) of 4-((3R,5S)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=539 $[M+1]^+$.

Step 2. 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0194] Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2-bromo-3,5-difluoroaniline (2.06 g, 9.91 mmol), bis(pinacolato)diboron (4.95 g, 19.49 mmol), $Pd(dppf)Cl_2$ (809 mg, 1.11 mmol), KOAc (2.23 g, 22.69 mmol), dioxane (20 mL). The reaction mixture was stirred at 100° C. for 19 h. The reaction mixture was concentrated under vacuum. The residue was applied onto a C_{18} column eluted with CH_3CN/H_2O (v/v=5%-100%). This resulted in 1.19 g of 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as off-white solid. LCMS: m/z=256 $[M+1]^+$.

Step 3. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile

[0195] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile (0.196 g, 0.36 mmol), 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.27 g, 1.06 mmol), $Pd(PPh_3)_4$ (78 mg, 0.07 mmol), Na_2CO_3 (207 mg, 1.95 mmol), dioxane (5 mL) and water (1 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residues was applied onto a silica gel column eluted with EA/hexane (v/v=50%-100%). This resulted in 223 mg of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile as yellow solid. LCMS: m/z=632 $[M+1]^+$.

Step 4

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile ("Compound 5")

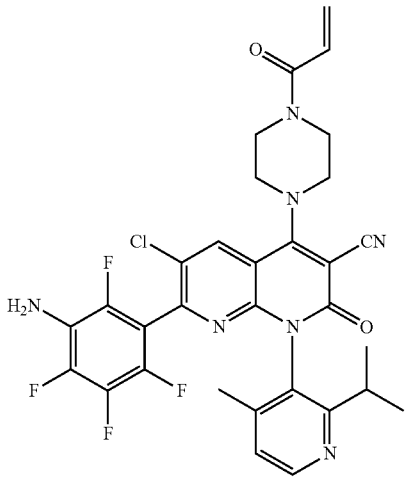
[0196] Into a 20-mL round-bottom flask was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile (223 mg, 0.35 mmol), NCS (98 mg, 0.73 mmol) and HOAc (3 mL). The reaction mixture was stirred at room temperature for 1 day. The reaction was heated to 45° C. and stirred at this temperature for 2 hours. The reaction mixture was concentrated under vacuum. The residues was purified by Prep-HPLC CH_3CN/H_2O (0.05% NH_4HCO_3) (v/v=2/1). This resulted in 55 mg (22%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,5-dichloro-4,6-difluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile ("Compound 5") as yellow solid. LCMS: m/z=700 $[M+1]^+$.

[0197] ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.43 (d, J=5.0 Hz, 1H), 7.27 (d, J=5.0 Hz, 1H), 6.95-6.82 (m, 1H), 6.33 (d, J=16.5 Hz, 1H), 5.84 (d, J=10.8 Hz, 1H), 4.77 (s, 2H), 4.13-3.92 (m, 2H), 3.84 (d, J=9.4 Hz, 2H), 2.80-2.60 (m, 1H), 2.08-1.93 (m, 3H), 1.72-1.59 (m, 6H), 1.25-1.10 (m, 3H), 1.10-0.89 (m, 3H).

Example 6

4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 6")

[0198]



Step 1. 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0199] Into a 30-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.039 g, 2.04 mmol), 1,1,1,2,2,2-Hexabutyldistannane (4.124 g, 7.11 mmol), $Pd(PPh_3)_4$ (0.566 g, 0.49 mmol) and dioxane (10 mL). The reaction mixture was stirred at 100° C. for 1 d. The reaction mixture was filtered and concentrated under vacuum. The residues was purified by silica gel column eluted with EA/hexane (v/v=2/1). This resulted in 273 mg (17%) of 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=767 $[M+1]^+$.

Step 2. 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 6")

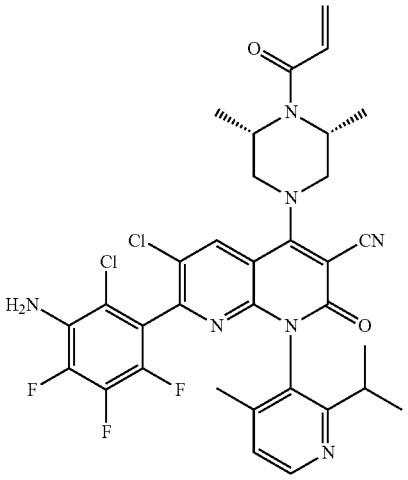
[0200] Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.272 g, 0.36 mmol), 2,3,4,6-tetrafluoro-5-iodoaniline (0.630 g, 2.17 mmol), $Pd(PPh_3)_4$ (0.187 g, 0.16 mmol), cuprous iodide (0.294 g, 1.54 mmol), dioxane (10 mL). The reaction mixture was stirred at 100° C. for 1 d. The reaction mixture was filtered and concentrated under vacuum. The residues was purified by prep-HPLC eluted with ACN/H_2O (v/v=1/2). This resulted in 6 mg (3%) of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 6") as yellow solid. LCMS: m/z=640 $[M+1]^+$.

[0201] ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.42 (d, J=4.9 Hz, 1H), 7.31-7.20 (m, 1H), 6.87 (dd, J=16.7, 10.6 Hz, 1H), 6.30 (dd, J=16.8, 1.7 Hz, 1H), 5.83 (dd, J=10.6, 1.8 Hz, 1H), 4.08-3.87 (m, 8H), 2.79-2.62 (m, 1H), 2.00 (s, 3H), 1.17 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H).

Example 7

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 7")

[0202]



Step 1. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0203] Into a 30-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.822 g, 1.52 mmol), (5-amino-2,3,4-trifluorophenyl) boronic acid (0.608 g, 2.23 mmol), $Pd(PPh_3)_4$ (0.650 g, 0.56 mmol), Na_2CO_3 (0.575 g, 5.43 mmol), dioxane (10 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=2/1). This resulted in 1.079 g (91%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=650 $[M+1]^+$.

Step 2. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 7")

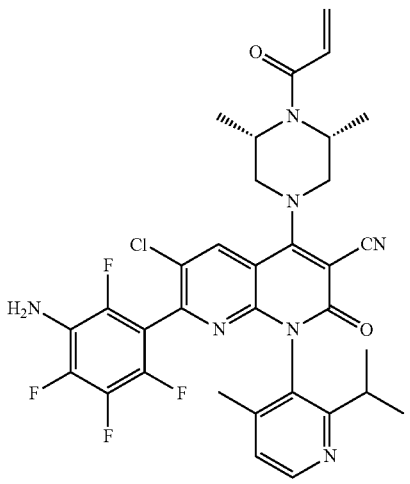
[0204] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.622 g, 0.96 mmol), NCS (0.703 g, 5.27 mmol), and AcOH (5 mL). The mixture was stirred at r.t. for 2 d. The reaction was then quenched by the addition of water (10 mL). The resulting solution was extracted with ethyl acetate (3×10 mL), the organic layers were combined and washed with brine (1×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residues was purified by Prep-HPLC (CH_3CN/H_2O (v/v=6/4)). This resulted in 35 mg (5%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 7") as yellow solid. LCMS: m/z=684 $[M+1]^+$.

[0205] ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.42 (d, J=5.0 Hz, 1H), 7.22-7.10 (m, 1H), 6.88 (dd, J=16.7, 10.7 Hz, 1H), 6.32 (d, J=16.5 Hz, 1H), 5.74 (dd, J=10.6, 2.0 Hz, 1H), 4.76 (s, 2H), 4.06-3.73 (m, 4H), 2.82-2.69 (m, 1H), 2.10-1.94 (m, 3H), 1.63-1.35 (m, 6H), 1.17 (d, J=6.5 Hz, 3H), 1.06-0.89 (m, 3H).

Example 8

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 8")

[0206]



Step 1. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0207] Into a 20-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6,7-dichloro-4-((3 S,5R)-3,5-dimethylpiperazin-1-yl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (6.503 g, 13.39 mmol), DIEA (5.21 g, 40.31 mmol), DCM (6 mL) and acryloyl chloride (1.18 g, 13.04 mmol). The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=1/1). This resulted in 1.80 g (crude) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=539 $[M+1]^+$.

Step 2. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0208] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.77 g, 3.28 mmol), hexabutyldistannane (23.85 g, 6.64 mmol), $Pd(PPh_3)_4$ (0.26 g, 0.23 mmol) and dioxane (20 mL). The reaction mixture was stirred at 110° C. for 18 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=2/1). This resulted in 0.52 g (crude) of 4-((3 S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=795 $[M+1]^+$.

Step 3. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile. ("Compound 8")

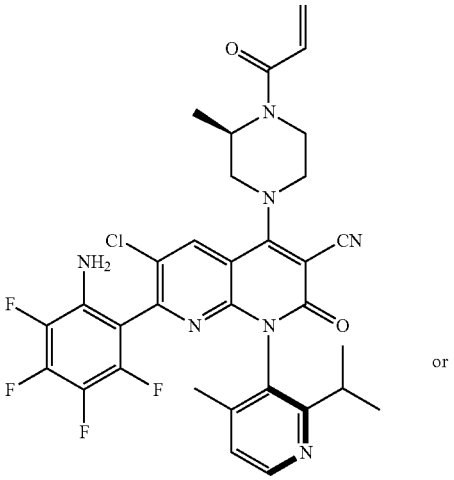
[0209] Into a 20-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-7-(tributylstannyl)-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.40 g, 0.51 mmol), 2,3,4,6-tetrafluoro-5-iodoaniline (0.27 g, 0.93 mmol), $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol), CuI (0.40 g, 2.11 mmol), DMA (15 mL). The reaction mixture was stirred at 90° C. for 18 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC (CH_3CN/H_2O (v/v=7/3)). This resulted in 8 mg (2.3% in two steps) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(3-amino-2,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 8") as yellow solid. LCMS: m/z=668 $[M+1]^+$.

[0210] ^1H NMR (400 MHz, CD_3OD) δ 8.73 (s, 1H), 8.34 (d, J=5.0 Hz, 1H), 7.23-7.15 (m, 1H), 6.79 (dd, J=16.7, 10.7 Hz, 1H), 6.23 (dd, J=16.7, 2.0 Hz, 1H), 5.74 (dd, J=10.6, 2.0 Hz, 1H), 4.73-4.58 (m, 2H), 3.95-3.70 (m, 4H), 2.66-2.57 (m, 1H), 1.93 (d, J=8.4 Hz, 3H), 1.55-1.57 (m, 6H), 1.07 (d, J=6.8 Hz, 3H), 0.89 (d, J=5.7 Hz, 3H).

Example 9

(P)-4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; or (M)-4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; ("Compound 9")

[0211]



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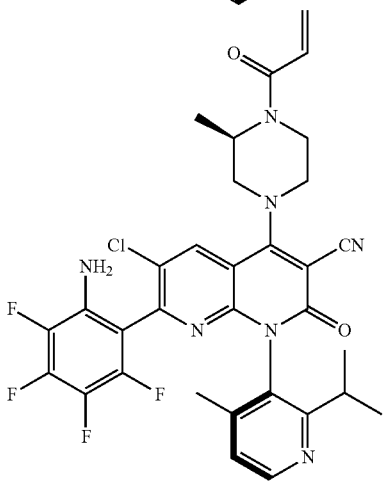


Step 1. 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0212] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-cyano-N-(2-isopropyl-4-methylpyridin-3-yl)-3-oxo-3-(2,5,6-trichloropyridin-3-yl)propanamide (5.89 g, 13.83 mmol) and THF (70 mL), the mixture was stirred at room temperature. This was followed by the addition of NaH (2.73 g, 68.25 mmol) in batch-wise. The mixture was stirred at 50° C. for 2 h. The reaction mixture was concentrated under vacuum. The residue was dissolved in 100 mL water and adjusted pH to 7 with AcOH. The resulting solid was filtered and dried under vacuum to provide 5.85 g (108% in two steps) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=389 $[M+1]^+$.

[0213] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J=5.7 Hz, 1H), 8.38 (s, 1H), 7.89 (d, J=5.4 Hz, 1H), 3.01-2.88 (m, 1H), 2.19 (s, 3H), 1.21 (d, J=6.9 Hz, 3H), 1.14 (d, J=6.9 Hz, 3H).

[0214] The mixture of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (10.59 g, "Intermediate B", several batches) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IC, 3.0×100 mm, 3 μm; mobile phase, IPA/ACN=1/1(V/V); Detection wavelength, UV 210 nm. This resulted in 4.99 g (47%) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Intermediate B-1", M or P atropisomer) as a brown solid;

[0215] ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.33-7.22 (m, 1H), 2.76-2.61 (m, 1H), 2.03 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H).

[0216] And 4.60 g (43%) of 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Intermediate B-2", P or M atropisomer) as a brown solid;

[0217] ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.28 (d, J=5.0 Hz, 1H), 2.76-2.63 (m, 1H), 2.03 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.079-1.00 (m, 3H).

Step 2. tert-butyl (R)-4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)-2-methylpiperazine-1-carboxylate (Single Isomer)

[0218] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer in step 1) (1.05 g, 2.71 mmol), $POCl_3$ (2.04 g, 13.27 mmol), DIEA (3.09 g, 23.93 mmol) and acetonitrile (20 mL). The mixture was stirred at 80° C. for 2 h. The reaction was cooled to room temperature and concentrated under vacuum. This resulted in 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile which was used directly in the next step.

[0219] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (crude) and acetonitrile (10 mL), DIEA (3.09 g, 23.93 mmol) and tert-butyl (R)-2-methylpiperazine-1-carboxylate (507 mg, 2.53 mmol) were added. The reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (3×50 mL), the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=5/4). This resulted in 0.95 g (65% in two steps) of tert-butyl (R)-4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthy-

ridin-4-yl)-2-methylpiperazine-1-carboxylate (single isomer, P or M) as red solid. LCMS: m/z=571 $[M+1]^+$.

Step 3. (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0220] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl (R)-4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)-2-methylpiperazine-1-carboxylate (P or M isomer, 1.01 g, 1.767 mmol), DCM (8 mL) and TFA (4.605 g, 40.386 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum. The residue was dissolved by DCM (10 mL) into a 50 mL round-bottom flask, triethylamine (1.30 g, 12.85 mmol) was added. The reaction mixture was cooled to 0° C. and acryloyl chloride (0.23 g, 2.541 mmol) was added. The mixture stirred at room temperature for 0.5 h. The reaction was then quenched by the addition of water (20 mL). The resulting solution was extracted with ethyl acetate (3×20 mL), the organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residues was purified by Prep-HPLC CH_3CN/H_2O (v/v=3/2). This resulted in 1.46 g (crude) of (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (P or M isomer) as yellow solid. LCMS: m/z=525 $[M+1]^+$.

Step 4. 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (P or M Isomer, "Compound 9")

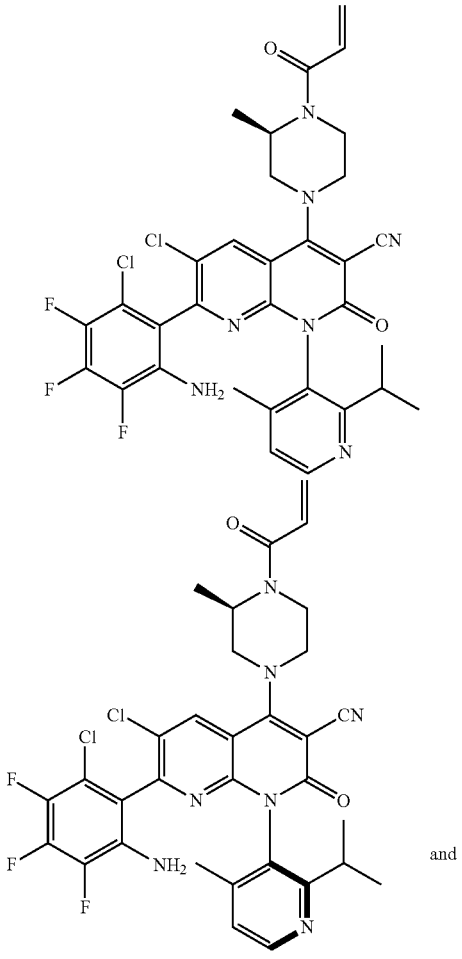
[0221] Into a 100 mL round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (P or M isomer, 1.64 g, 3.11 mmol), (2-amino-3,4,5,6-tetrafluorophenyl)boronic acid (1.37 g, 6.57 mmol), $Pd(PPh_3)_4$ (0.37 g, 315.86 μmop, Na_2CO_3 (1.11 g, 10.49 mmol), 1,4-Dioxane (15 mL) and Water (2 mL). The resulting mixture was stirred at 80° C. for 30 min. Three batches of (2-amino-3,4,5,6-tetrafluorophenyl)boronic acid (2.84 g, 13.59 mmol) was added in 3 h. After the reaction was completed, the reaction was evaporated under vacuum and applied onto a silica gel column eluted with EA/Hexane (v/v=7/3), the crude was purified by HPLC eluted with CH_3CN/H_2O (v/v=3/2), this resulted in (784 mg, 38.50%) of 7-(2-amino-3,4,5,6-tetrafluoro-phenyl)-6-chloro-1-(2-isopropyl-4-methyl-3-pyridyl)-4-[(3R)-3-methyl-4-prop-2-enoyl-piperazin-1-yl]-2-oxo-1,8-naphthyridine-3-carbonitrile (P or M isomer, "Compound 9") as light yellow solid. LCMS: m/z=654 $[M+1]^+$.

[0222] ^1H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.42-8.31 (m, 1H), 7.23 (d, J=5.0 Hz, 1H), 6.76 (dd, J=16.7, 10.7 Hz, 1H), 6.20 (dd, J=16.7, 1.8 Hz, 1H), 5.73 (dd, J=10.6, 1.9 Hz, 1H), 4.40 (s, 1H), 4.18-4.10 (m, 2H), 3.94-3.83 (m, 2H), 3.65-3.54 (m, 2H), 2.64-2.51 (m, 1H), 2.06-1.92 (m, 3H), 1.44-1.30 (m, 3H), 1.10-1.03 (m, 3H), 0.96-0.81 (m, 3H).

Example 10

4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 10"); (P)-4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; and (M)-4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0223]



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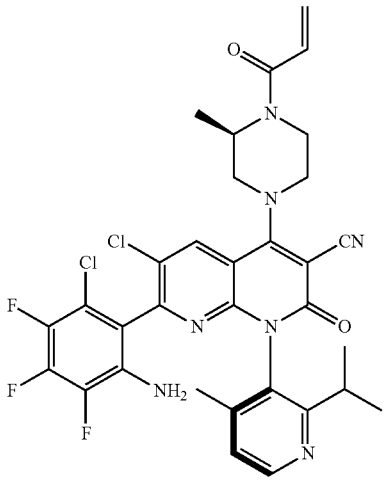


Step 1. (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0224] Into a 20-mL round-bottom flask was placed (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.114 g, 2.12 mmol), (2-amino-3,4,5-trifluorophenyl)boronic acid (0.787 g, 4.12 mmol), $Pd(PPh_3)_4$ (0.527 g, 0.45 mmol), Na_2CO_3 (0.652 g, 6.15 mmol), dioxane (15 mL) and water (3 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC CH_3CN/H_2O (0.05% NH_4HCO_3) (v/v=2/1). This resulted in 1.941 g (69%) of (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=636 $[M+1]^+$.

Step 2. 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 10")

[0225] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.904 g, 3.00 mmol), NCS (0.946 g, 6.17 mmol) and AcOH (5 mL). The mixture was stirred at r.t. for 1 d. The residue was purified by Prep-HPLC (CH_3CN/H_2O)(v/v=6/4). This resulted in 0.497 g (25%) of 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 10") as yellow solid. LCMS: m/z=670 $[M+1]^+$.

Step 3. 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting isomer, "Compound 10-1") & 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting isomer, "Compound 10-2")

[0226] The mixture of 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (495 mg) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRAL ART Cellulose-SB, 3 cm×25 cm, Sum; mobile phase, (Hex:DCM=3:1): EtOH (v/v=90:10); Detection wavelength, UV 220 nm. This resulted in 204 mg (41.21%) of 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Compound 10-1") as a yellow solid. LCMS: m/z=670 $[M+1]^+$.

[0227] ^1H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.41 (dd, J=5.0, 1.4 Hz, 1H), 7.23 (dd, J=8.4, 3.2 Hz, 1H), 6.85 (dd, J=16.7, 10.7 Hz, 1H), 6.29 (dd, J=16.8, 1.8 Hz, 1H), 5.82 (dd, J=10.6, 1.9 Hz, 1H), 4.88 (s, 2H), 4.60 (s, 1H), 4.29-4.22 (m, 1H), 4.09-3.90 (m, 2H), 3.62 (s, 1H), 2.89-2.70 (m, 1H), 1.95 (d, J=12.6 Hz, 3H), 1.45 (d, J=6.5 Hz, 3H), 1.18 (t, J=8.0 Hz, 3H), 1.00 (dd, J=12.5, 6.8 Hz, 3H).

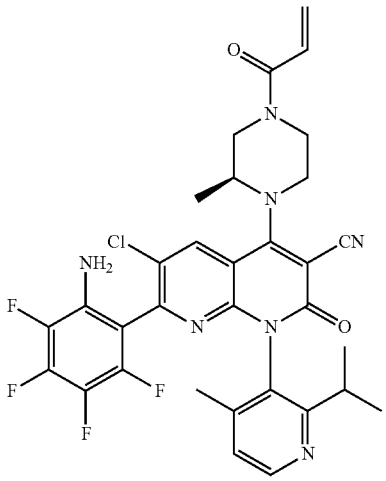
[0228] And 170 mg (28.34%) of 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-6-chloro-3,4,5-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 10-2") as a yellow solid. LCMS: m/z=670 $[M+1]^+$.

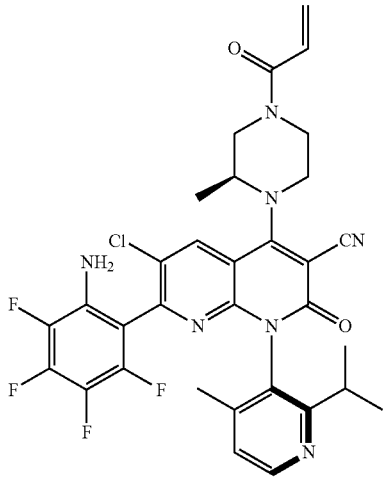
[0229] ^1H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.41 (d, J=5.0 Hz, 1H), 7.34-7.17 (m, 1H), 6.85 (dd, J=16.7, 10.7 Hz, 1H), 6.29 (dd, J=16.8, 1.8 Hz, 1H), 5.82 (dd, J=10.6, 1.9 Hz, 1H), 4.88 (s, 2H), 4.60 (s, 1H), 4.27-4.18 (m, 1H), 4.00 (s, 2H), 3.73-3.56 (m, 1H), 2.77-2.49 (m, 1H), 2.05 (d, J=10.4 Hz, 3H), 1.46 (d, J=6.5 Hz, 3H), 1.16 (dd, J=6.8, 1.3 Hz, 3H), 1.06-0.84 (m, 3H).

Example 11

4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 11"); (P)-4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; and (M)-4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0230]





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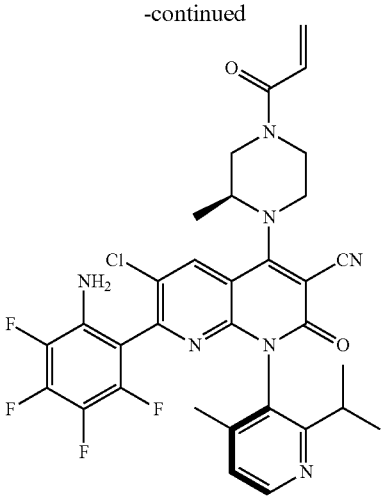


Step 1. 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 11")

[0231] Into a 20-mL round-bottom flask was placed (S)-4-(4-acryloyl-2-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.311 g, 0.59 mmol), (2-amino-3,4,5,6-tetrafluorophenyl)boronic acid (0.512 g, 1.49 mmol), $Pd(PPh_3)_4$ (0.085 g, 0.073 mmol), Na_2CO_3 (0.126 g, 1.19 mmol), dioxane (8 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC CH_3CN/H_2O (0.05% NH_4HCO_3)(v/v=2/1). This resulted in 135 mg (35%) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid ("Compound 11"). LCMS: m/z=654 $[M+1]^+$.

Step 2. 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting isomer, "Compound 11-1") & 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting isomer, "Compound 11-2")

[0232] The mixture of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (135 mg) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IF, 2 cm×25 cm, 5 um mobile phase, ((Hex:DCM=3:1):IPA=80:20; Detection wavelength, UV 220 nm. This resulted in 67 mg (49%) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

(the first eluting isomer, "Compound 11-1") as a yellow solid. LCMS: m/z=654 $[M+1]^+$.

[0233] ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.43-8.44 (m, 1H), 7.26 (t, J=5.5 Hz, 1H), 7.02-6.77 (m, 1H), 6.33 (d, J=16.2 Hz, 1H), 5.85 (d, J=10.5 Hz, 1H), 4.67-4.39 (m, 2H), 4.17-4.18 (m, 3H), 3.78-3.56 (m, 2H), 2.81-2.83 (m, 1H), 1.93-1.94 (m, 3H), 1.38-1.40 (m, 3H), 1.18-1.19 (m, 3H), 1.01-1.04 (m, 3H).

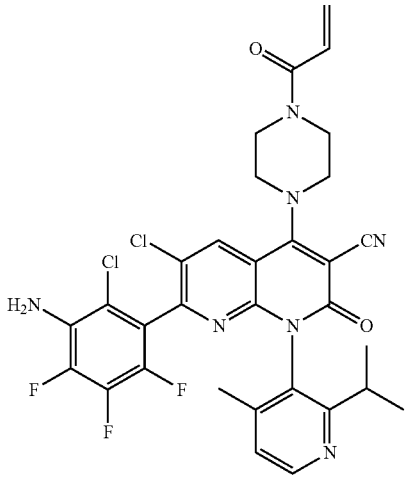
[0234] And 61 mg (45%) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 11-2") as a yellow solid. LCMS: m/z=654 $[M+1]^+$.

[0235] ^1H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.43-8.44 (m, 1H), 7.29-7.25 (m, 1H), 6.85-6.86 (m, 1H), 6.33 (d, J=15.3 Hz, 1H), 5.85 (d, J=10.7 Hz, 1H), 4.53-4.54 (m, 2H), 4.16-4.17 (m, 3H), 3.65-3.67 (m, 2H), 2.58-2.59 (m, 1H), 2.16-2.02 (m, 3H), 1.38-1.40 (m, 3H), 1.19-1.11 (m, 3H), 0.98-0.99 (m, 3H).

Example 12

4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 12"); (P)-4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; and (M)-4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0236]



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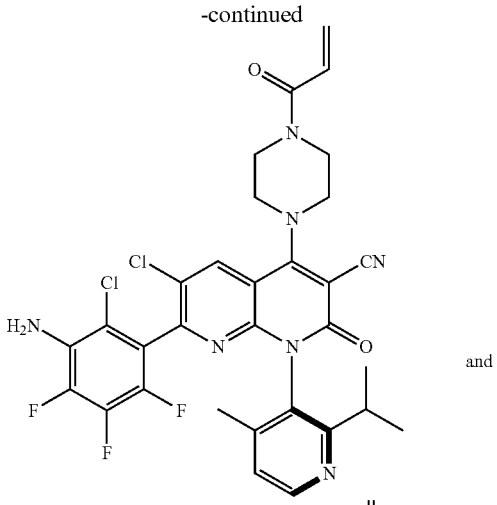

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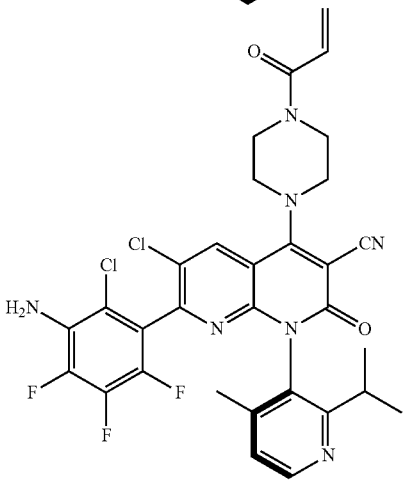


Step 1. 2,3,4-trifluoro-1-iodo-5-nitrobenzene

[0237] Into a 250-mL three-neck bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,2,3-trifluoro-4-nitrobenzene (4.98 g, 28.12 mmol), N-iodosuccinimide (15.99 g, 71.07 mmol), trifluoromethanesulfonic acid (25 mL) and stirred. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of water (200 mL) slowly. The resulting solution was extracted with EA (2×100 mL), the organic layers were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, the residue was concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with ACN/H_2O (v/v=0%100%). This resulted in 4.66 g (54.69% yield) of 2,3,4-trifluoro-1-iodo-5-nitrobenzene.

Step 2. 2,3,4-trifluoro-5-iodoaniline

[0238] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2,3,4-trifluoro-1-iodo-5-nitrobenzene (4.66 g, 15.38 mmol), Fe iron (5.02 g, 89.93 mmol), ammonium chloride (8.57 g, 160.25 mmol), EtOH (30 mL) and water (30 mL). The reaction mixture was stirred at 55° C. for 1 h. The reaction was filtered and the filter cake was washed with EA (2×20

mL). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4. The resulting solution was concentrated under vacuum and applied onto a silica gel column eluted with EA/hexane (v/v=1/1). This resulted in 3.69 g (87% yield) of 2,3,4-trifluoro-5-iodoaniline as yellow oil. LCMS: m/z=274 $[M+1]^+$.

Step 3. (5-amino-2,3,4-trifluorophenyl)boronic Acid

[0239] Into a 250-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 2,3,4-trifluoro-5-iodoaniline (2.09 g, 7.67 mmol), Bis(pinacolato) diboron (9.46 g, 37.25 mmol), $Pd(dppf)Cl_2$ (1.06 g, 1.45 mmol), KOAc (5.10 g, 52.00 mmol) and NMP (80 mL). The reaction mixture was stirred at 95° C. for 2 h. The reaction was then quenched by the addition of saturated sodium carbonate aqueous solution (100 mL). The reaction mixture was stirred at room temperature for 2 h. The resulting solution was extracted with EA (3×100 mL), the organic layers were combined, then washed with brine (100 mL), dried over anhydrous Na_2SO_4, the residue was concentrated under vacuum. The resulting crude was further purified by C_{18} column eluted with ACN/H_2O (v/v=30° A-50%). This resulted in 1.48 g (106% yield) of (5-amino-2,3,4-trifluorophenyl)boronic acid as yellow oil. LCMS: m/z=192 $[M+1]^+$.

Step 4. 4-(4-acryloylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0240] Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.68 g, 1.34 mmol), (5-amino-2,3,4-trifluorophenyl)boronic acid (0.51 g, 2.67 mmol), $Pd(PPh_3)_4$ (0.31 g, 0.27 mmol), Na_2CO_3 (0.41 g, 3.86 mmol), dioxane (20 mL) and water (4 mL). The reaction mixture was stirred at 80° C. for 2 h. The reaction was then quenched by the addition of water (50 mL) and ethyl acetate (20 mL). The resulting solution was extracted with ethyl acetate (1×50 mL), the organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with ACN/H_2O (v/v=0%~60%). This resulted in 0.15 g (18% yield) of 4-(4-acryloylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=622 $[M+1]^+$.

Step 5. 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 12")

[0241] Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.15 g, 0.25 mmol), NCS (0.10 g, 0.77 mmol) and AcOH (4 mL). The mixture was stirred for overnight at room temperature. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (2×50 mL), the organic layers were combined and washed with saturated sodium bicarbonate aqueous solution (2×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with ACN/H_2O (0.15% NH_4HCO_3) (v/v=30%~80%). This resulted in 21 mg (13% yield) of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihyd ro-1,8-naphthyridine-3-carbonitrile ("Compound 12") as yellow solid. LCMS: m/z=656 $[M+1]^+$.

[0242] ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (d, J=4.7 Hz, 1H), 7.23 (t, J=4.6 Hz, 1H), 6.92 (dd, J=16.7, 10.5 Hz, 1H), 6.20 (dd, J=16.6, 2.3 Hz, 1H), 5.86 (s, 2H), 5.77 (dd, J=10.4, 2.2 Hz, 1H), 4.29-3.50 (m, 8H), 3.72-3.66 (m, 1H), 1.89 (d, J=10.7 Hz, 3H), 1.08 (dd, J=6.6, 2.4 Hz, 3H), 0.97-0.77 (m, 3H).

Step 6. 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting isomer, "Compound 12-1") & 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting isomer, "Compound 12-2")

[0243] The mixture of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (110 mg, several batches) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRAL ART Cellulose-SB, 3 cm×25 cm, Sum; mobile phase, (Hex:DCM=3:1): EtOH (v/v=95:5); Detection wavelength, UV 220 nm. This resulted in 53 mg (48.18%) of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Compound 12-1") as a yellow solid. LCMS: m/z=656 $[M+1]^+$.

[0244] ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (dd, J=4.9, 1.5 Hz, 1H), 7.24 (t, J=4.8 Hz, 1H), 6.92 (dd, J=16.7, 10.4 Hz, 1H), 6.21 (dd, J=16.6, 2.4 Hz, 1H), 5.88 (s, 2H), 5.77 (dd, J=10.4, 2.4 Hz, 1H), 4.25-2.64 (d, J=27.7 Hz, 8H), 2.78-2.60 (m, 1H), 1.89 (d, J=10.4 Hz, 3H), 1.12-1.01 (m, 3H), 0.97-0.83 (m, 3H).

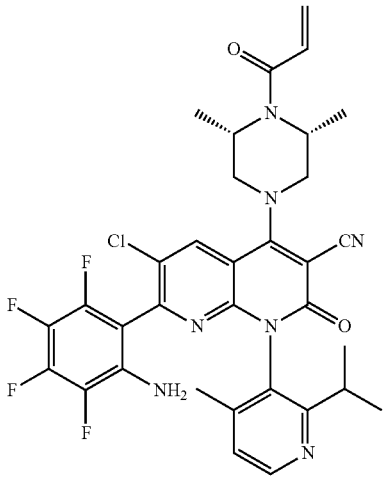
[0245] And 51 mg (46.36%) of 4-(4-acryloylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 12-2") as a yellow solid. LCMS: m/z=656 $[M+1]^+$.

[0246] ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (d, J=4.9 Hz, 1H), 7.24 (t, J=4.7 Hz, 1H), 6.92 (dd, J=16.6, 10.4 Hz, 1H), 6.21 (dd, J=16.6, 2.5 Hz, 1H), 5.88 (s, 2H), 5.77 (dd, J=10.3, 2.4 Hz, 1H), 3.89 (d, J=25.8 Hz, 8H), 2.73-2.64 (m, 1H), 1.89 (d, J=10.5 Hz, 3H), 1.08 (dd, J=6.8, 2.6 Hz, 3H), 0.90 (dd, J=19.2, 6.7 Hz, 3H).

Example 13

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 13"); (P)-4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; and (M)-4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0247]



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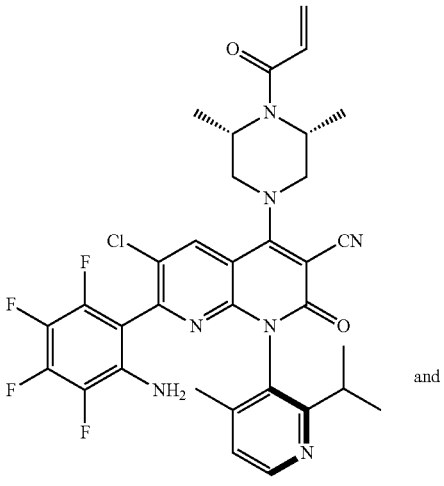

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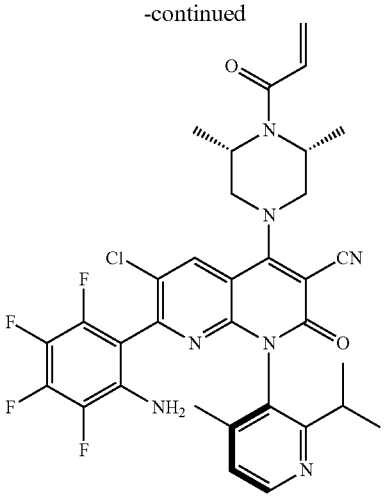


Step 1. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 13")

[0248] Into a 20-mL round-bottom flask was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.312 g, 0.58 mmol), 2,3,4,5-tetrafluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.601 g, 2.07 mmol), $Pd(pph_3)_4$ (0.125 g, 0.11 mmol), Na_2CO_3 (0.189 g, 1.78 mmol), dioxane (8 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC CH_3CN/H_2O (0.05% NH_4HCO_3)(v/v=2/1). This resulted in 0.132 g (34%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 13") as yellow solid. LCMS: m/z=668 $[M+1]^+$.

[0249] ^1H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 8.67 (d, J=5.8 Hz, 1H), 7.85 (d, J=5.9 Hz, 1H), 6.94-6.81 (m, 1H), 6.33 (d, J=16.6 Hz, 1H), 5.84 (d, J=10.8 Hz, 1H), 4.78 (s, 2H), 4.09-3.95 (m, 2H), 3.95-3.81 (m, 2H), 3.13-2.99 (m, 1H), 2.33-2.18 (m, 3H), 1.68-1.59 (m, 6H), 1.36-1.24 (m, 3H), 1.23-1.09 (m, 3H).

Step 2. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting isomer, "Compound 13-1") & 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting isomer, "Compound 13-2")

[0250] The mixture of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluoro phenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (930

mg, several batches) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IA, 3 cm×25 cm, 5 um; mobile phase, Hex:EtOH=80:20; Detection wavelength, UV 220 nm. This resulted in 424 mg (45.59%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Compound 13-1") as a yellow solid. LCMS: m/z=668 $[M+1]^+$.

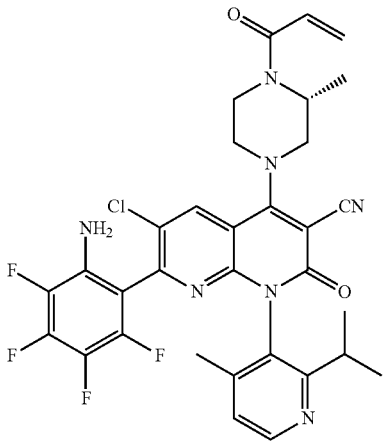
[0251] ^{1}H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.52 (d, J=5.3 Hz, 1H), 7.47 (d, J=5.2 Hz, 1H), 6.88 (dd, J=16.7, 10.6 Hz, 1H), 6.33 (dd, J=16.7, 1.9 Hz, 1H), 5.84 (dd, J=10.6, 1.9 Hz, 1H), 4.77 (s, 2H), 4.10-3.94 (m, 2H), 3.91-3.79 (m, 2H), 2.81-2.83 (m, 1H), 2.08-2.10 (m, 3H), 1.65 (t, J=6.0 Hz, 6H), 1.26-1.19 (m, 3H), 1.01-1.02 (m, 3H).

[0252] And 372 mg (40.00%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 13-2") as a yellow solid. LCMS: m/z=668 $[M+1]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.52 (d, J=5.3 Hz, 1H), 7.47 (d, J=5.2 Hz, 1H), 6.88 (dd, J=16.7, 10.6 Hz, 1H), 6.33 (dd, J=16.7, 1.9 Hz, 1H), 5.84 (dd, J=10.6, 1.9 Hz, 1H), 4.77 (s, 2H), 4.10-3.94 (m, 2H), 3.91-3.79 (m, 2H), 2.82-2.83 (m, 1H), 2.09-2.11 (m, 3H), 1.65 (t, J=6.0 Hz, 6H), 1.26-1.19 (m, 3H), 1.04-1.06 (m, 3H).

Example 14

4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 14")

[0253]



Step 1. 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 14")

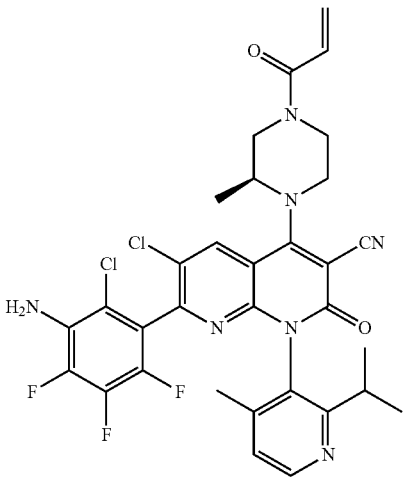
[0254] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed (R)-4-(4-acryloyl-3-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (353 mg, 0.67 mmol), 2,3,4,5-tetrafluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (604 mg, 2.08 mmol), $Pd(PPh_3)_4$ (185 mg, 0.16 mmol), Na_2CO_3 (235 mg, 2.22 mmol), dioxane (7 mL) and water (0.7 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (CH_3CN/H_2O (v/v=7/3)). This resulted in 29 mg (7% yield) of 4-((R)-4-acryloyl-3-methylpiperazin-1-yl)-7-(2-amino-3,4,5,6-tetrafluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 14") as yellow solid. LCMS: m/z=654 $[M+1]^+$.

[0255] ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J=52.4 Hz, 2H), 7.27 (s, 1H), 6.96-6.66 (m, 1H), 6.29 (d, J=16.2 Hz, 1H), 5.83 (d, J=9.6 Hz, 1H), 4.70-4.43 (m, 1H), 4.18-4.08 (m, 4H), 3.70-3.60 (m, 2H), 2.82-2.48 (m, 1H), 2.03 (s, 3H), 1.48-1.40 (m, 3H), 1.24-0.84 (m, 6H).

Example 15

4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 15"); (P)-4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile; and (M)-4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0256]



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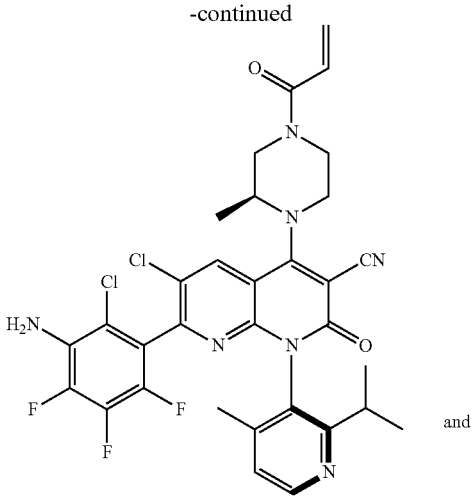

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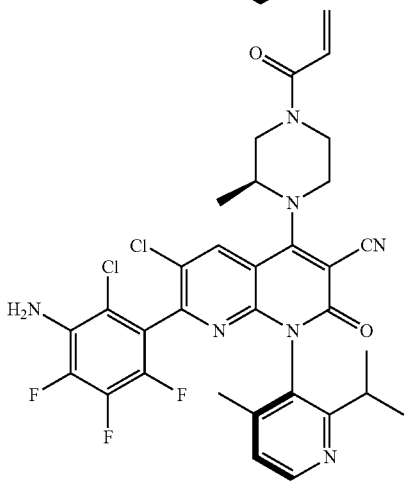

Step 1. (S)-4-(4-acryloyl-2-methylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0257] Into a 20-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed (S)-4-(4-acryloyl-2-methylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.310 g, 0.59 mmol), (5-amino-2,3,4-trifluorophenyl)boronic acid (0.285 g, 1.49 mmol), $Pd(PPh_3)_4$ (0.085 g, 0.073 mmol), Na_2CO_3 (0.126 g, 1.19 mmol), dioxane (8 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 1 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC CH_3CN/H_2O (0.05% NH_4HCO_3)(v/v=2/1). This resulted in 135 mg (35%) of (S)-4-(4-acryloyl-2-methylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-m ethylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=636 $[M+1]^+$.

Step 2. 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 15")

[0258] Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed (S)-4-(4-acryloyl-2-methylpiperazin-1-yl)-7-(5-amino-2,3,4-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (0.123 g, 193.376 mmol), NCS (0.053 g, 396.906 mmol) and AcOH (2 mL). The mixture was stirred for overnight at room temperature. The reaction was then quenched by the addition of saturated sodium bicarbonate aqueous solution (100 mL). The resulting solution was extracted with ethyl acetate (3×100 mL), the organic layers were combined and concentrated under vacuum. The resulting crude product was further purified by C_{18} column eluted with ACN/H_2O (0.15% NH_4HCO_3) (v/v=30%-80%). This resulted in 55 mg (42% yield) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound 15") as yellow solid. LCMS: m/z=670 $[M+1]^+$.

[0259] ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.41 (d, J=4.8 Hz, 1H), 7.24 (dd, J=11.5, 5.9 Hz, 1H), 6.98-6.74 (m, 1H), 6.33 (d, J=16.3 Hz, 1H), 5.84 (d, J=10.5 Hz, 1H), 4.69-3.97 (m, 5H), 3.78-3.52 (m, 2H), 2.86-2.56 (m, 1H), 2.12-1.88 (m, 3H), 1.47-1.30 (m, 3H), 1.25-1.10 (m, 3H), 1.07-0.88 (m, 3H).

Step 2. 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (first eluting isomer, "Compound 15-1") & 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (second eluting isomer, "Compound 15-2")

[0260] The mixture of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (53 mg) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRALPAK IF, 2 cm×25 cm, Sum mobile phase, (Hex:DCM=3:1):EtOH (v/v=9:1); Detection wavelength, UV 220 nm. This resulted in 20 mg (49%) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer. "Compound 15-1") as a yellow solid. LCMS: m/z=670 $[M+1]^+$.

[0261] ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.43 (d, J=5.0 Hz, 1H), 7.28 (t, J=4.9 Hz, 1H), 6.99-6.79 (m, 1H),

6.35 (d, J=18.0 Hz, 1H), 5.87 (d, J=10.7 Hz, 1H), 4.68-4.06 (m, 5H), 3.78-3.56 (m, 2H), 2.69-2.56 (m, 1H), 2.09 (d, J=9.8 Hz, 3H), 1.42 (s, 3H), 1.17 (d, J=6.8 Hz, 3H), 0.98 (dd, J=18.6, 6.8 Hz, 3H).

[0262] And 17 mg (45%) of 4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-7-(3-amino-2-chloro-4,5,6-trifluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Compound 15-2") as a yellow solid. LCMS: m/z=670 $[M+1]^+$.

[0263] ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.26 (t, J=5.4 Hz, 1H), 6.87 (d, J=27.5 Hz, 1H), 6.97-6.80 (m, 1H), 5.87 (d, J=11.5 Hz, 1H), 4.65-4.05 (m, 5H), 3.78-3.57 (m, 2H), 2.88-2.78 (m, 1H), 1.95 (d, J=12.5 Hz, 3H), 1.44-1.34 (m, 3H), 1.22 (d, J=6.7 Hz, 3H), 1.03 (dd, J=11.9, 6.8 Hz, 3H).

[0264] The following compounds can be synthesized following the similar methods as described in the above-mentioned examples:

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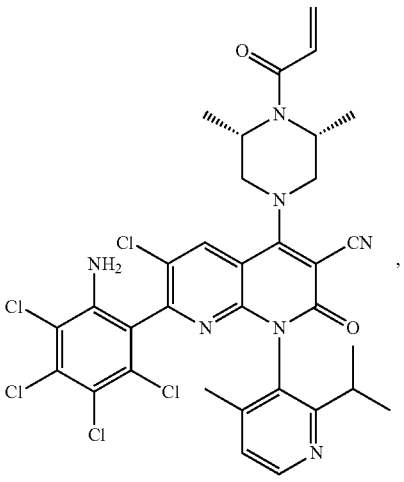

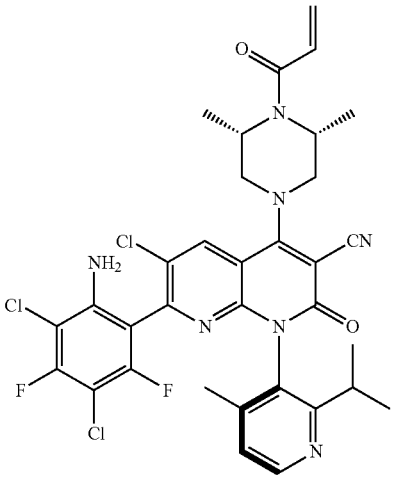

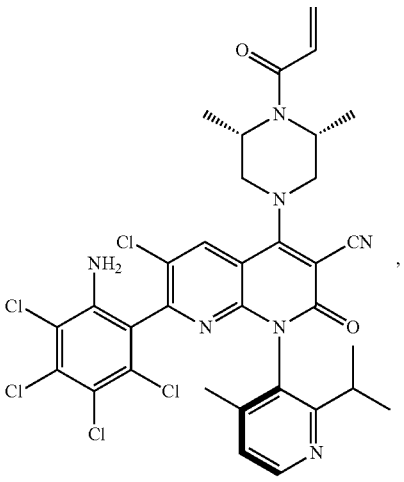

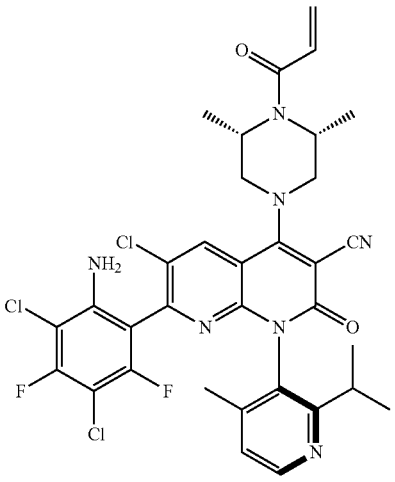

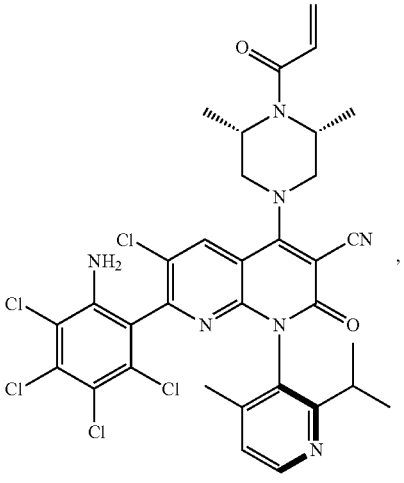

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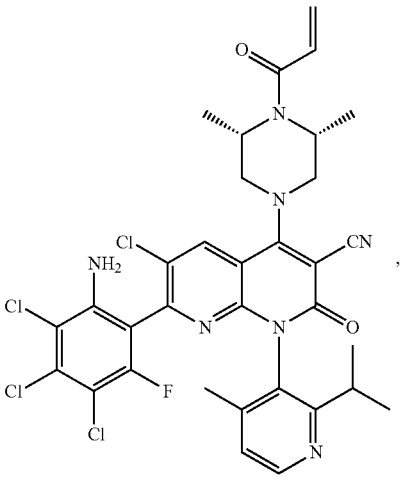

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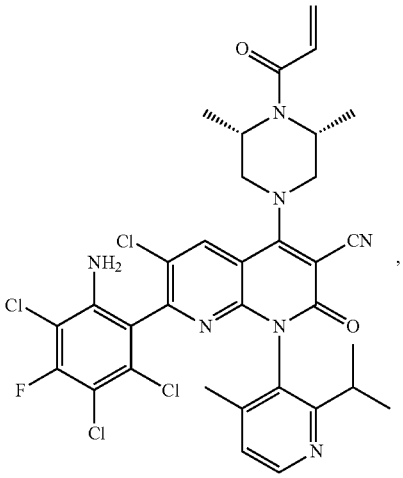

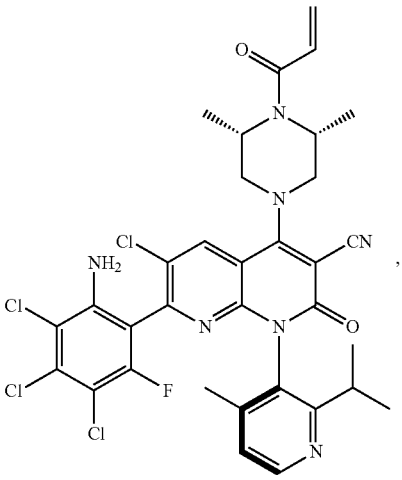

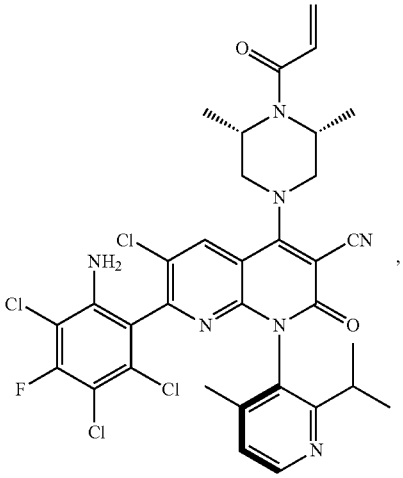

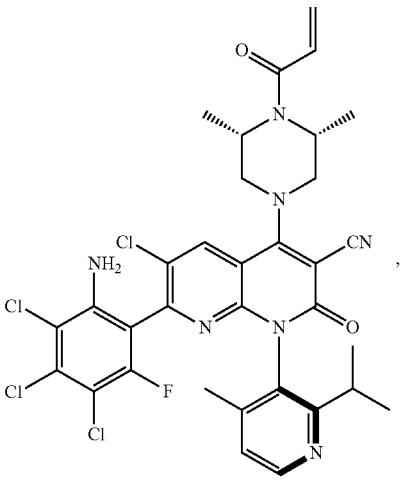

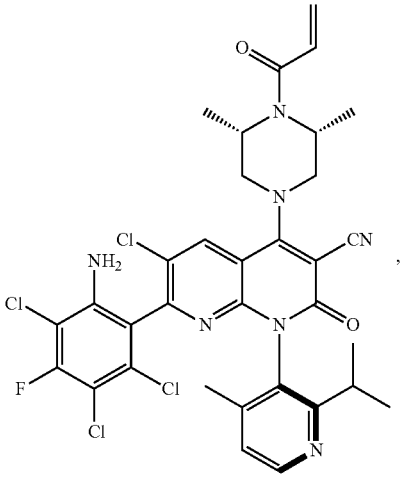

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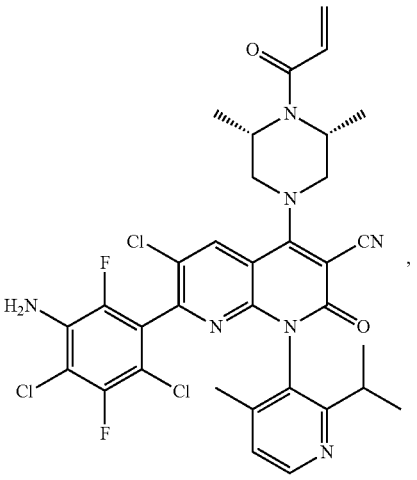

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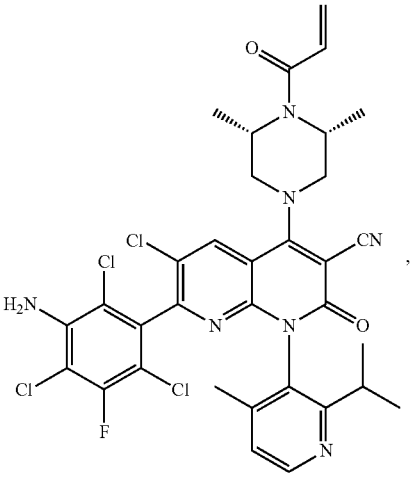

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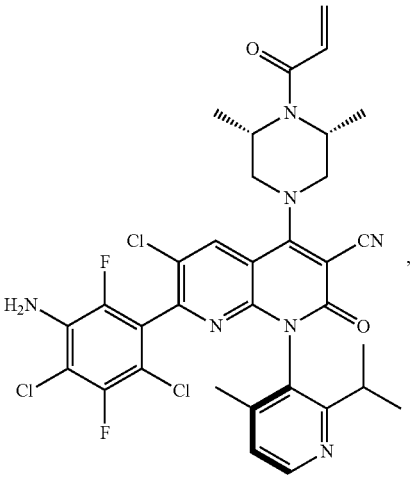

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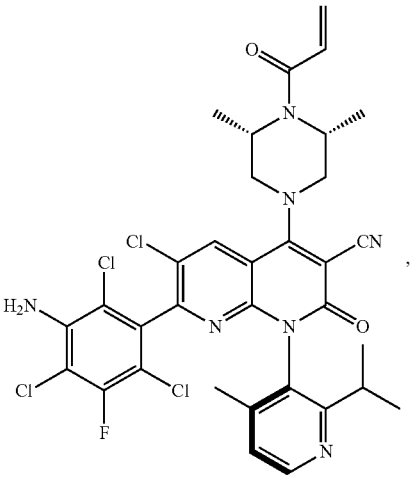

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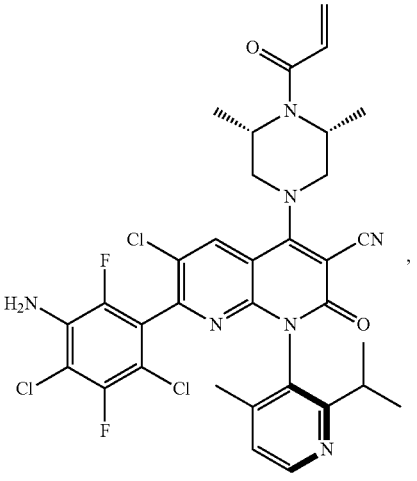

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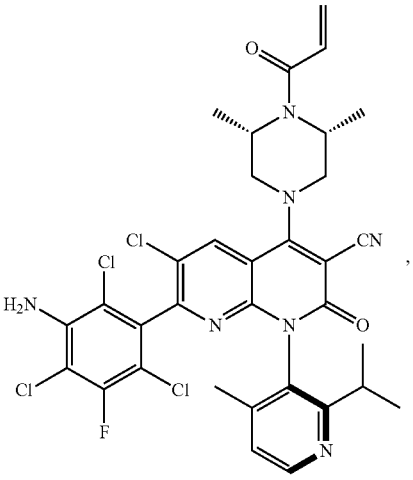

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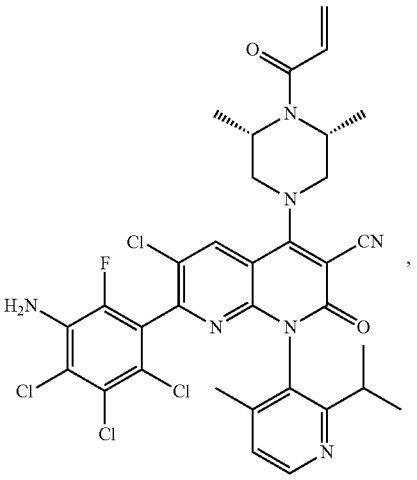

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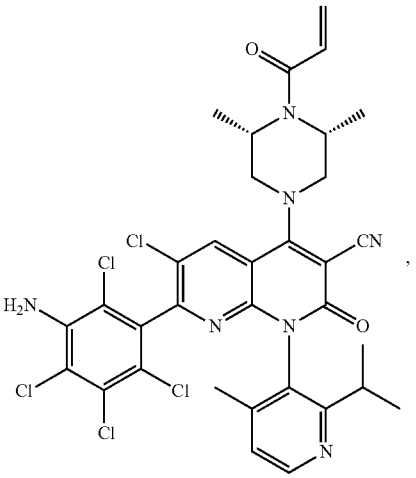

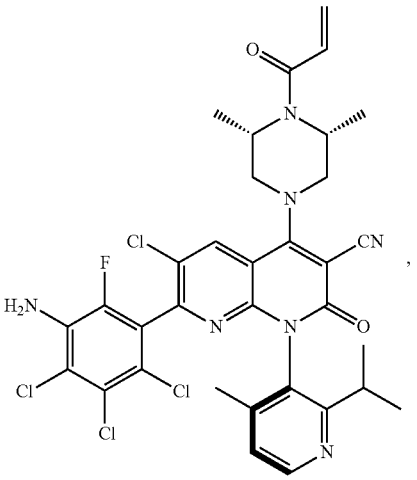

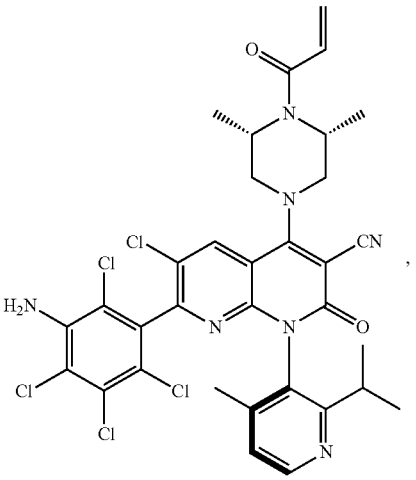

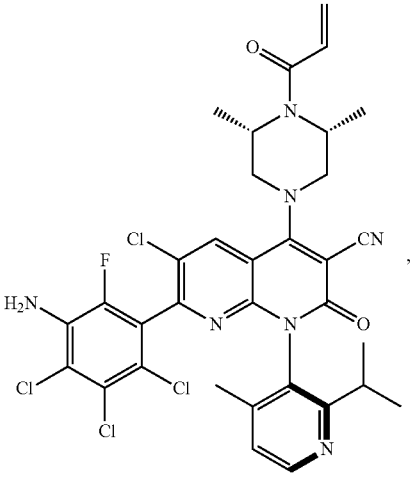

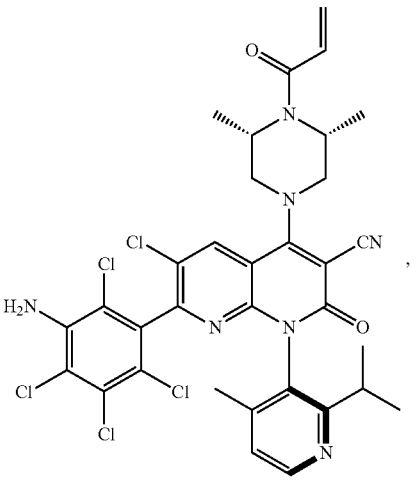

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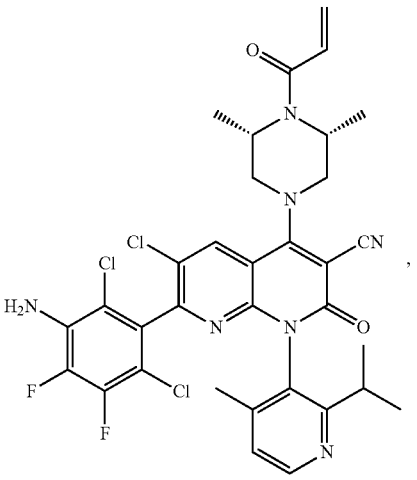

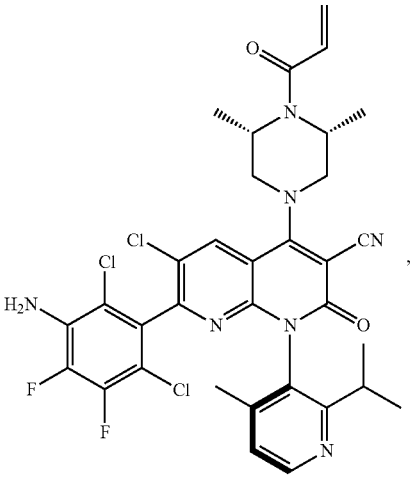

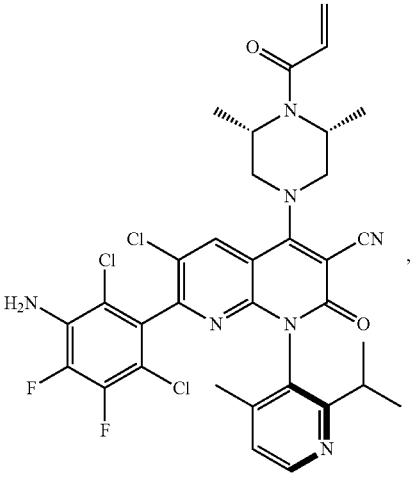

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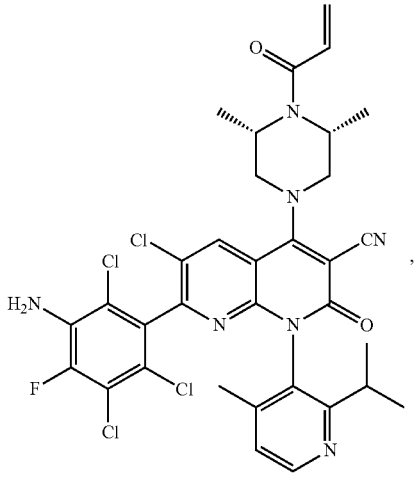

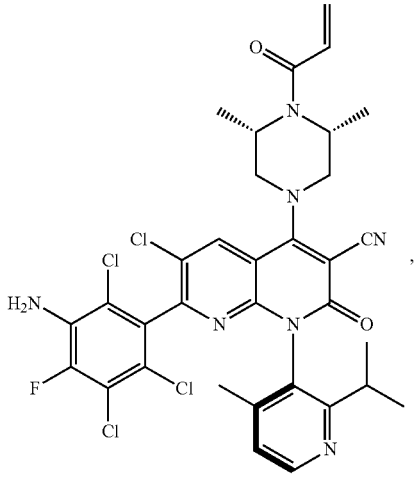

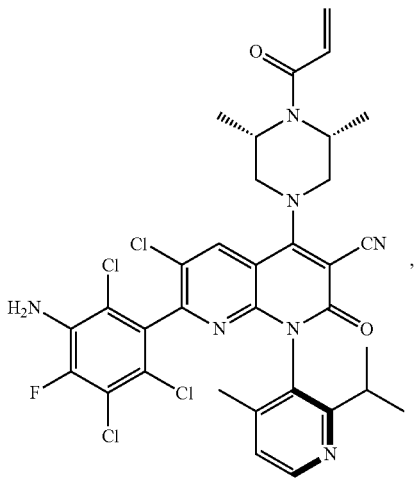

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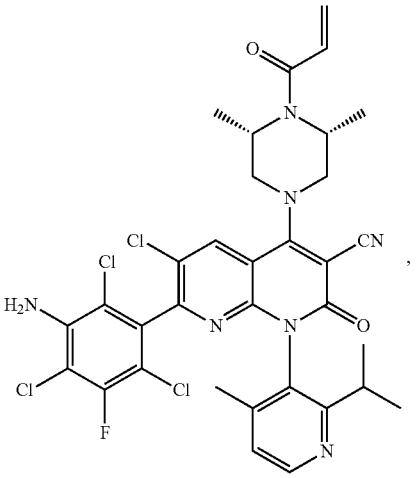

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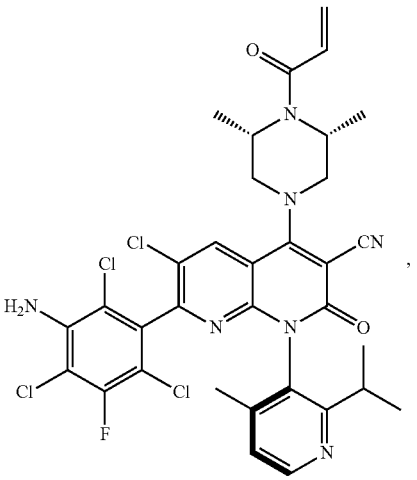

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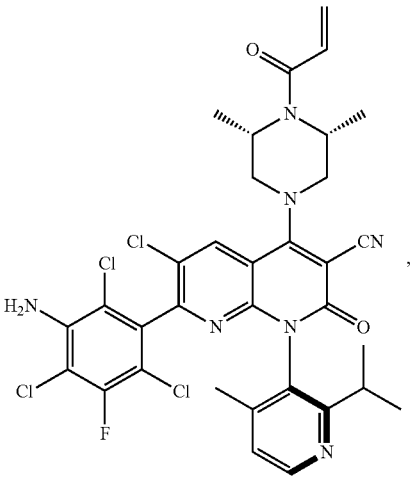

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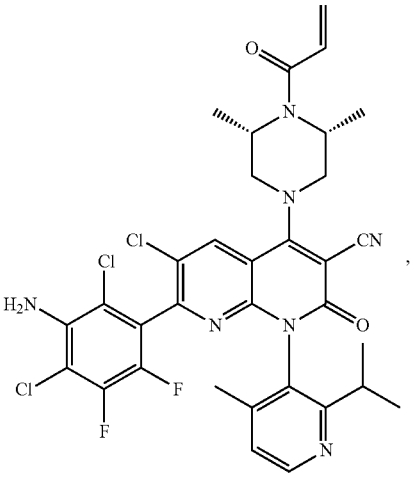

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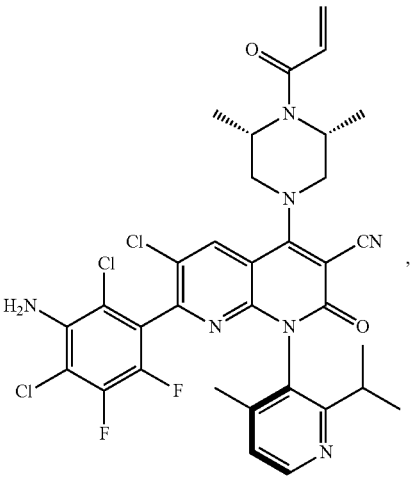

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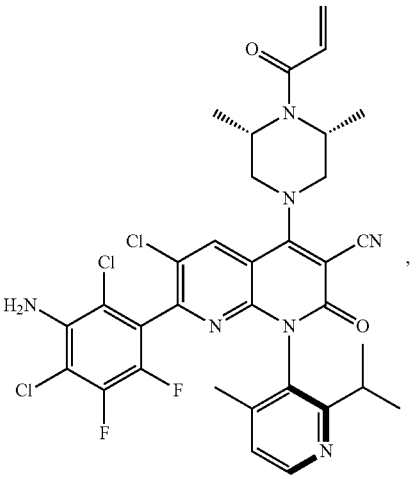

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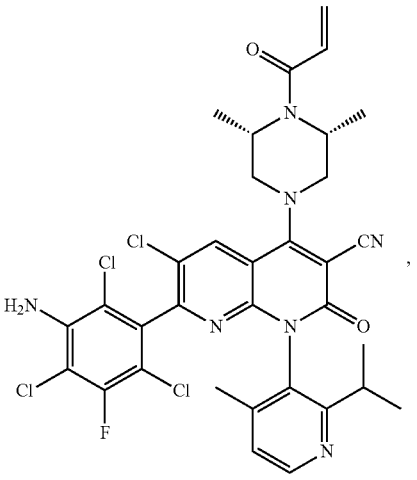

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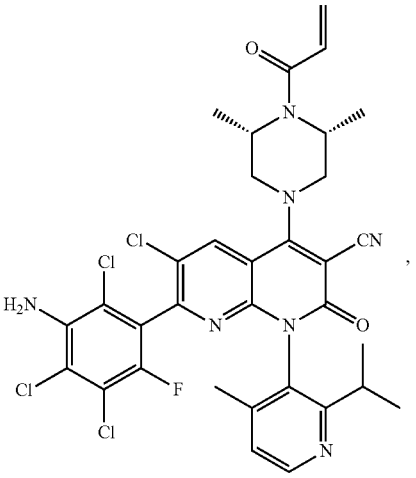

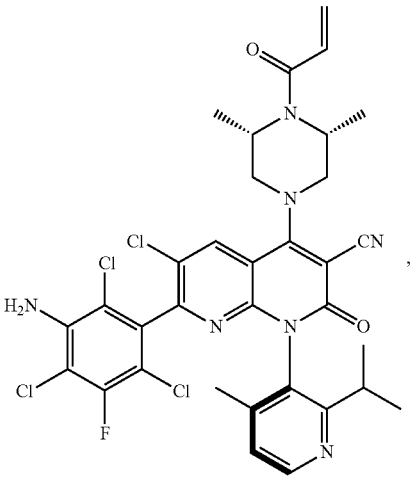

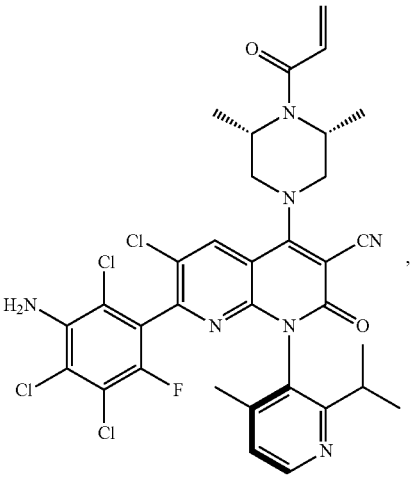

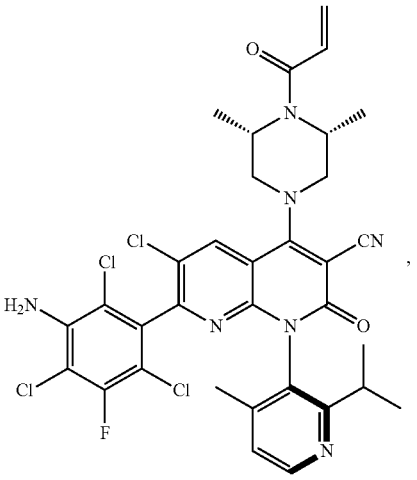

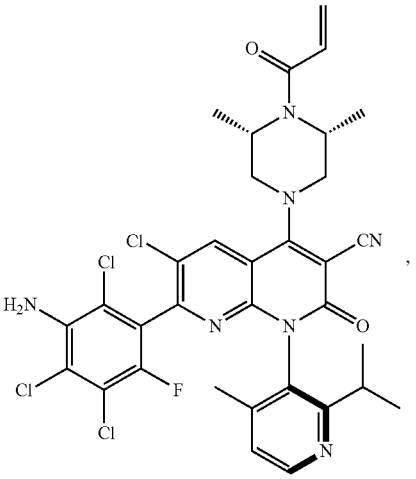

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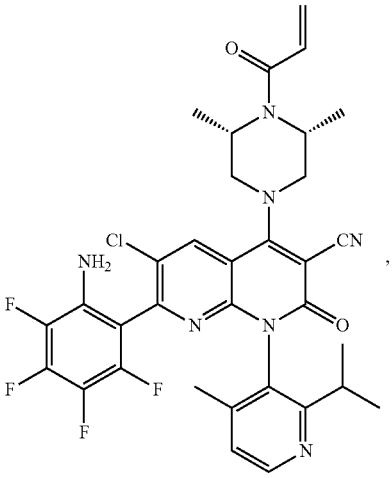

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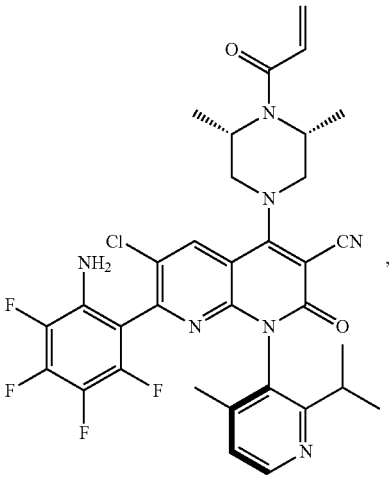

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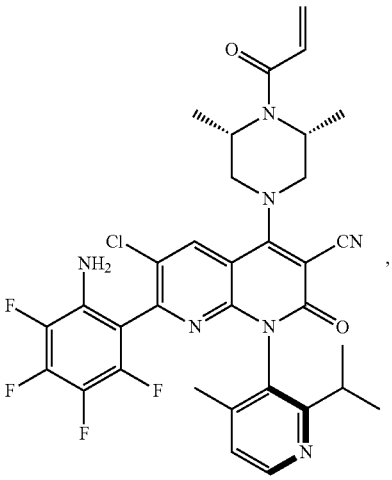

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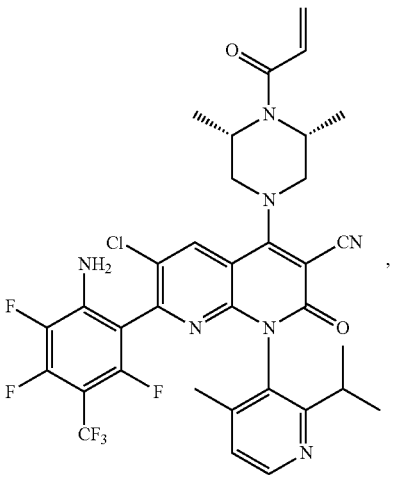

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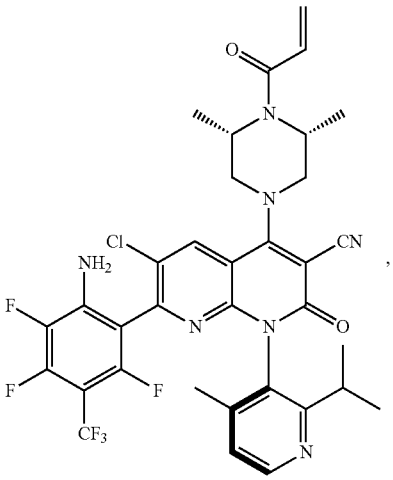

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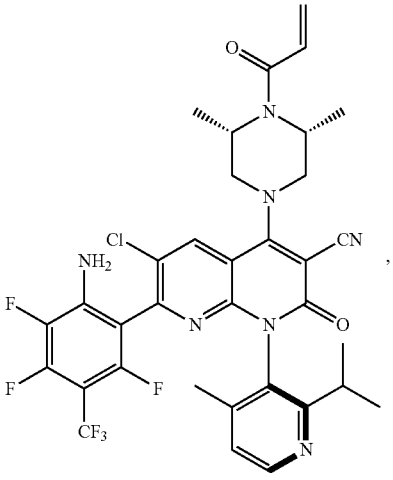

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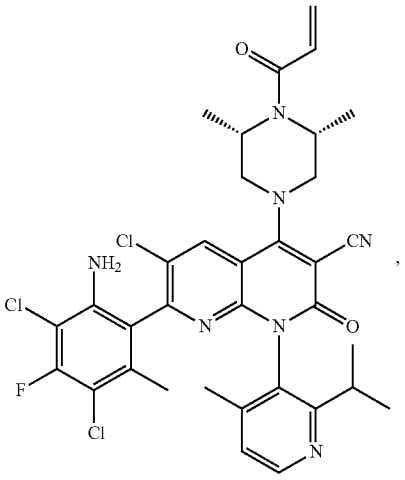

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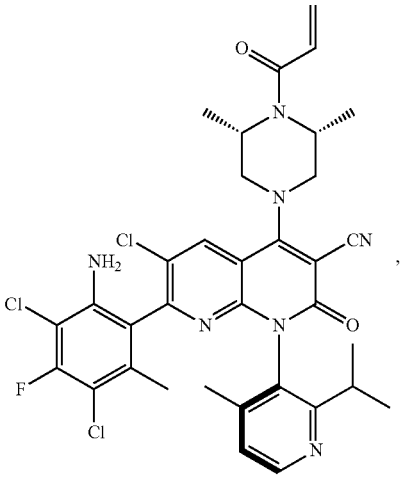

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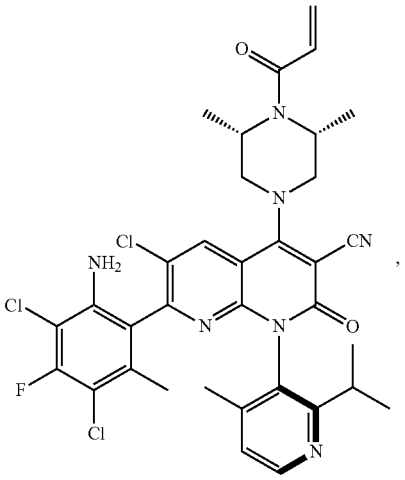

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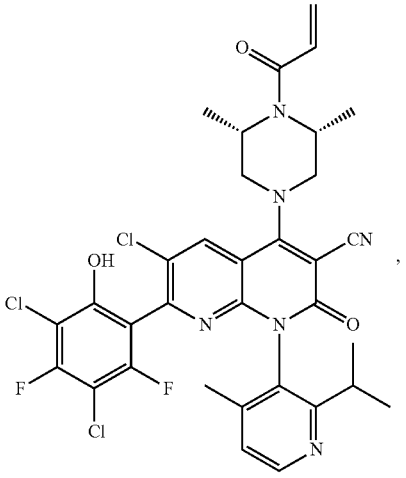

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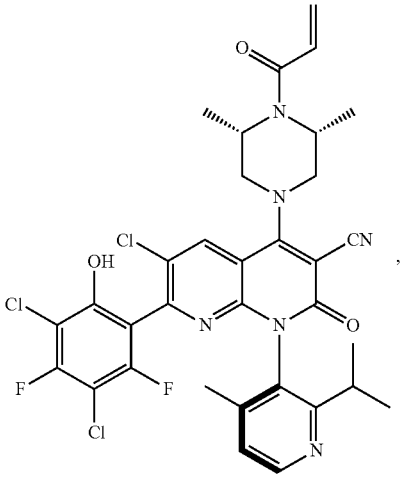

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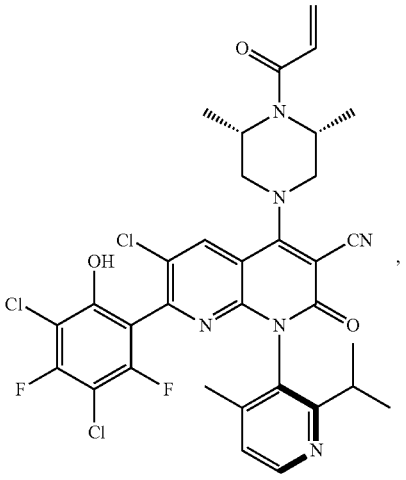

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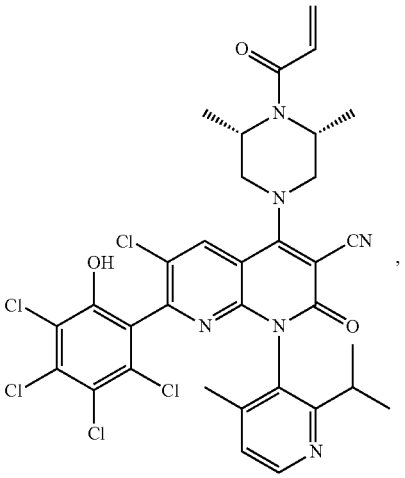

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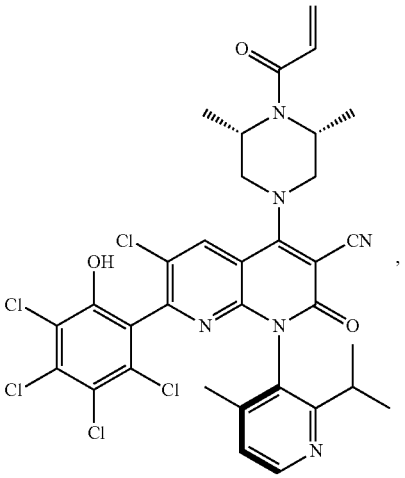

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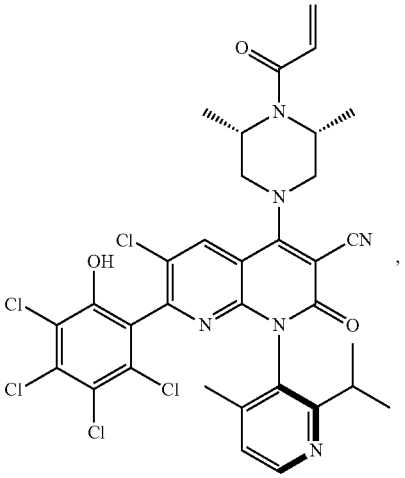

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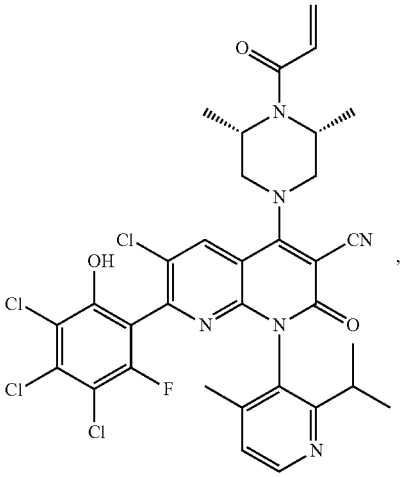

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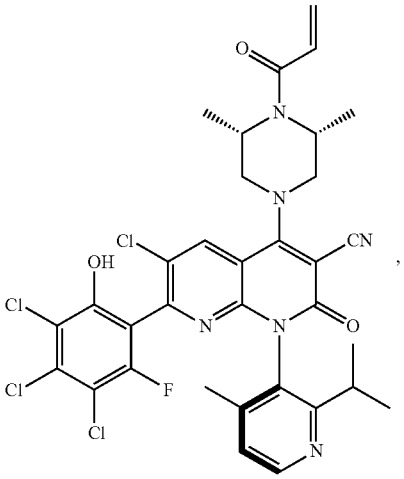

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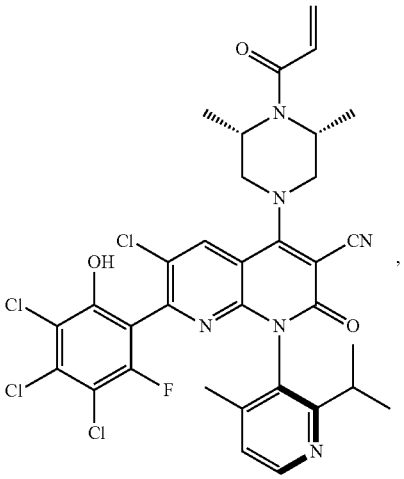

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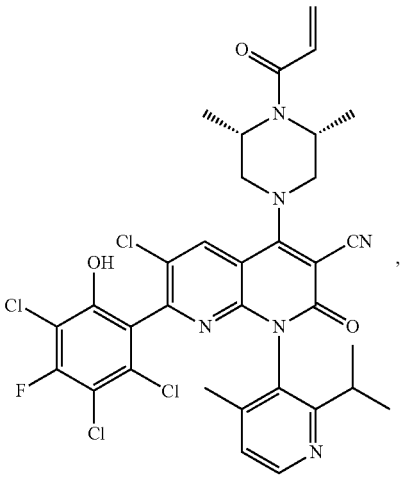

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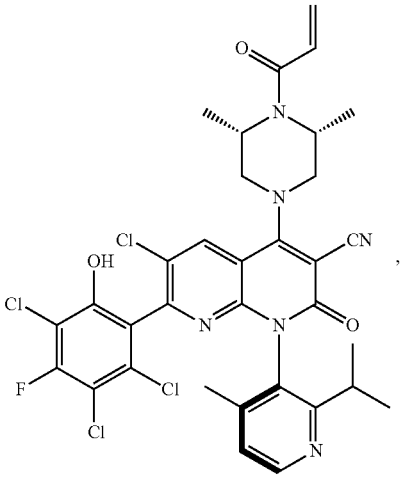

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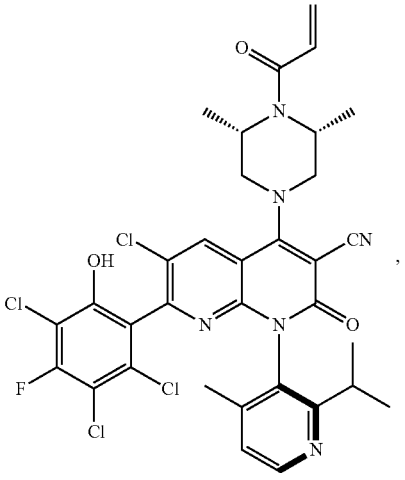

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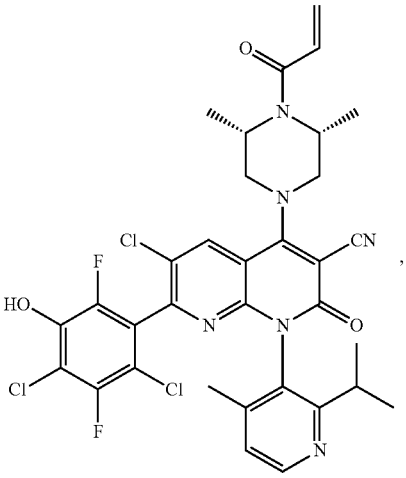

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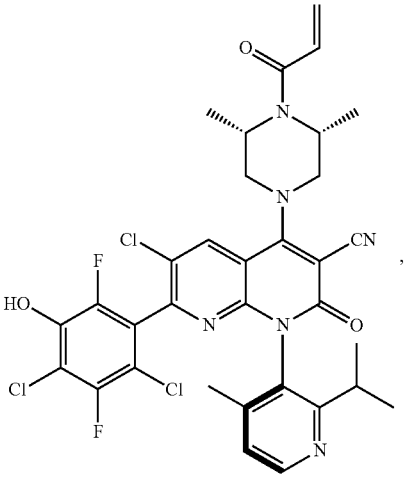

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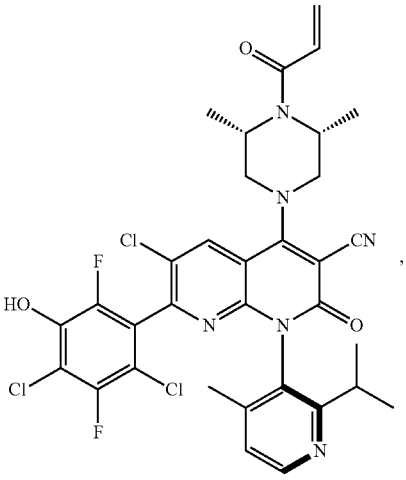

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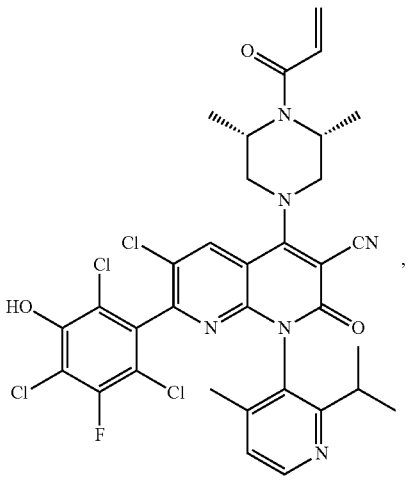

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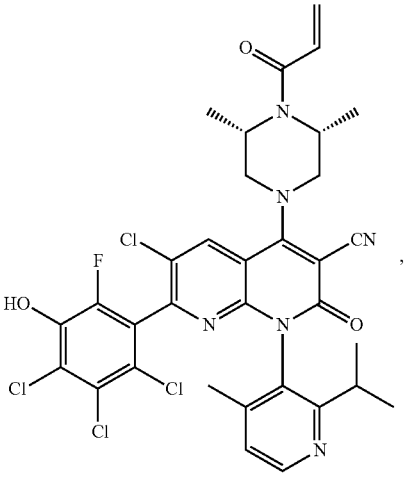

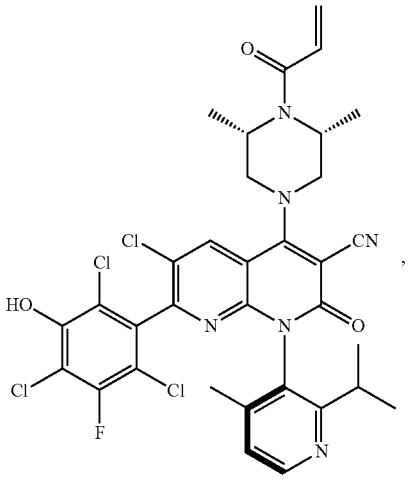

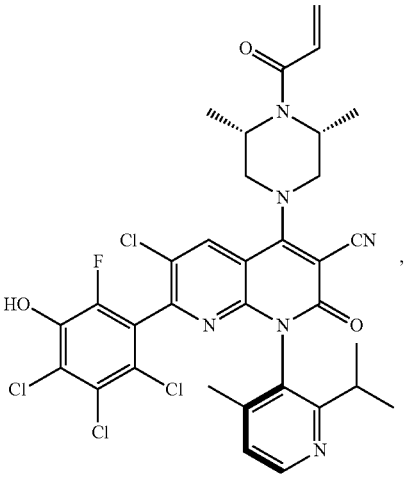

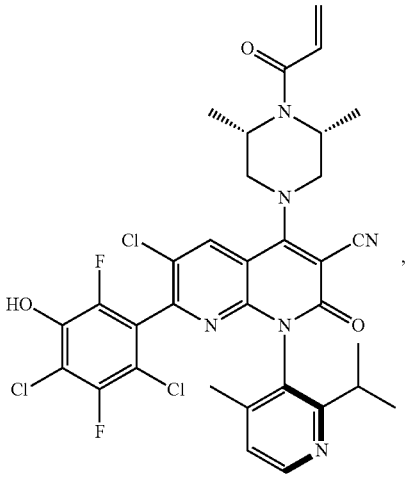

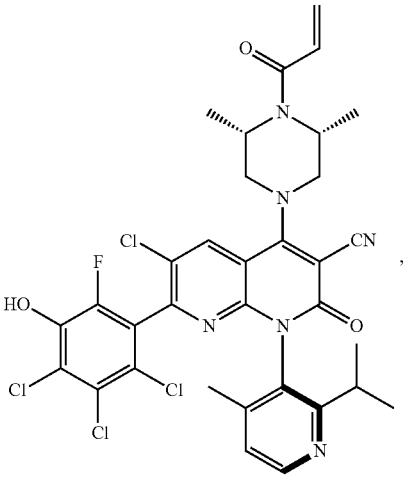

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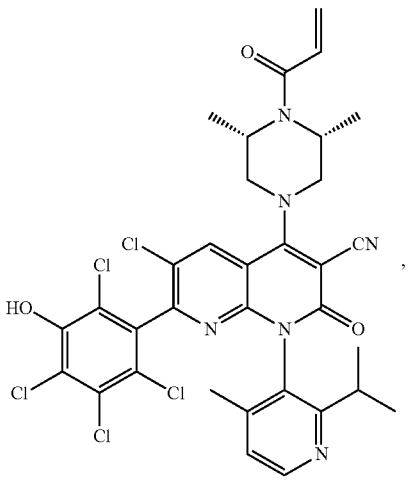

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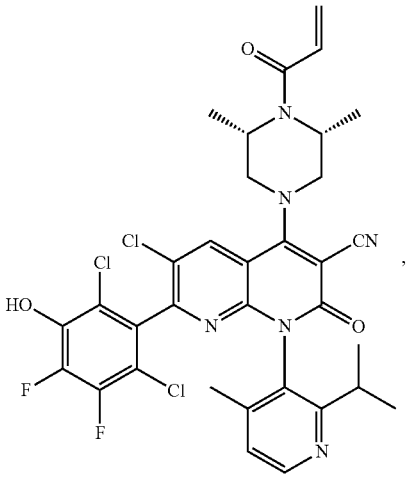

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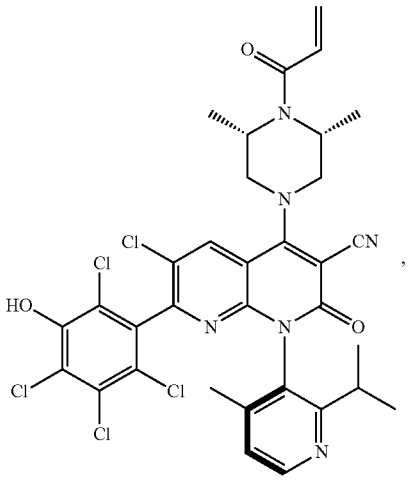

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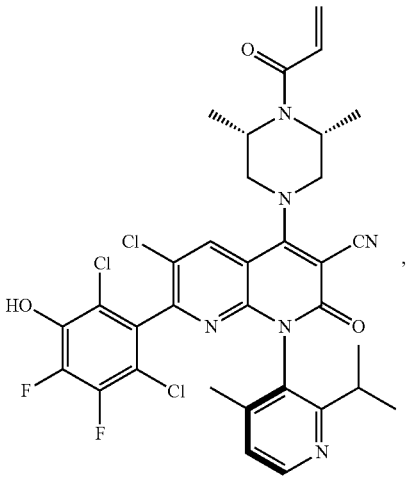

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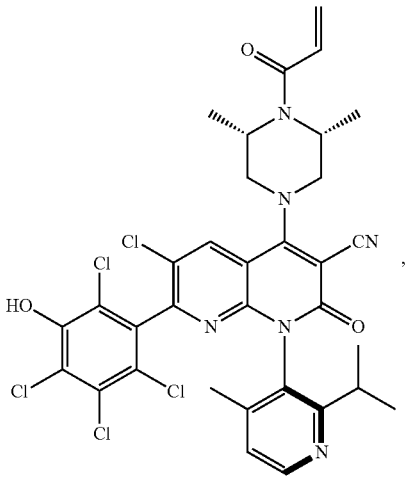

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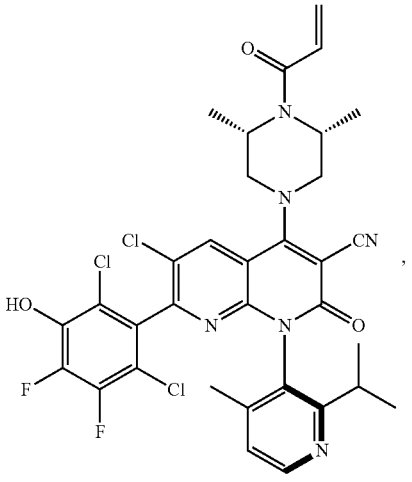

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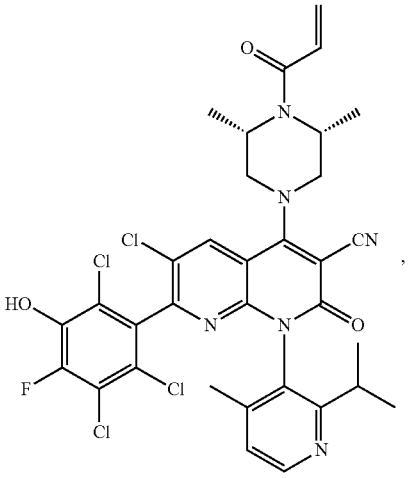

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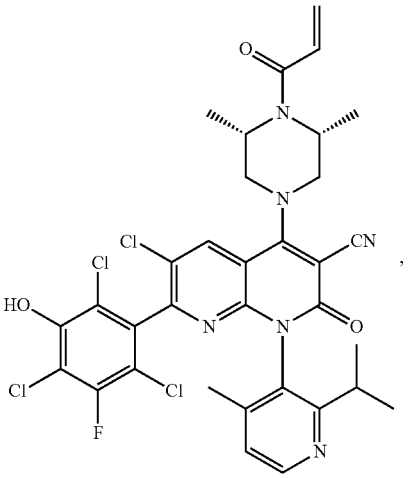

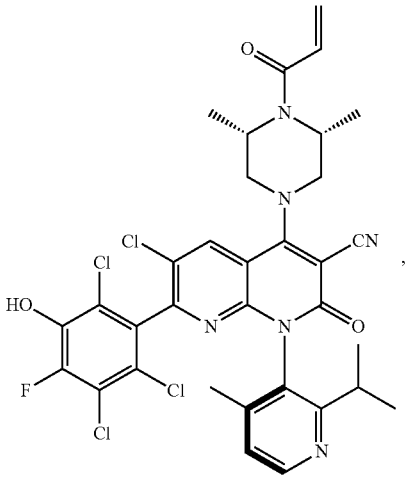

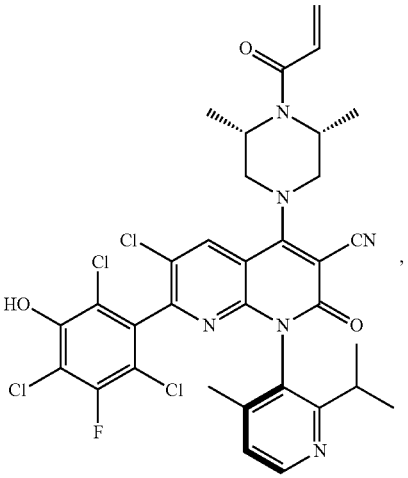

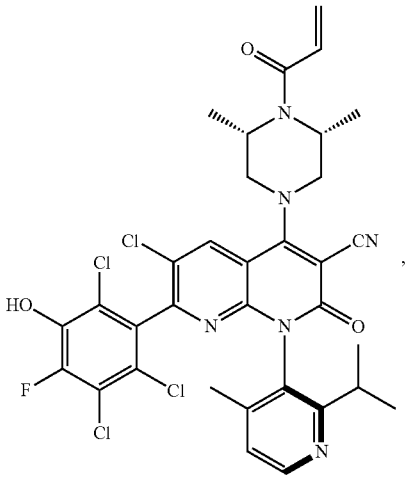

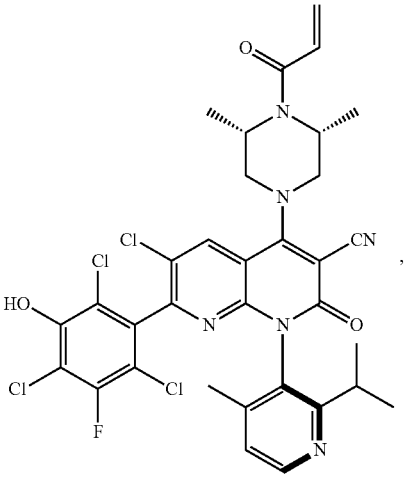

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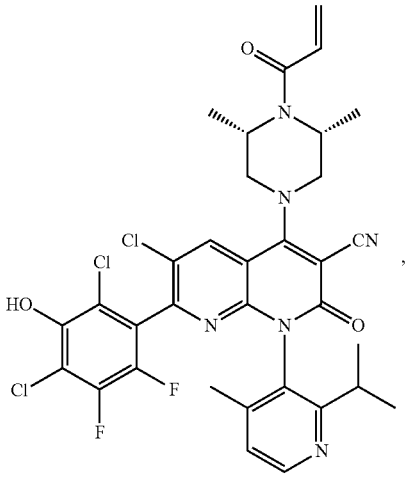

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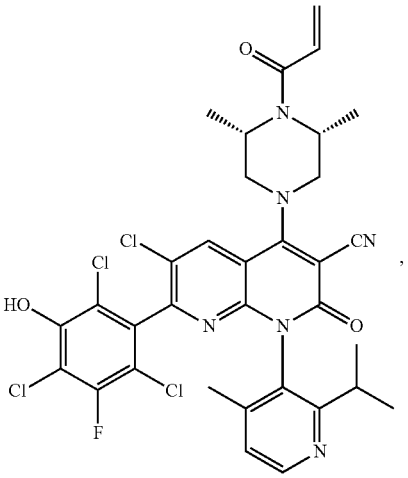

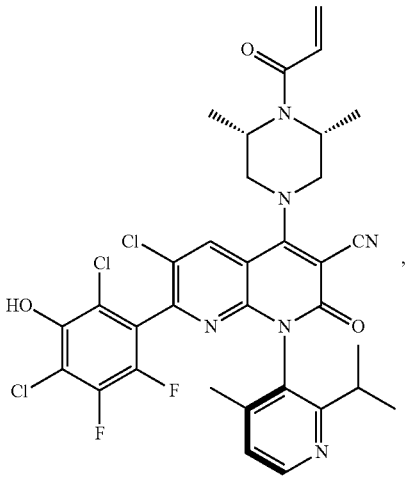

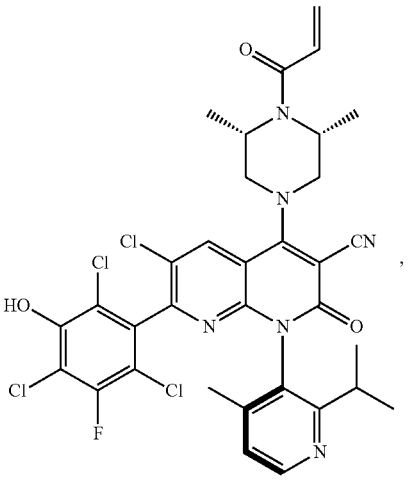

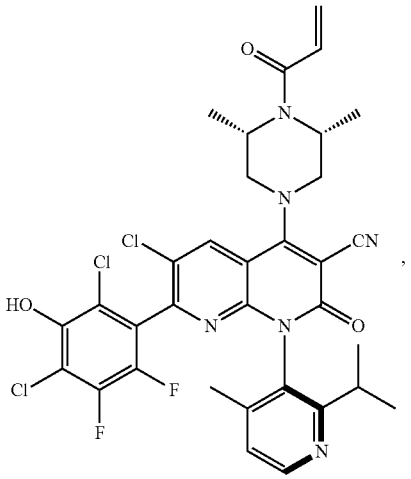

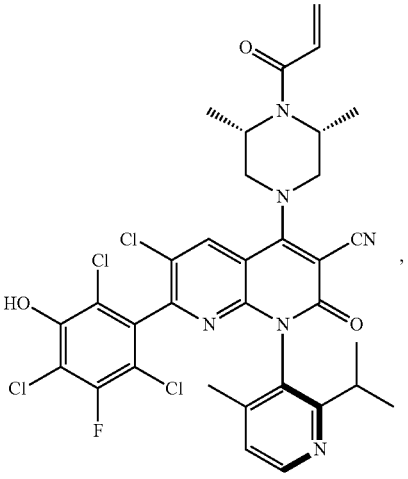

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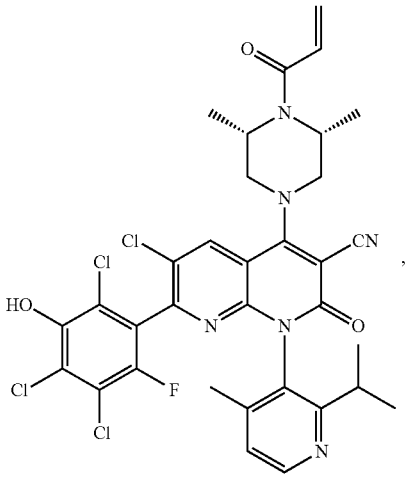

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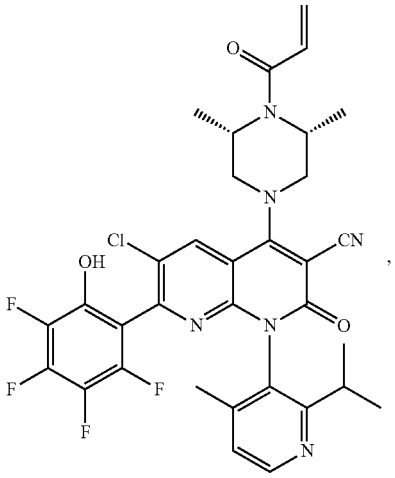

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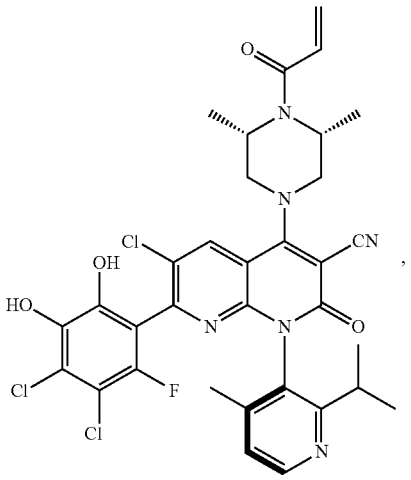

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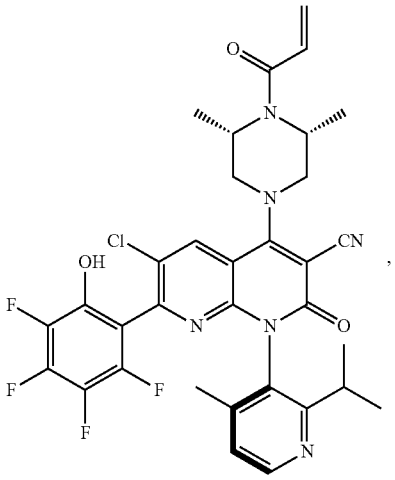

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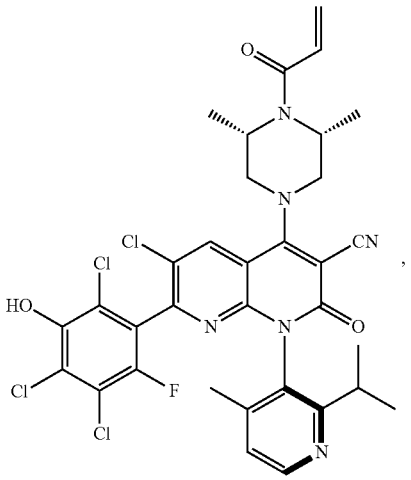

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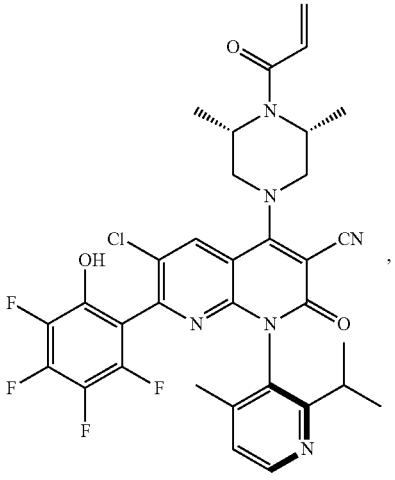

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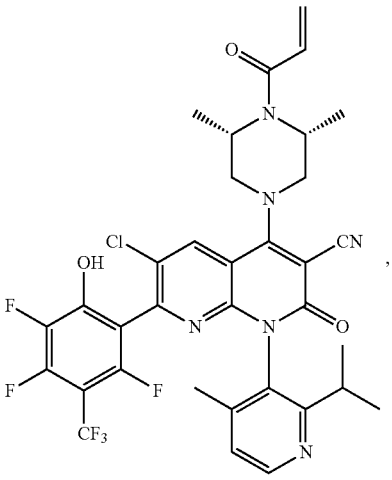

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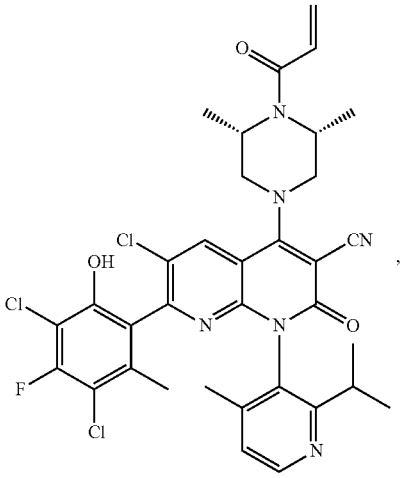

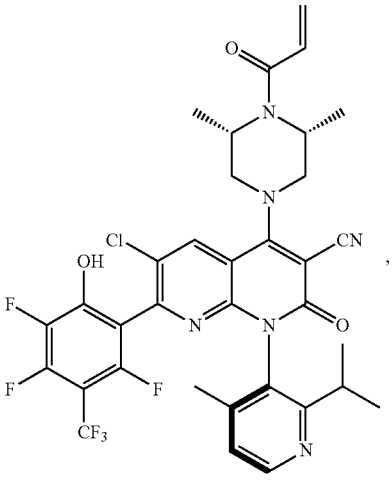

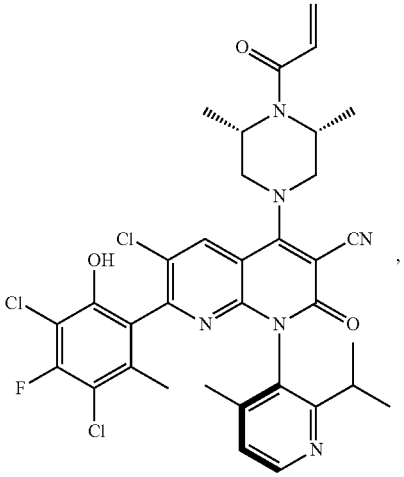

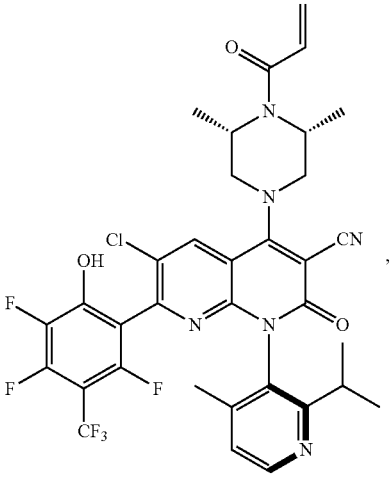

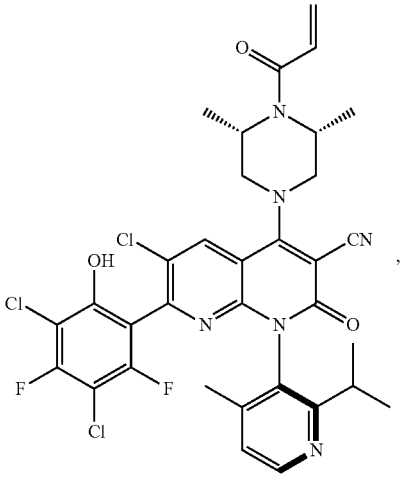

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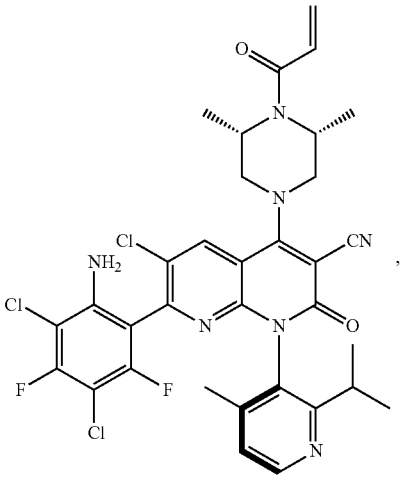

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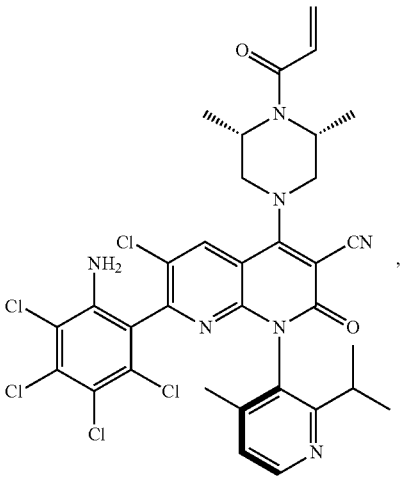

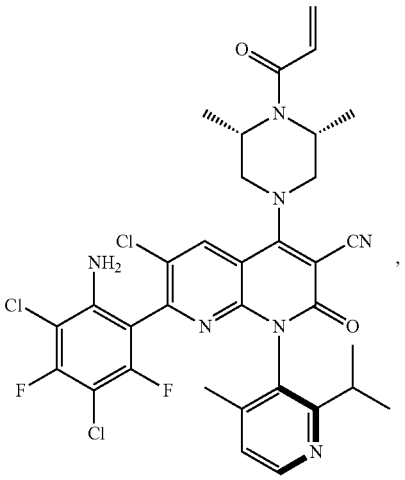

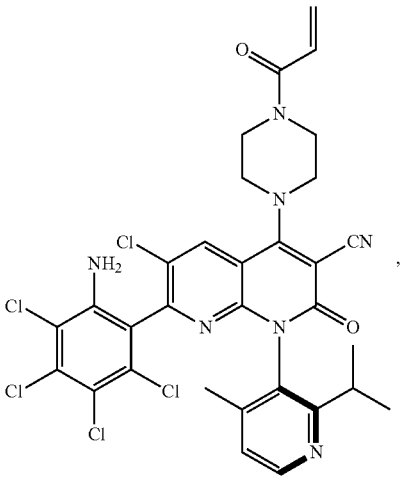

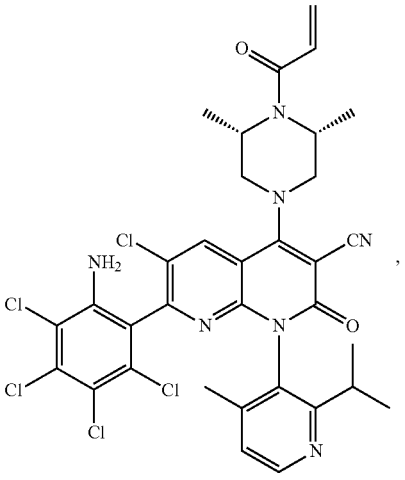

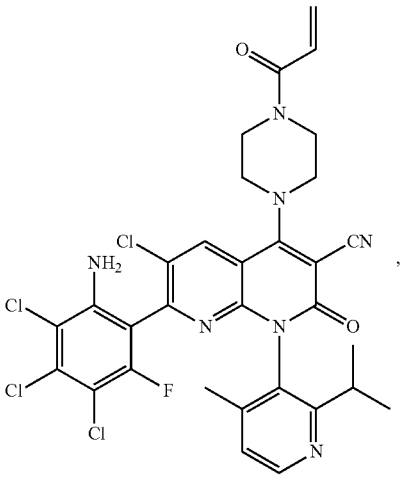

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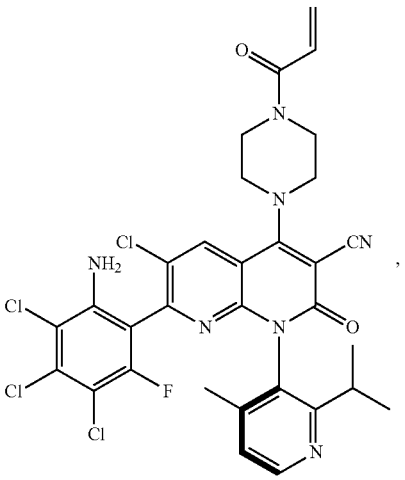

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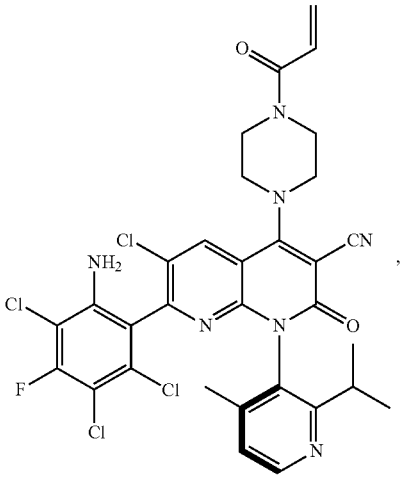

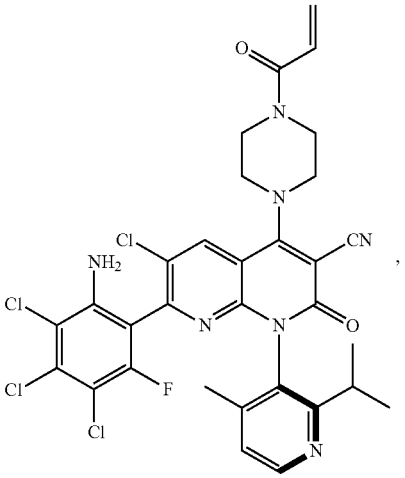

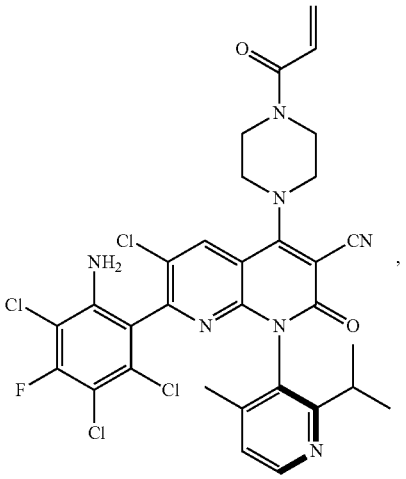

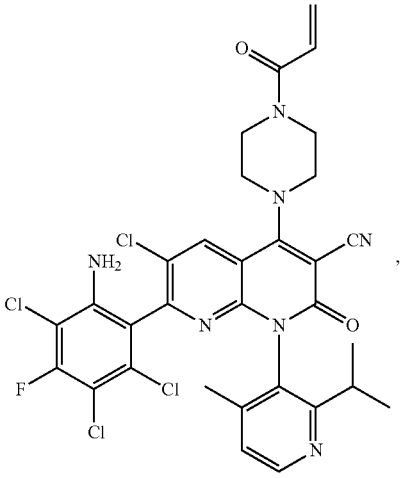

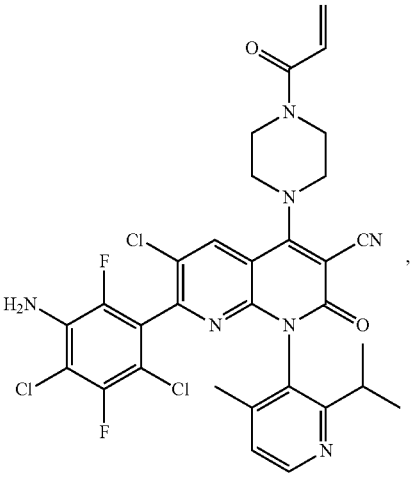

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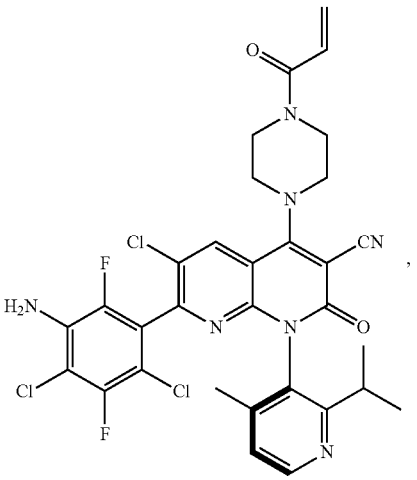

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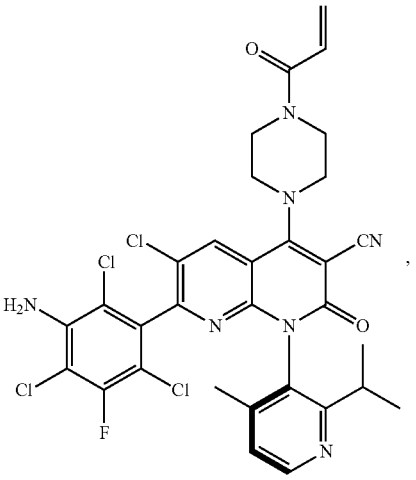

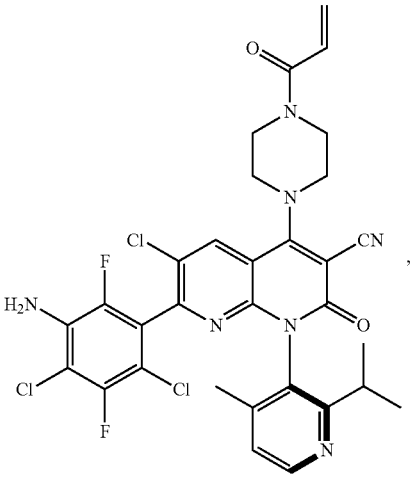

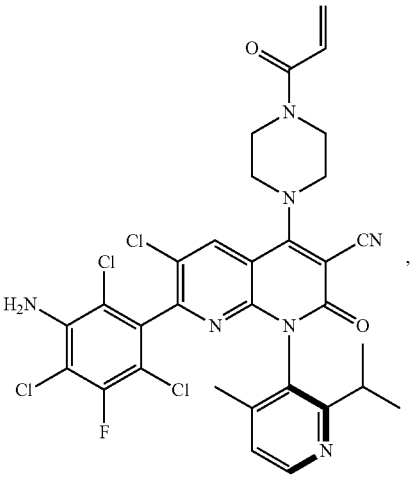

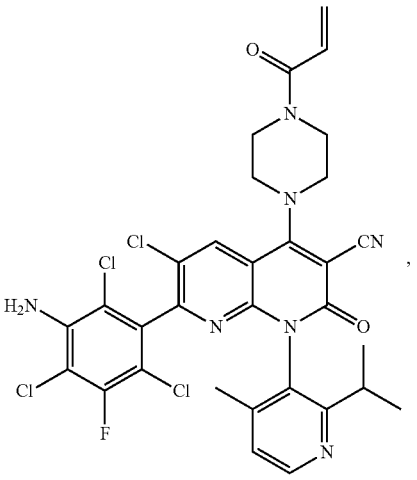

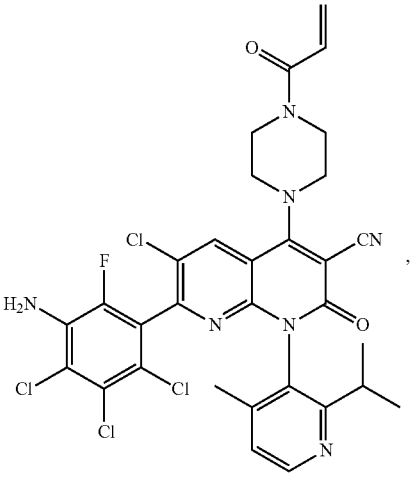

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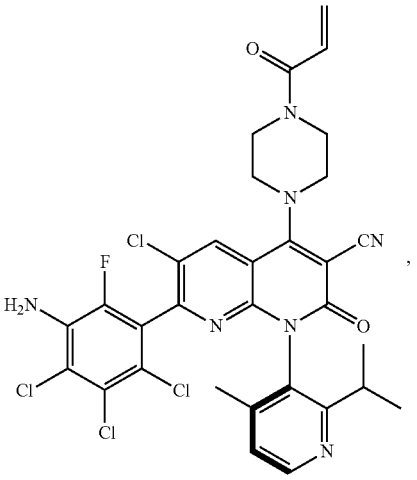

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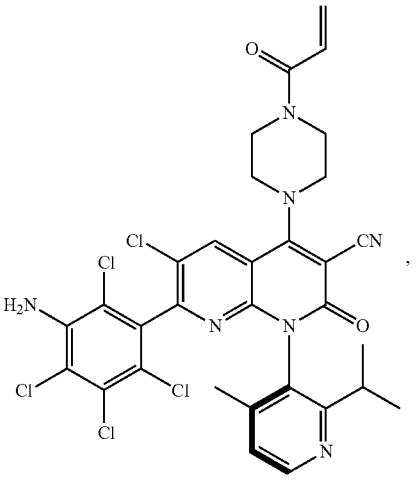

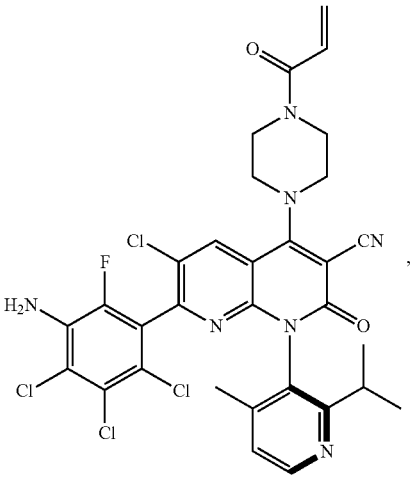

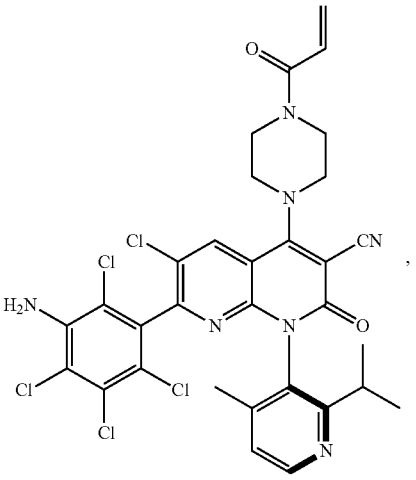

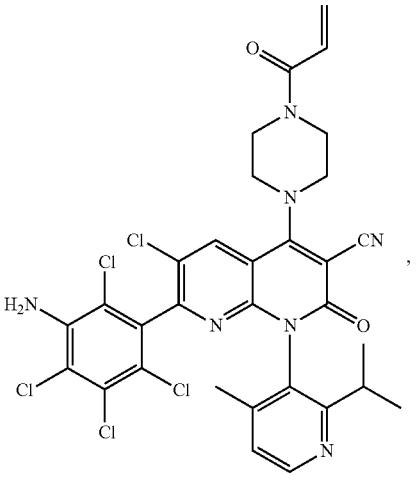

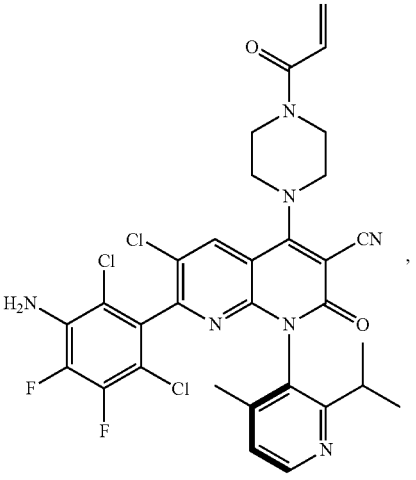

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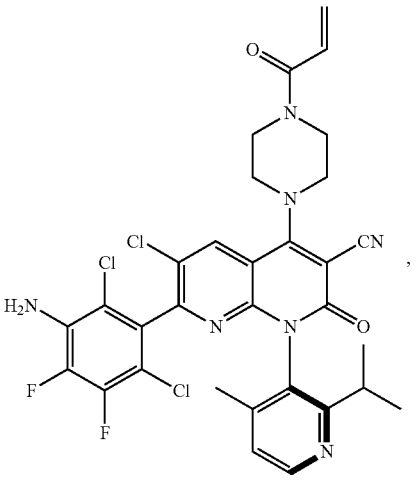

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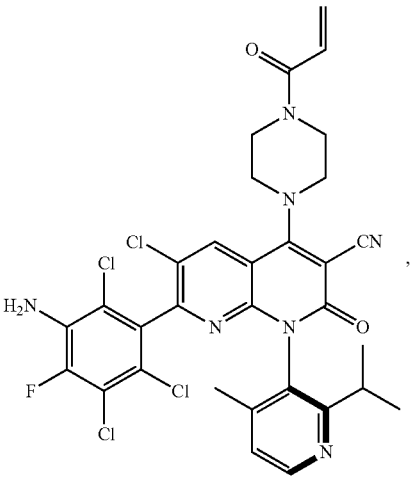

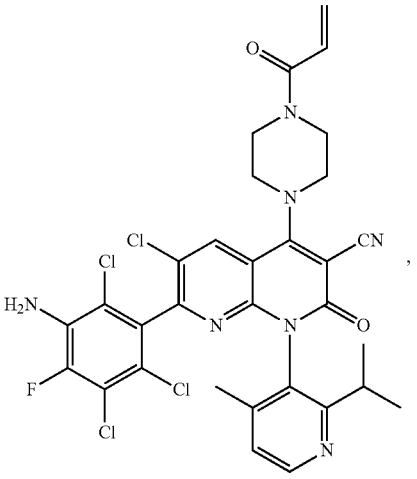

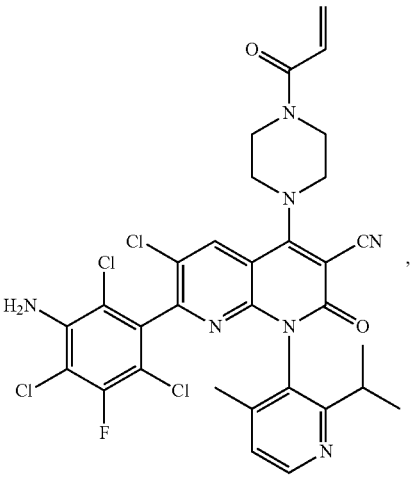

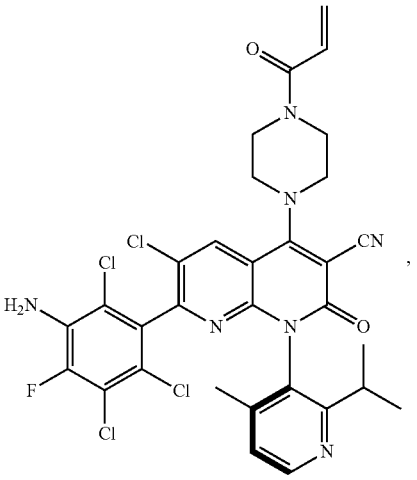

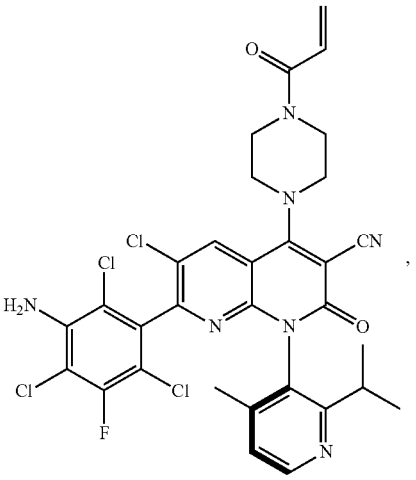

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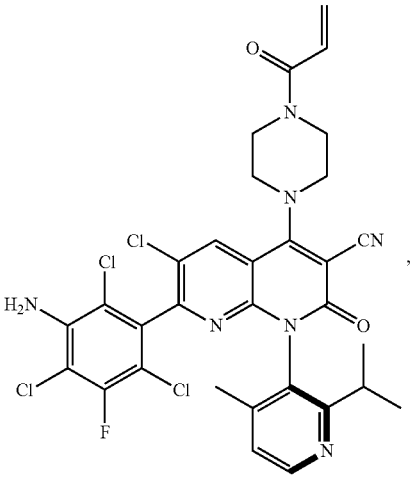

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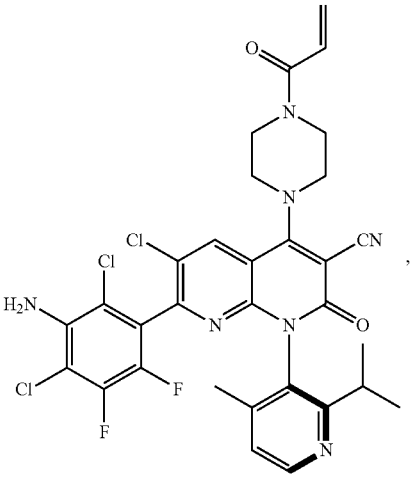

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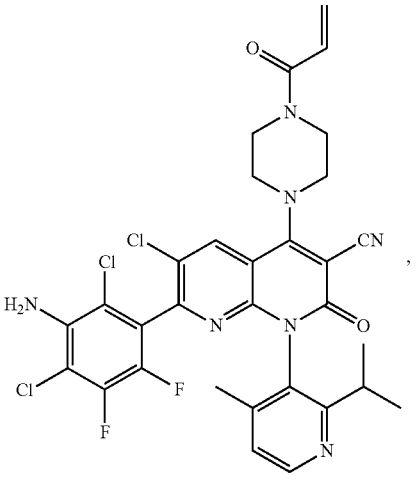

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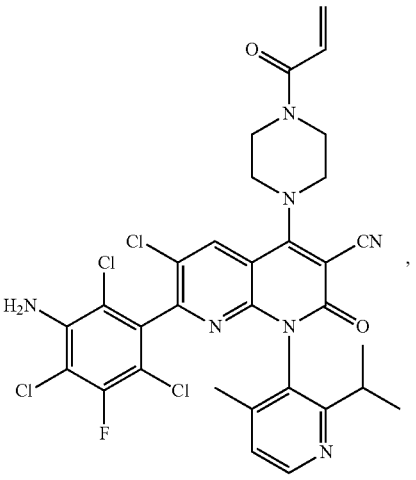

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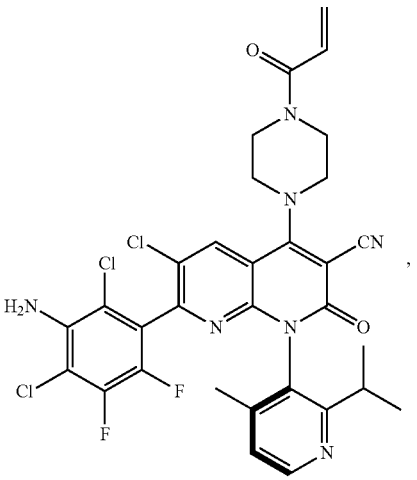

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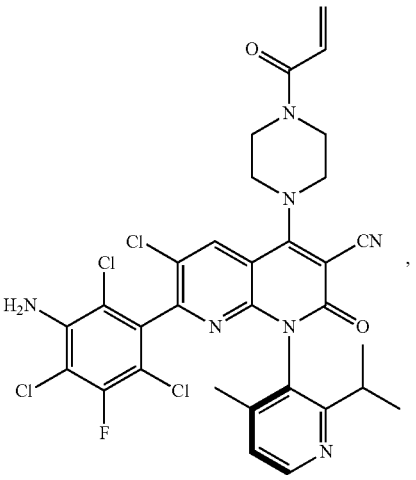

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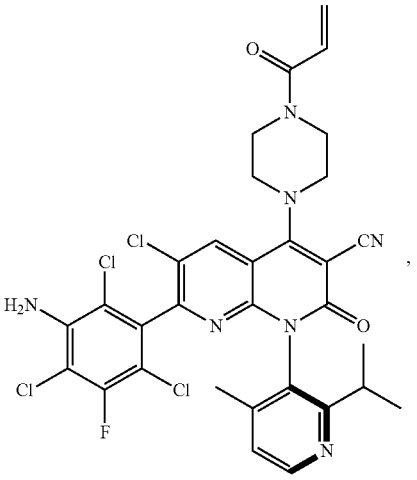

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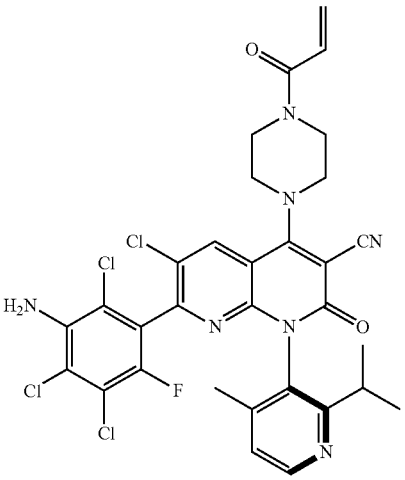

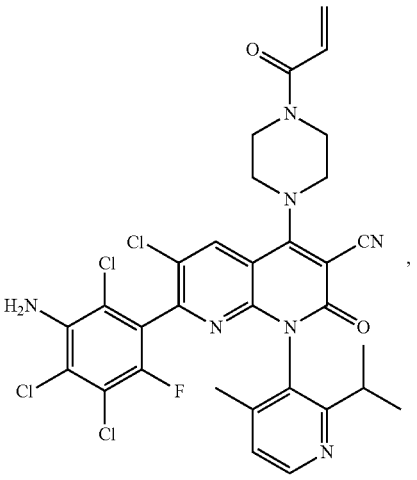

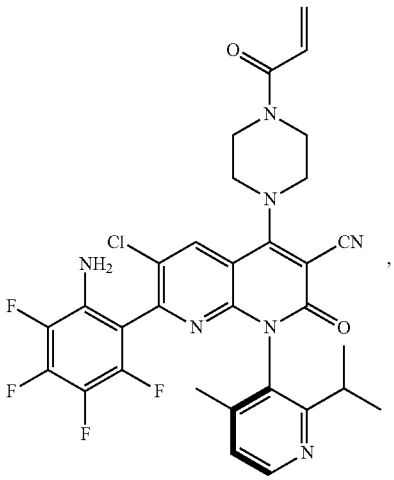

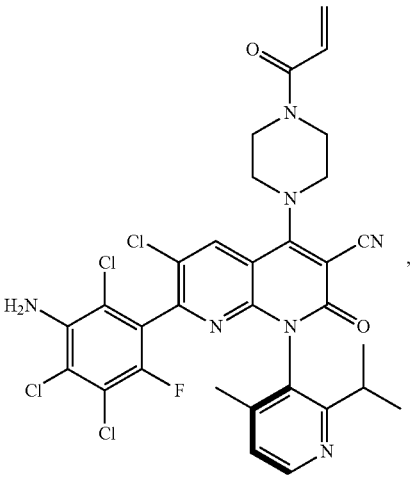

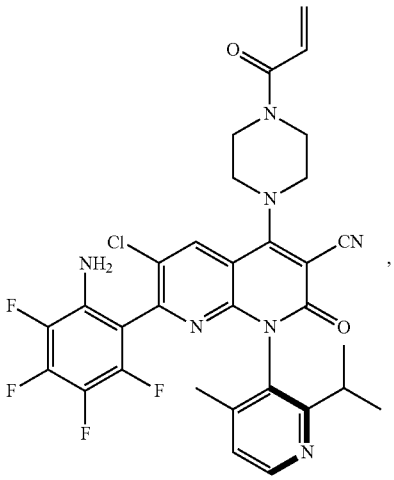

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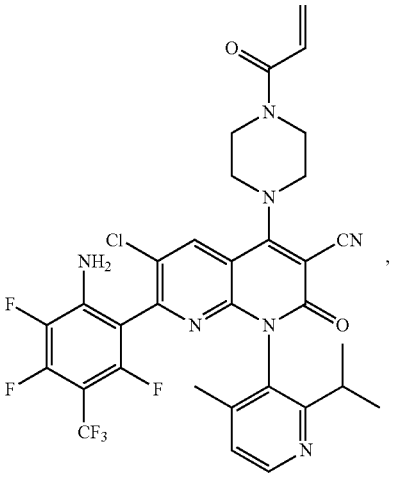

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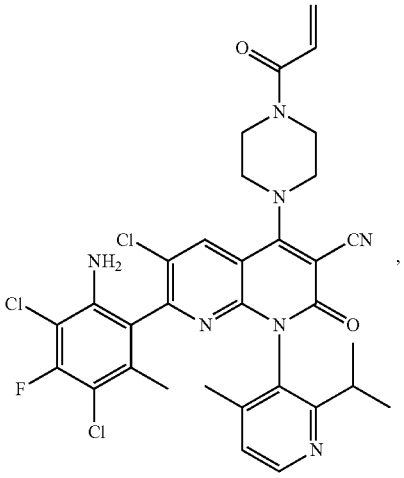

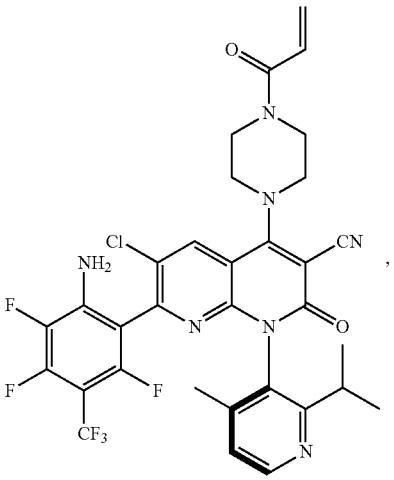

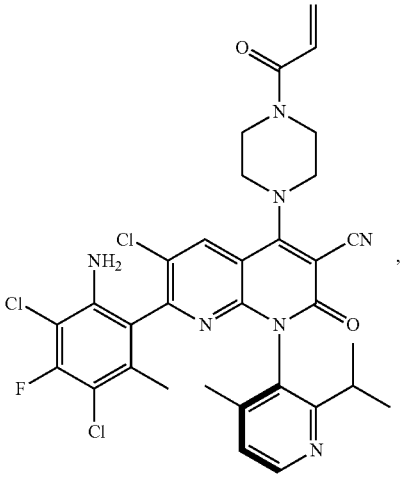

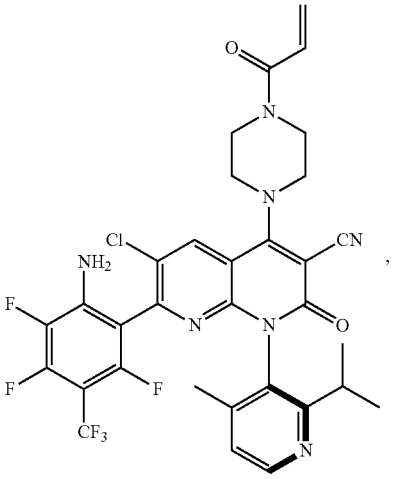

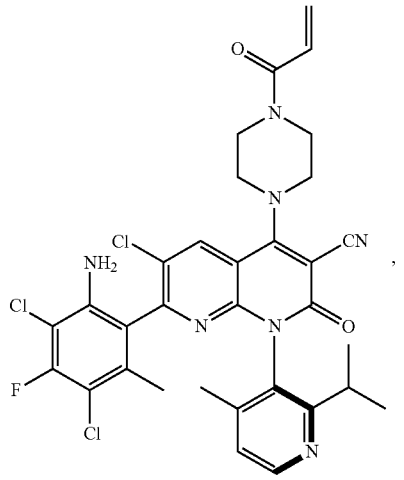

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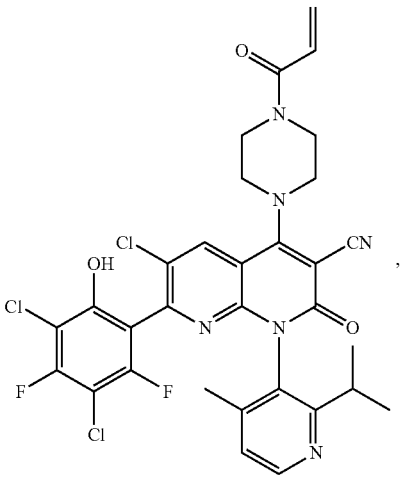

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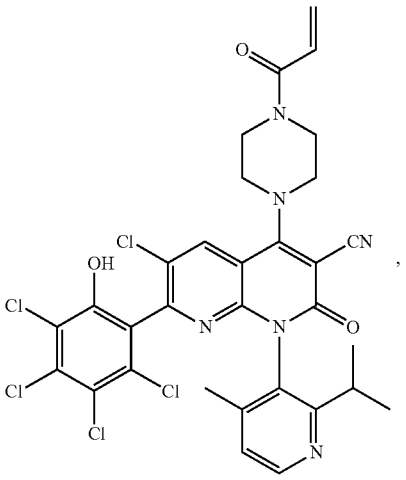

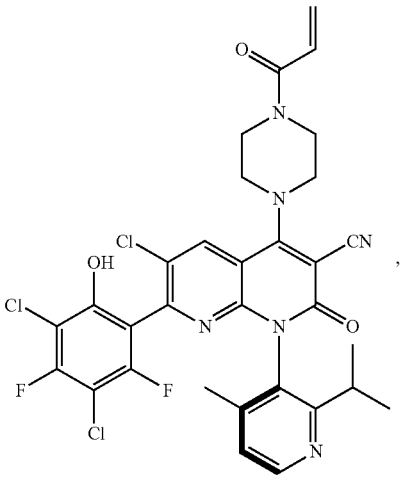

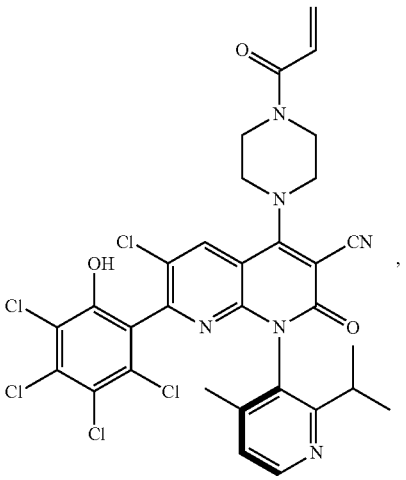

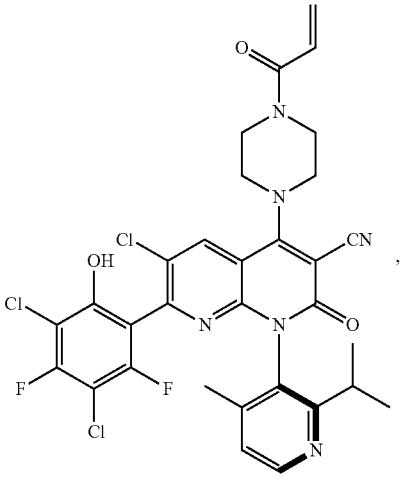

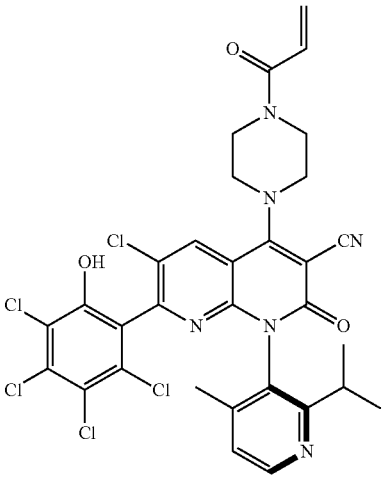

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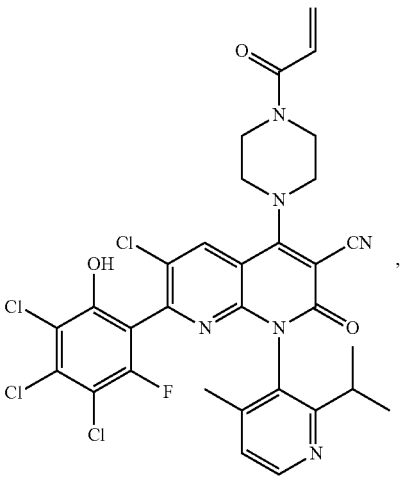

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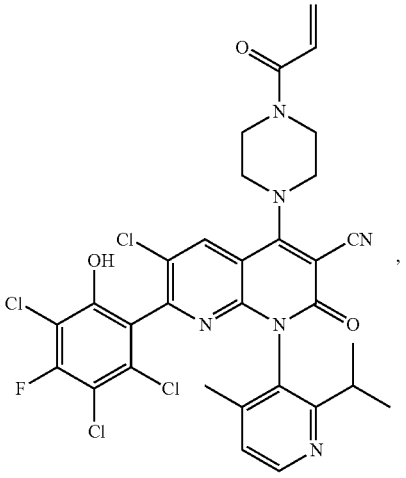

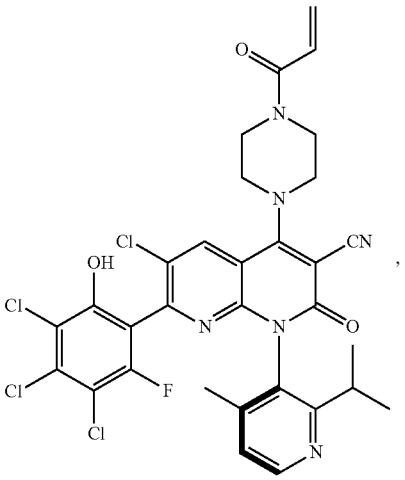

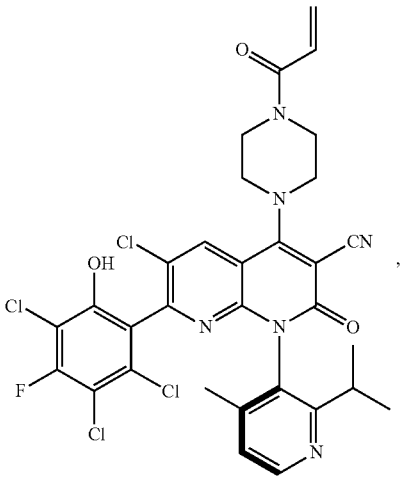

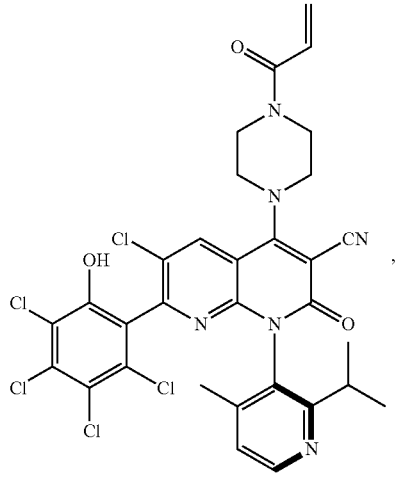

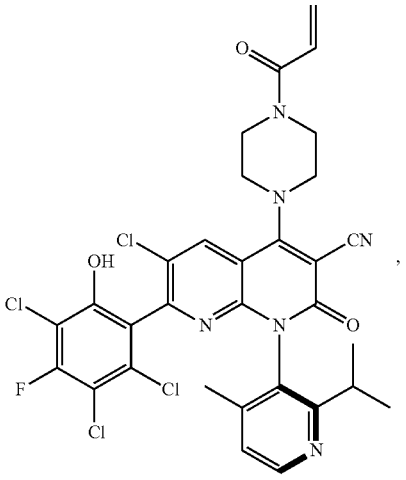

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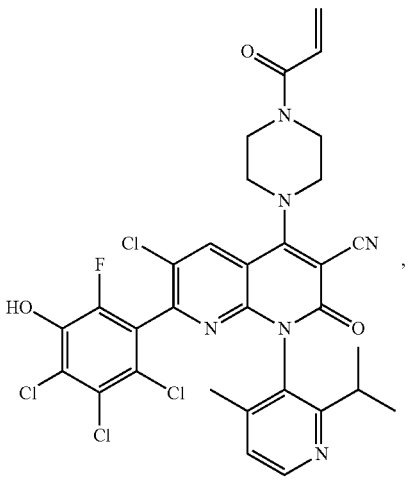

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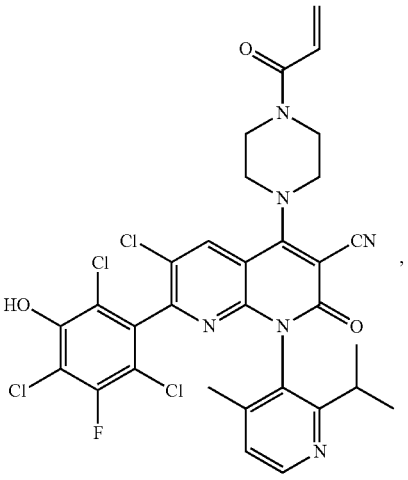

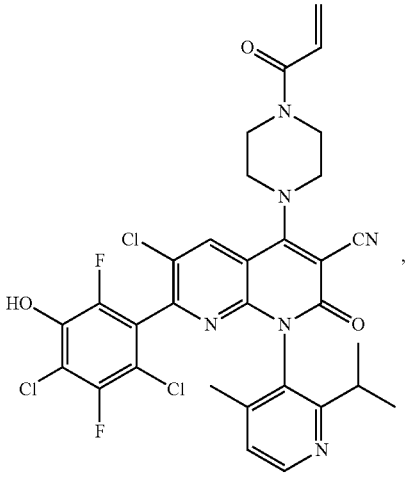

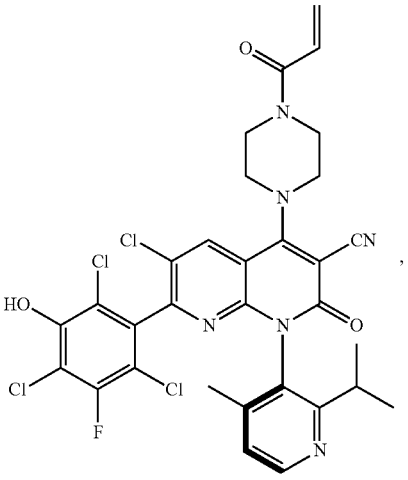

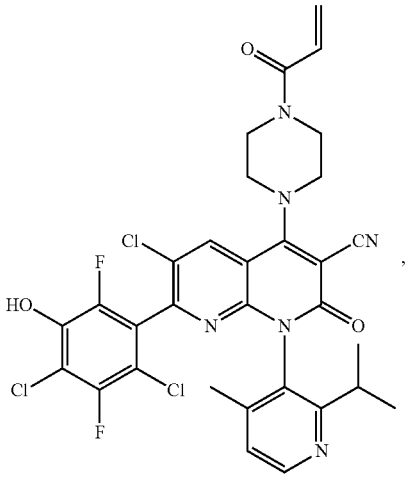

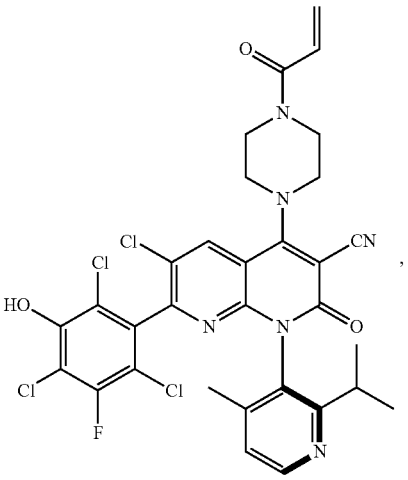

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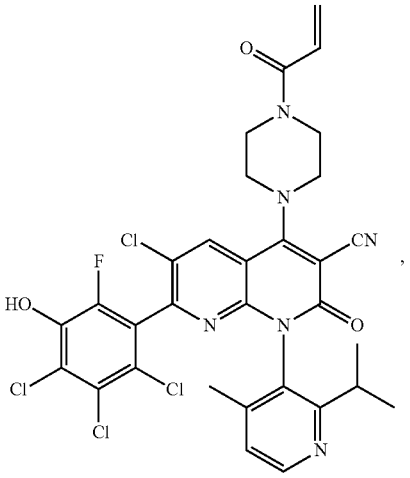

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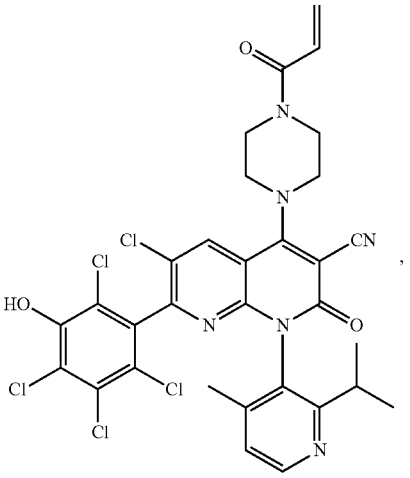

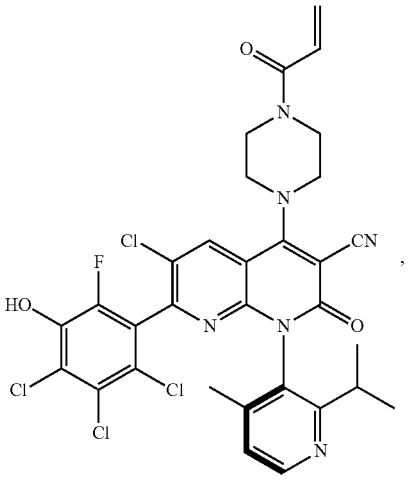

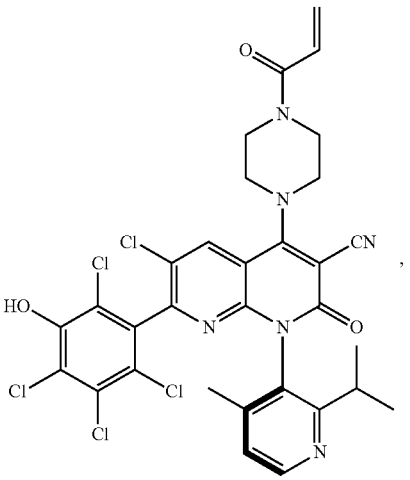

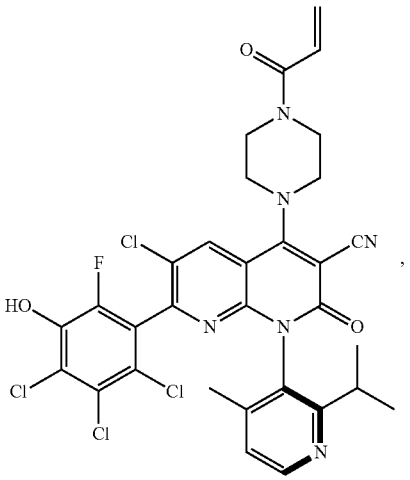

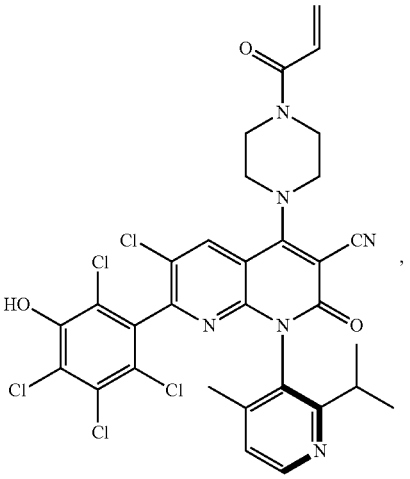

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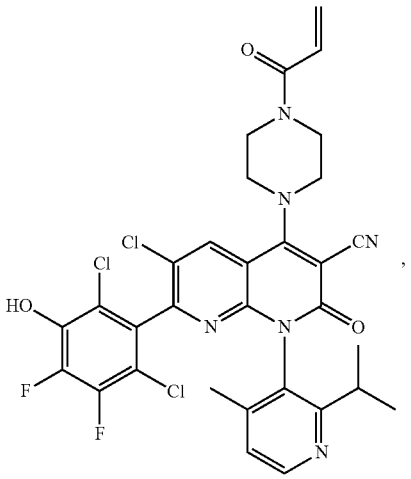

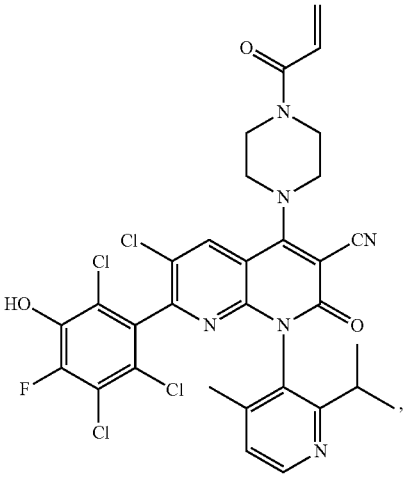

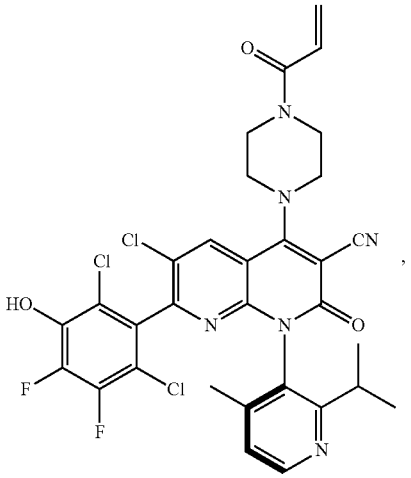

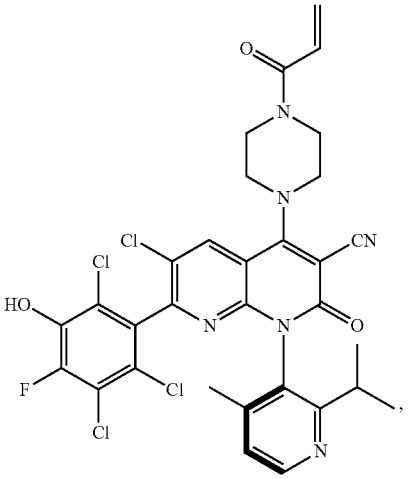

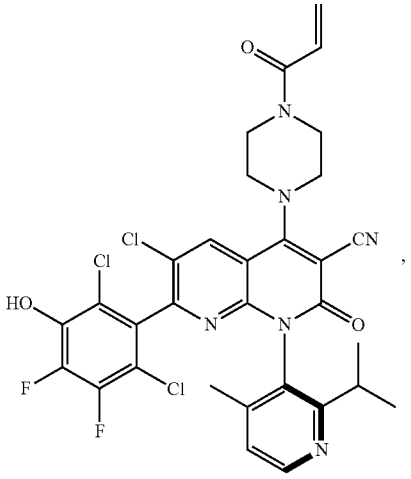

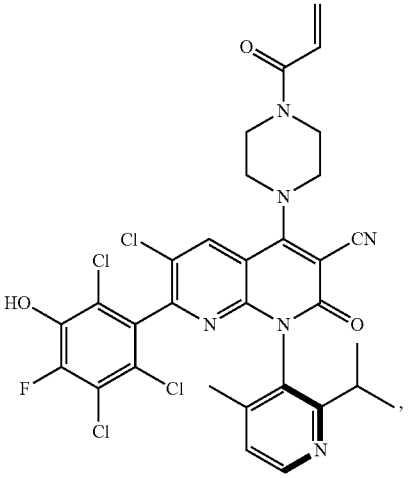

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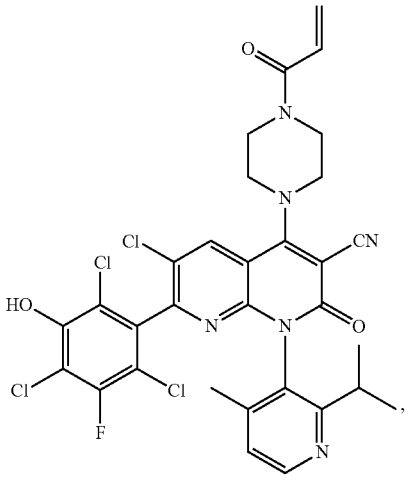

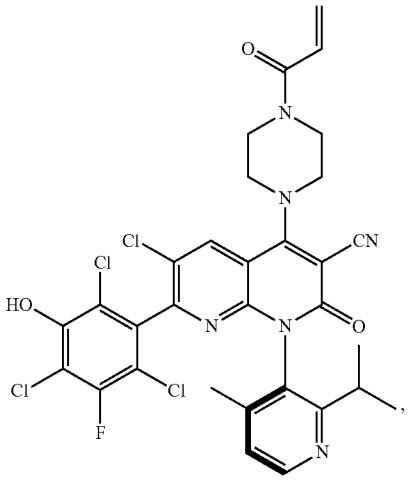

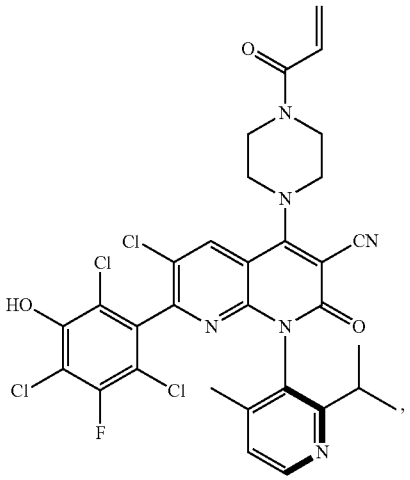

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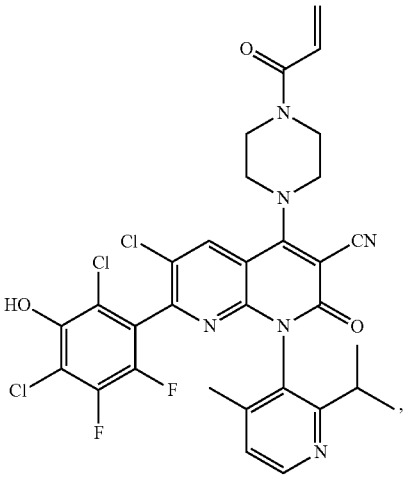

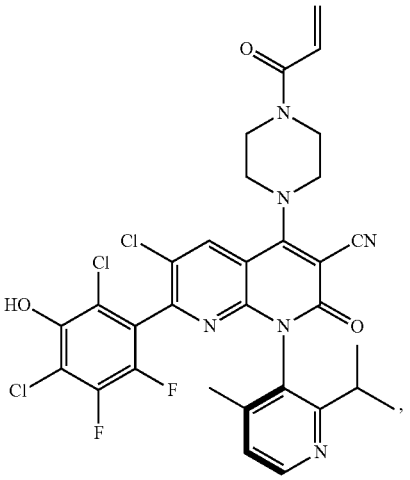

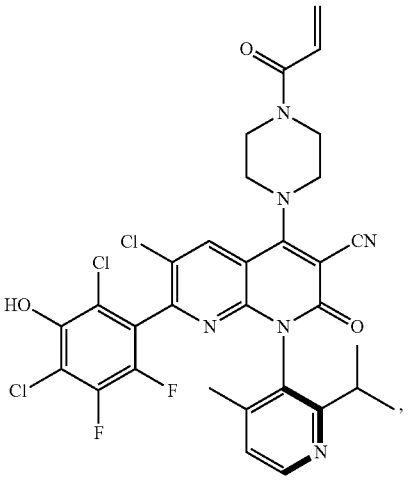

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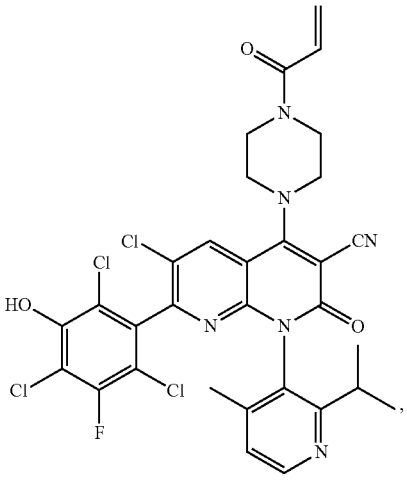

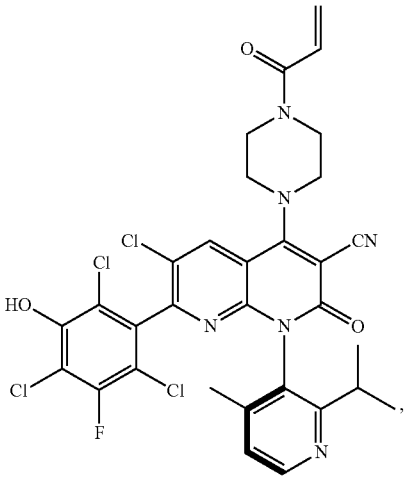

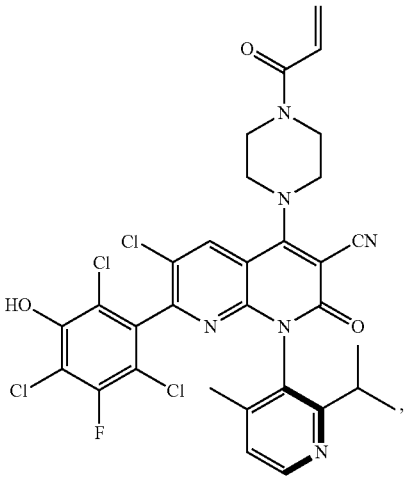

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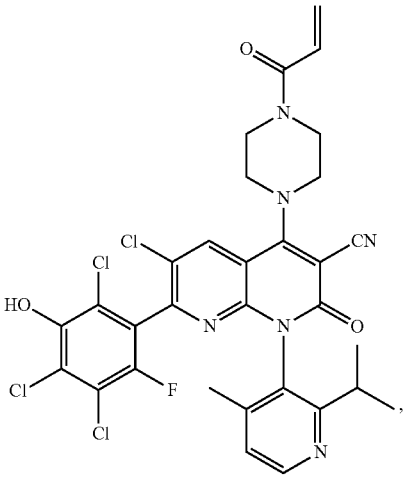

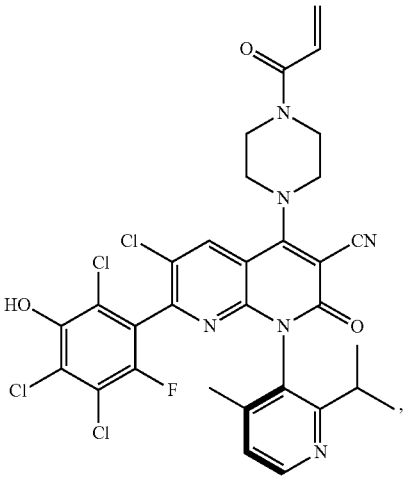

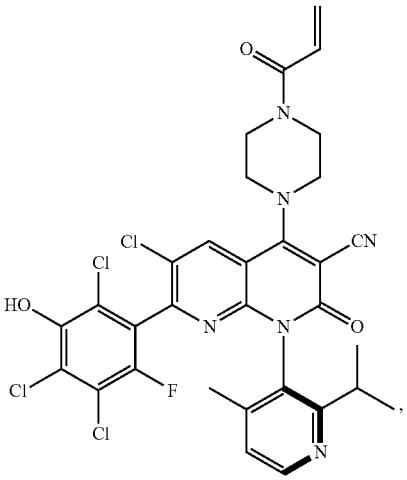

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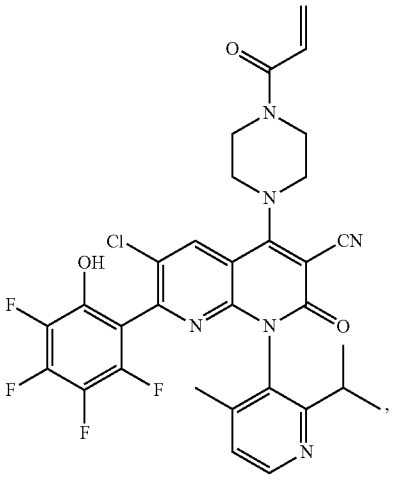

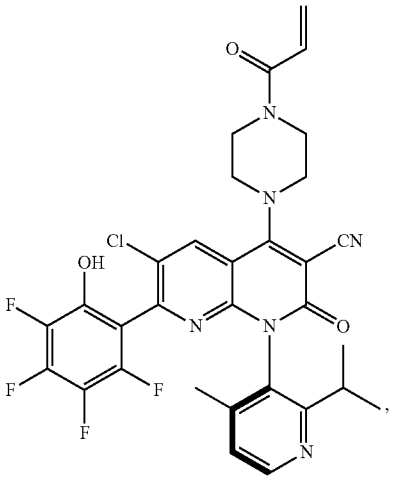

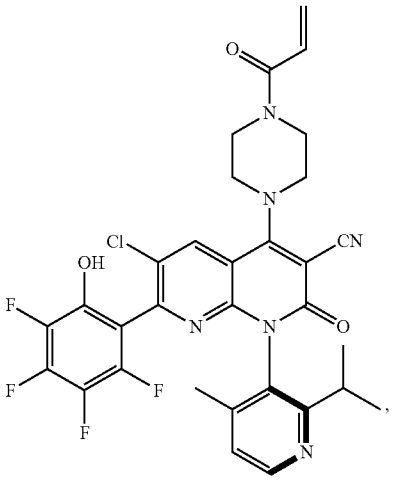

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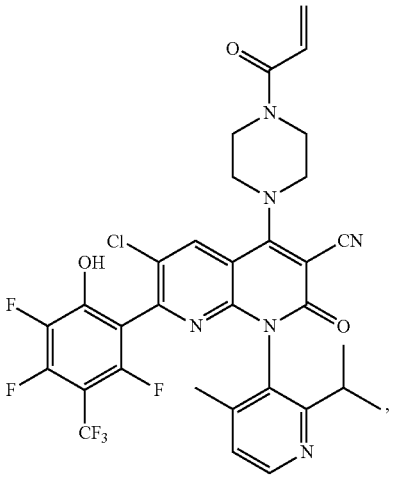

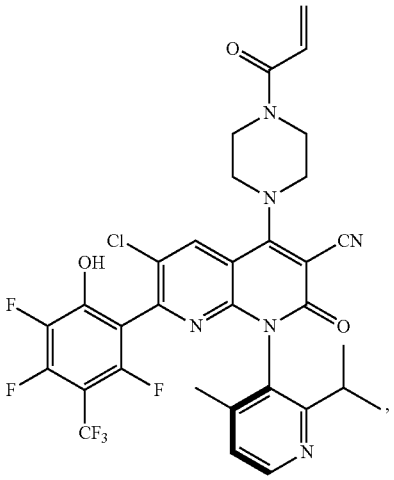

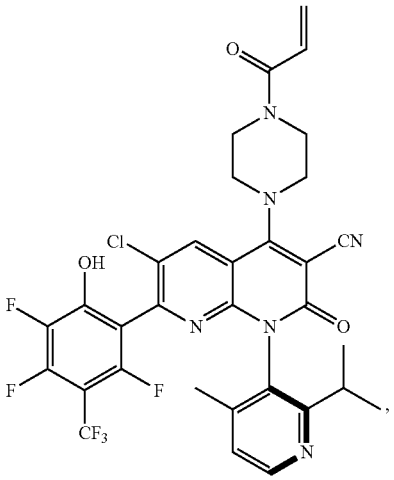

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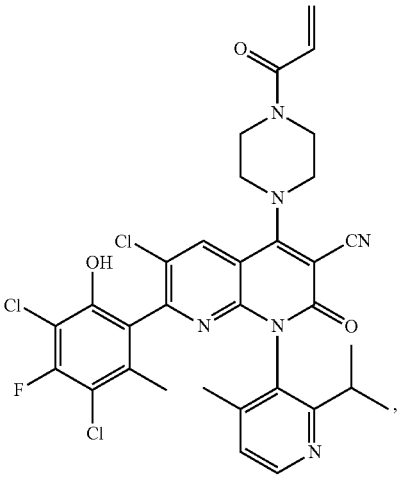

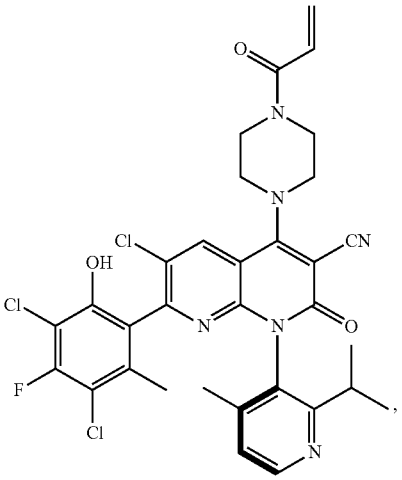

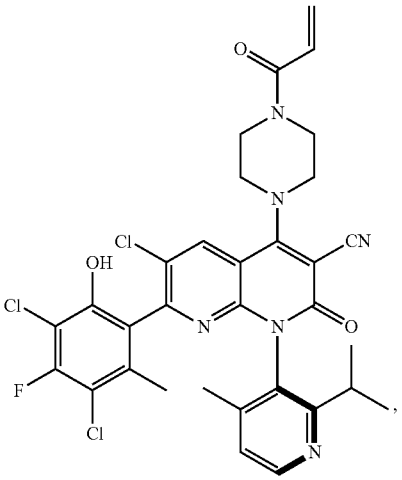

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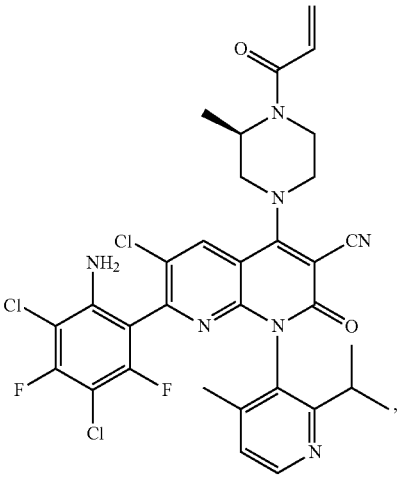

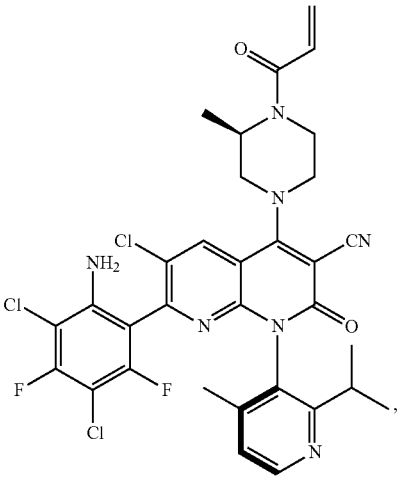

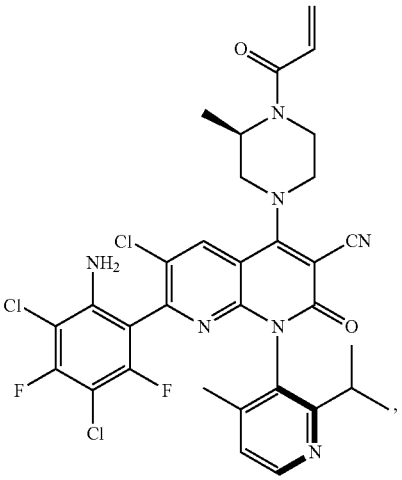

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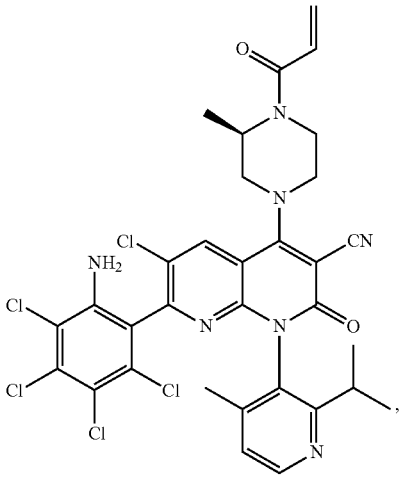

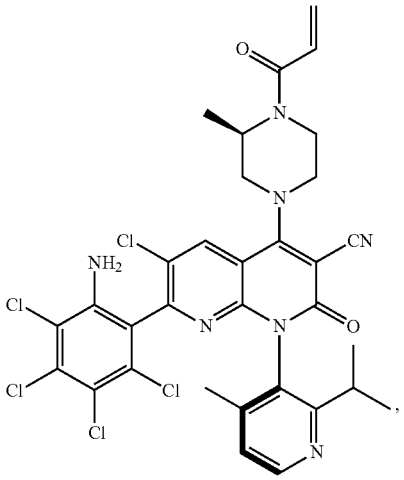

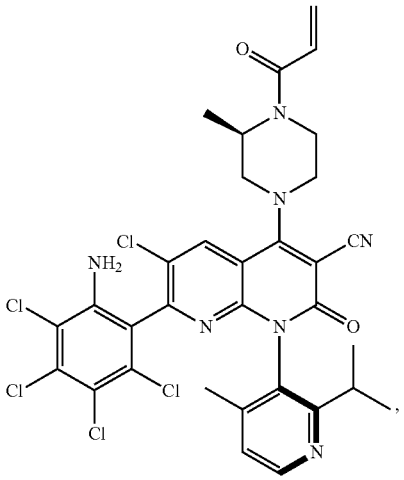

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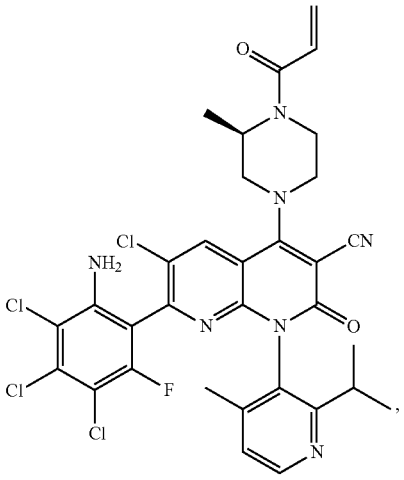

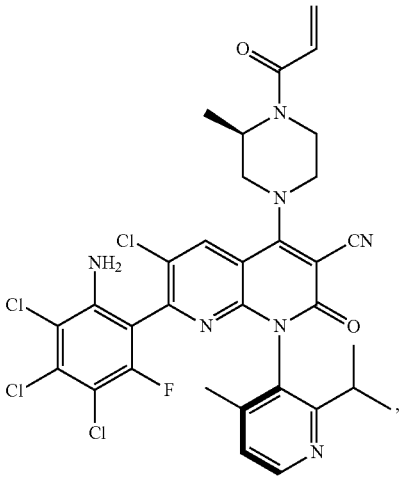

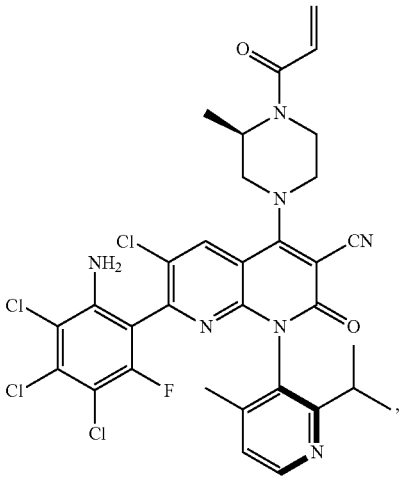

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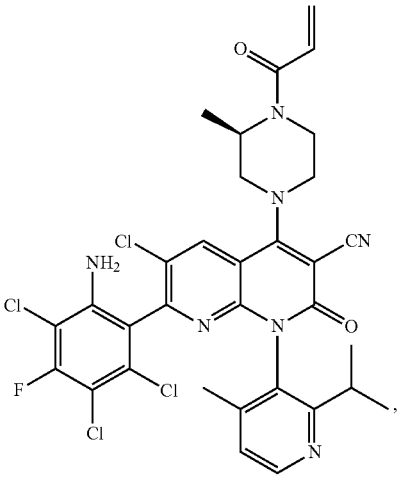

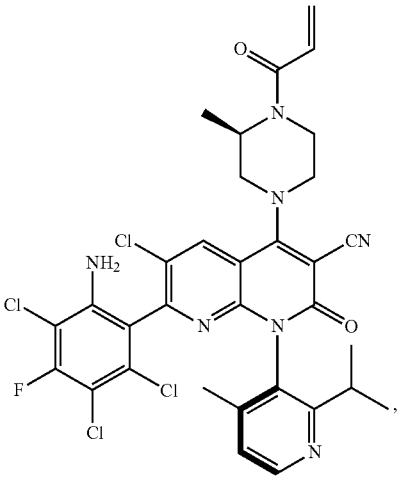

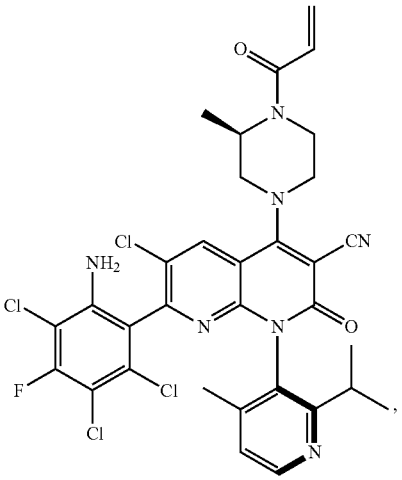

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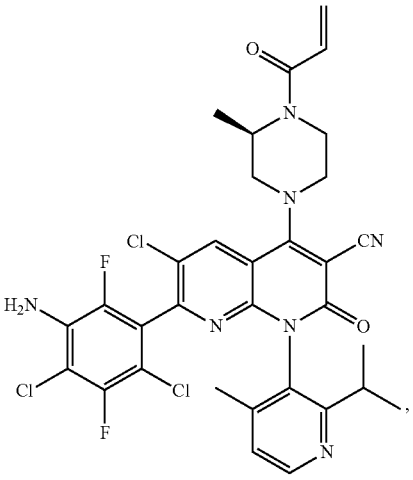

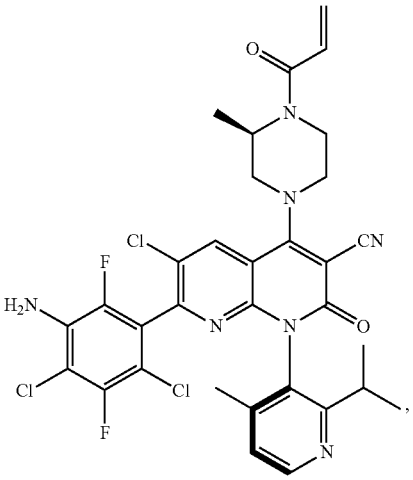

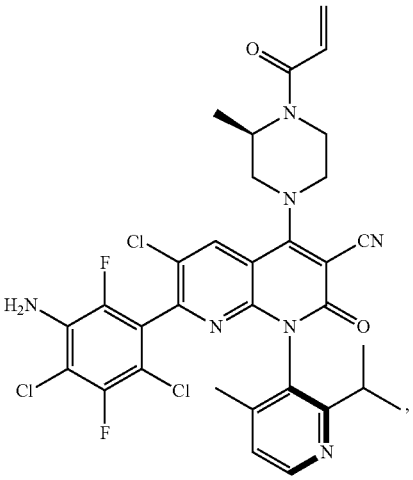

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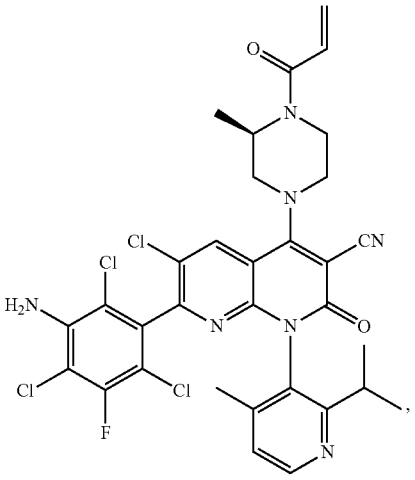

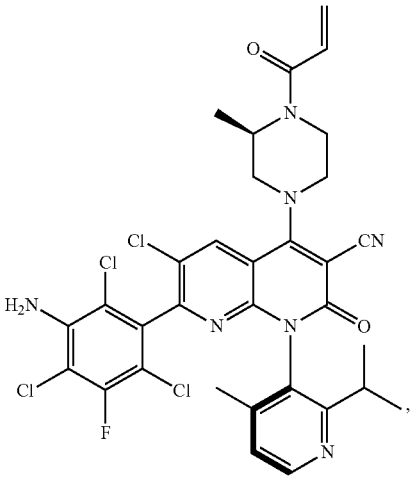

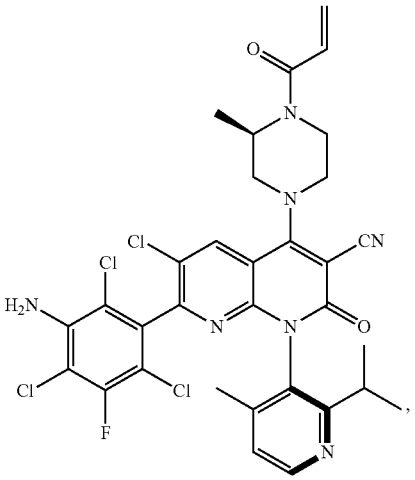

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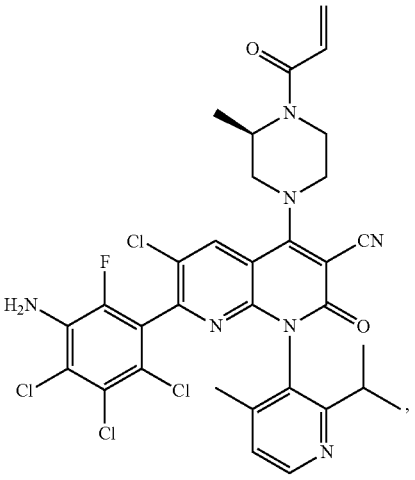

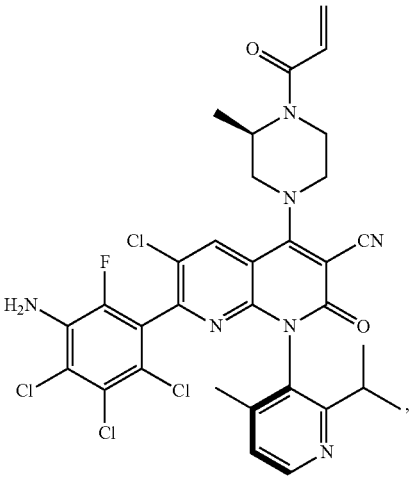

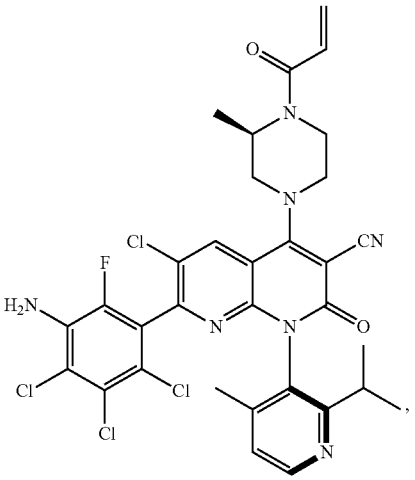

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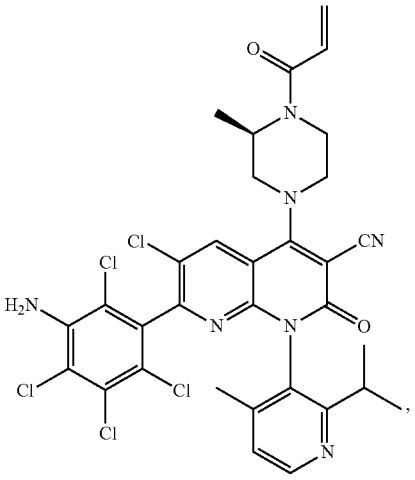

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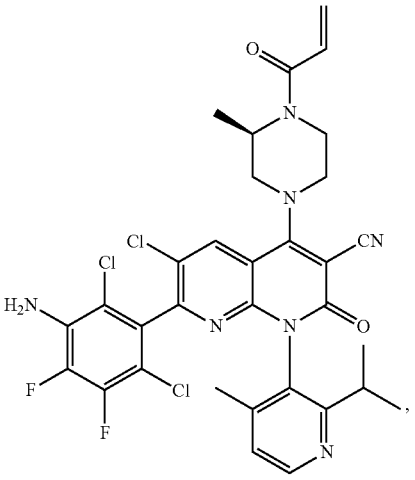

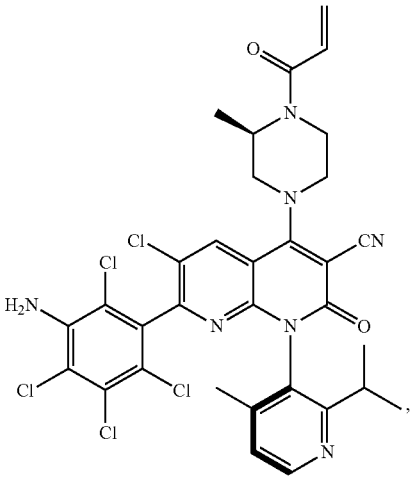

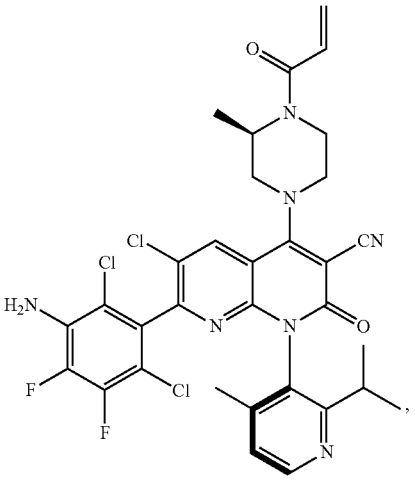

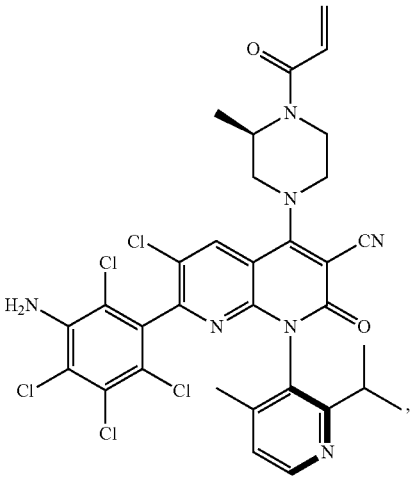

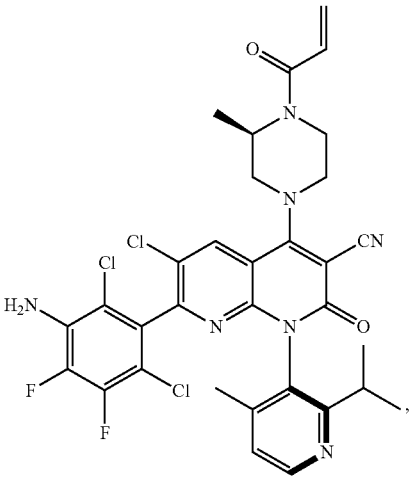

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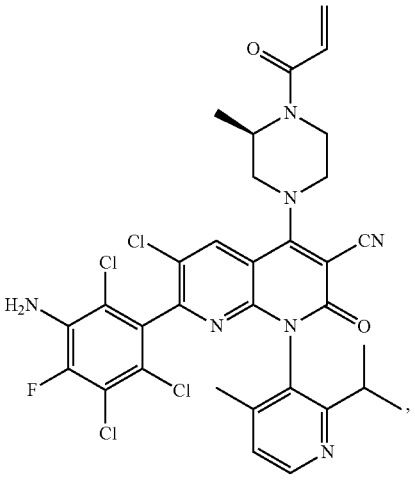

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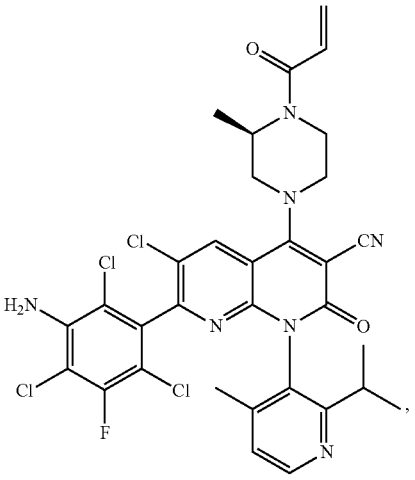

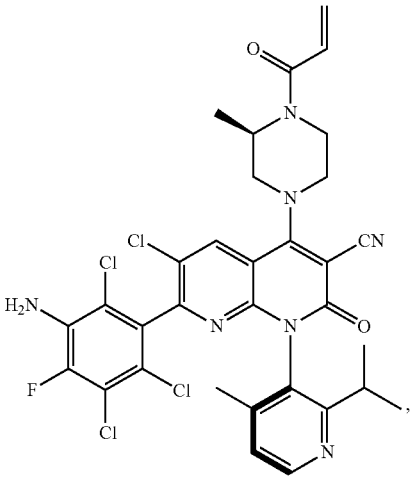

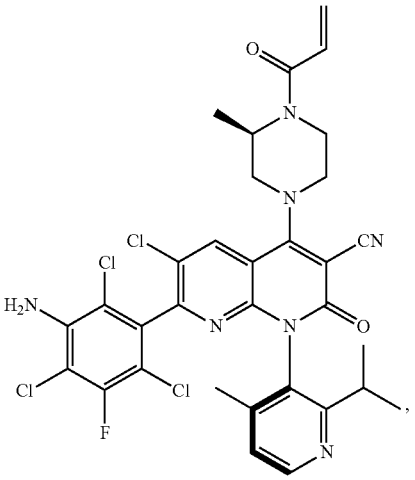

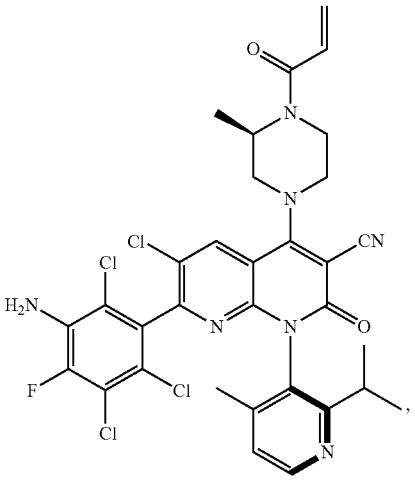

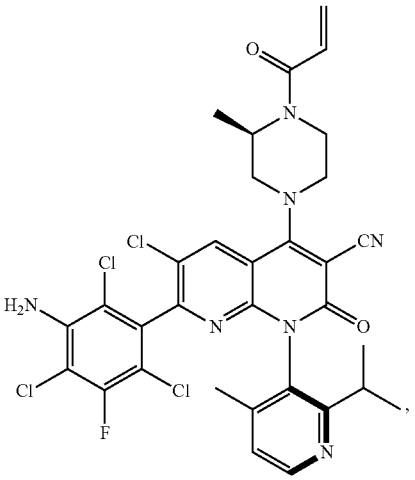

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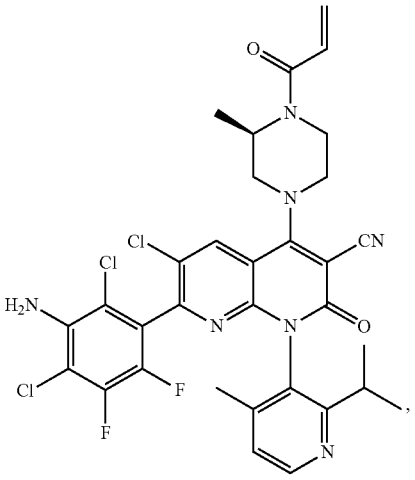

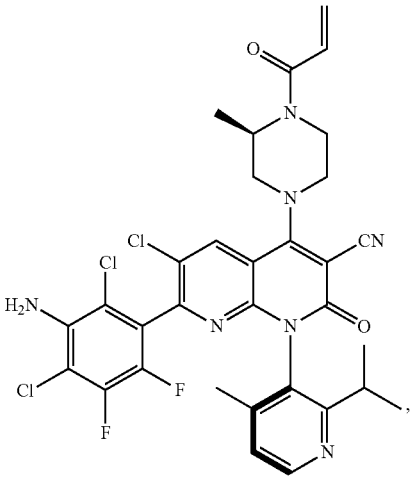

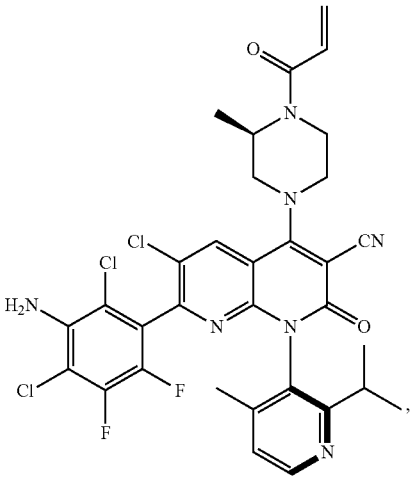

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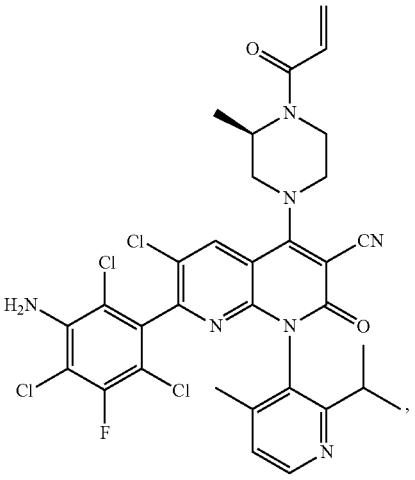

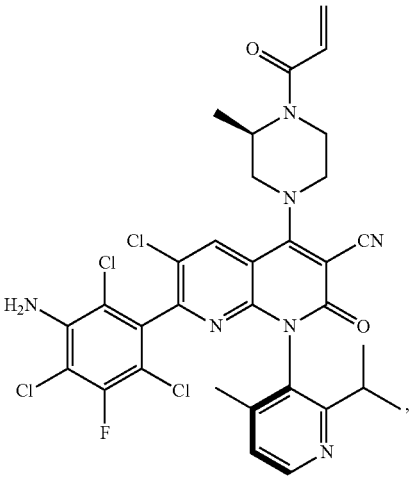

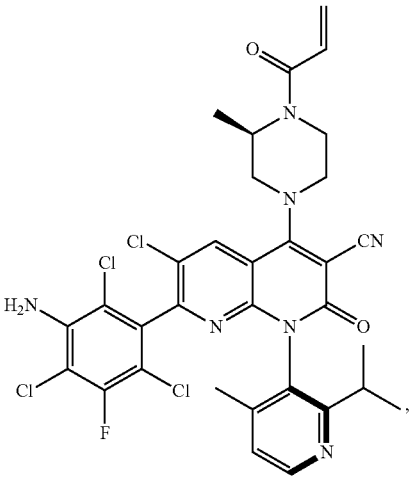

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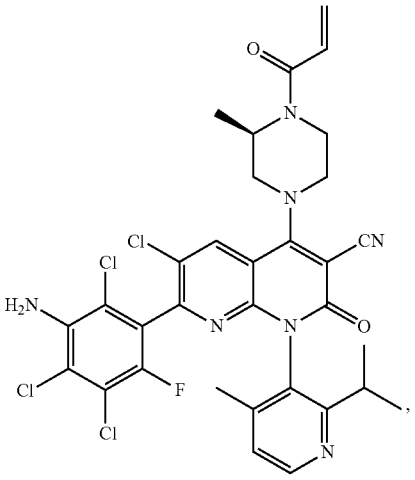

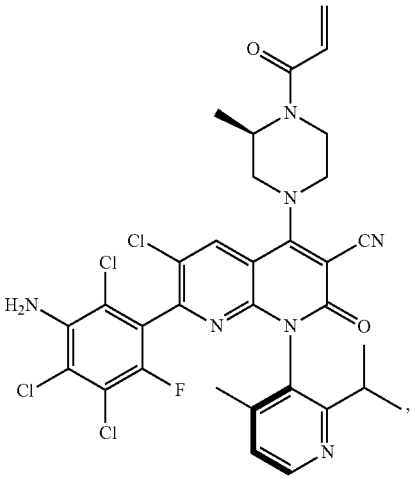

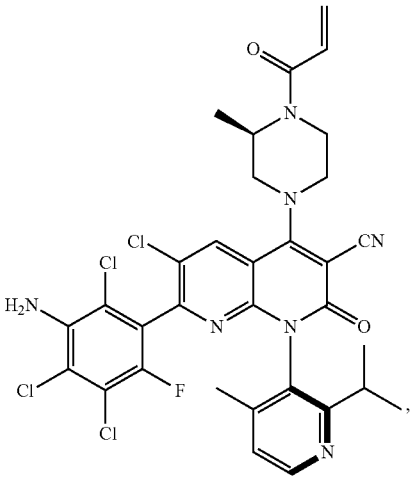

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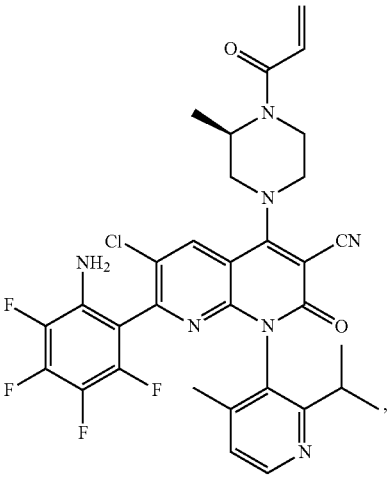

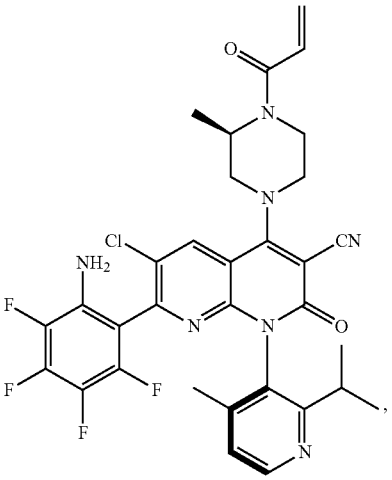

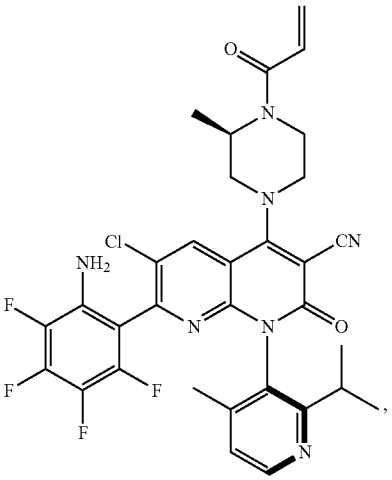

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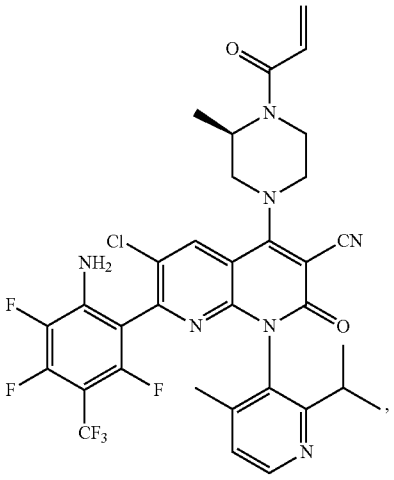

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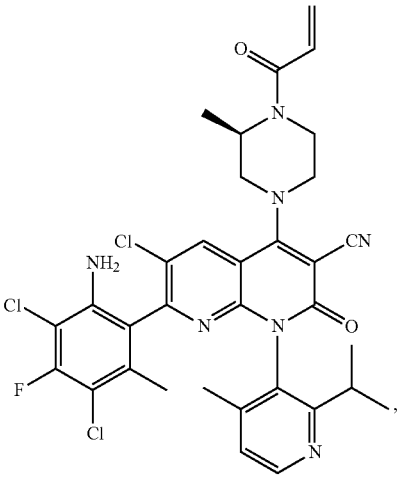

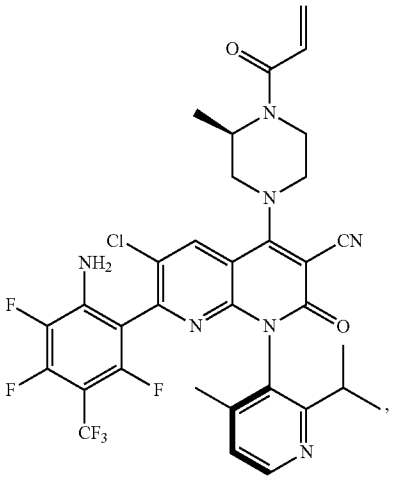

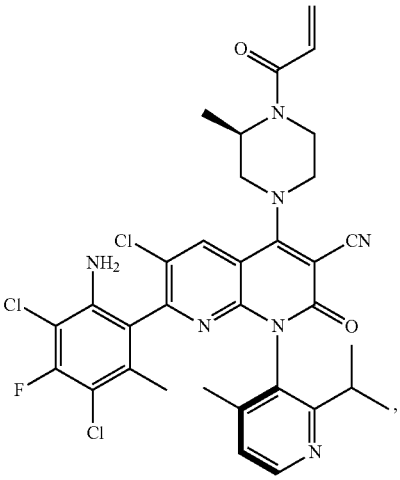

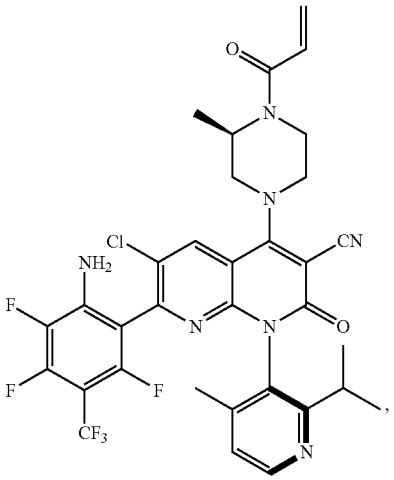

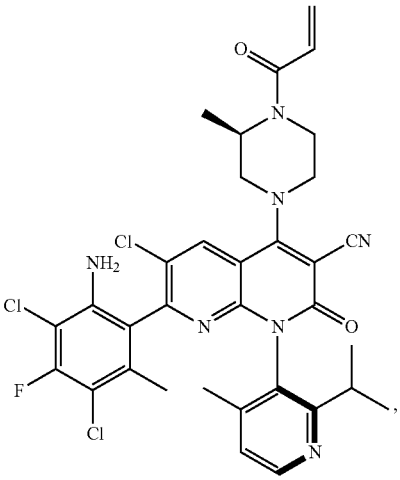

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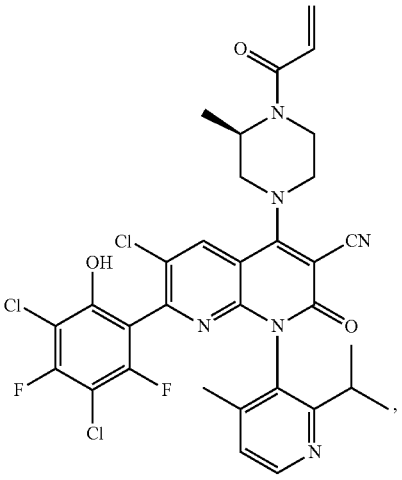

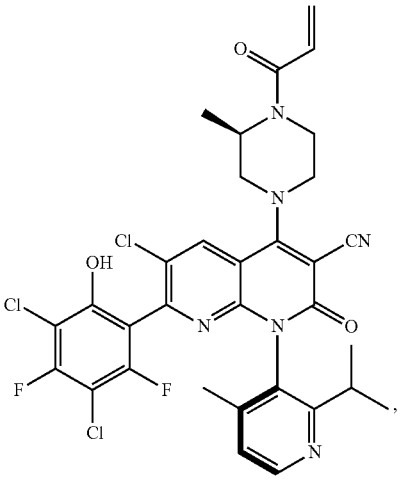

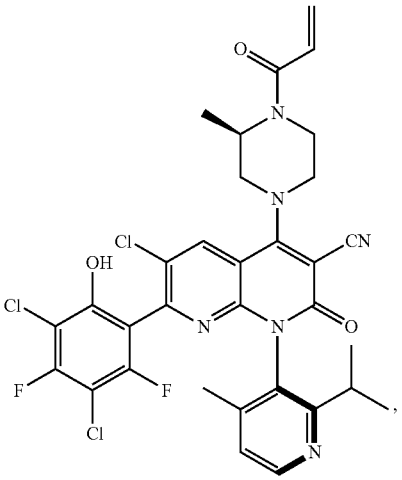

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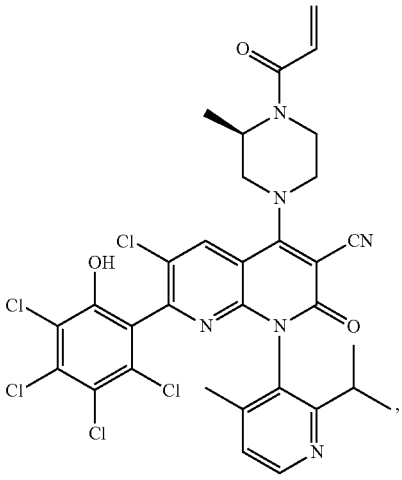

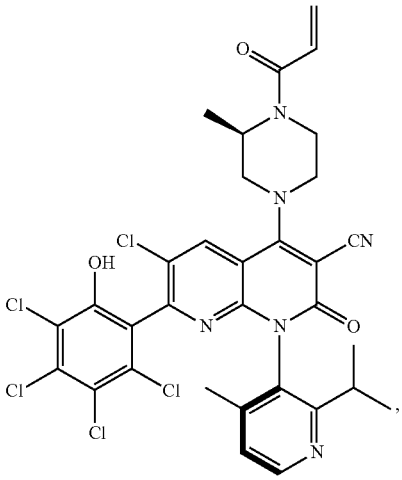

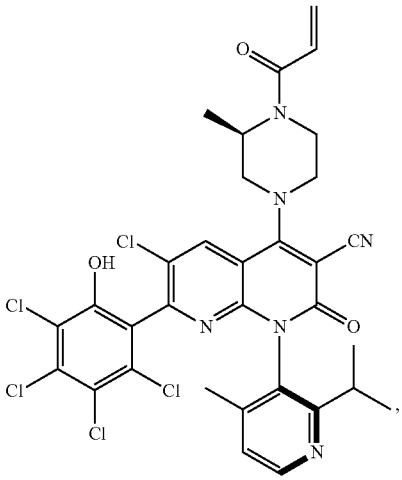

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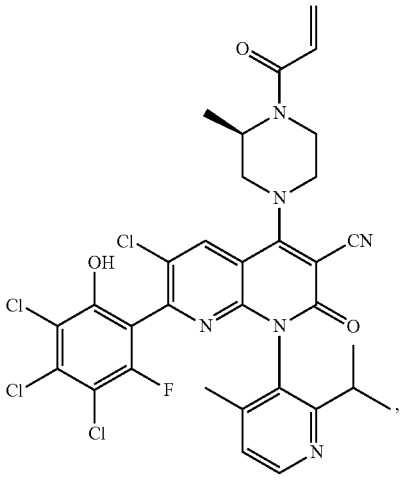

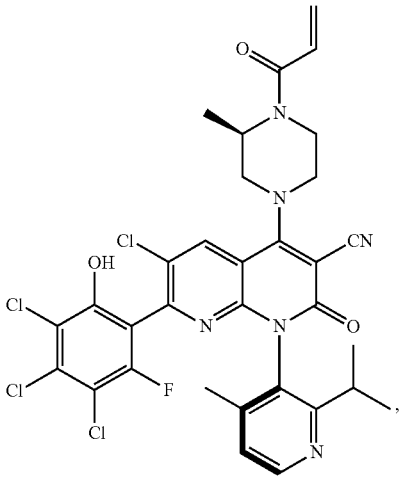

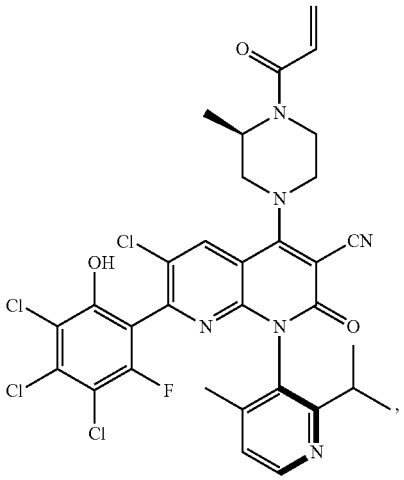

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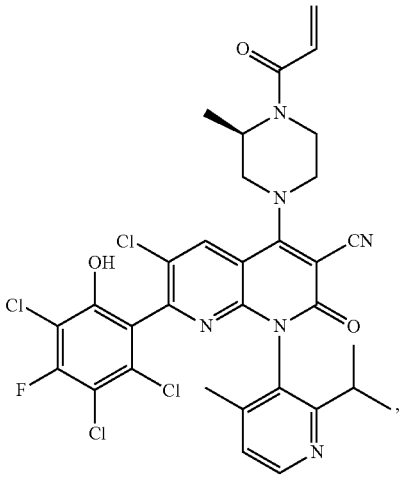

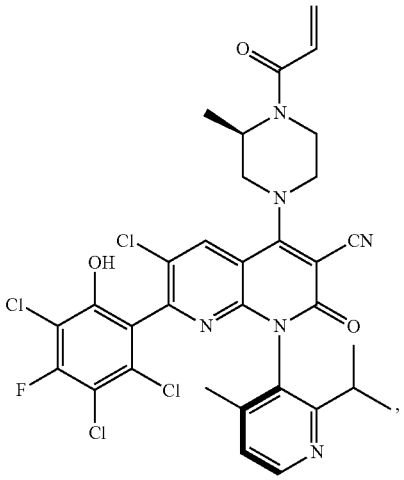

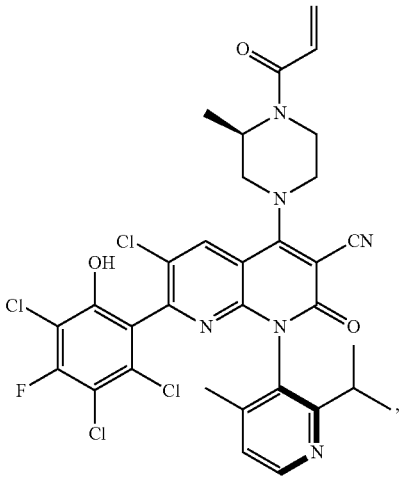

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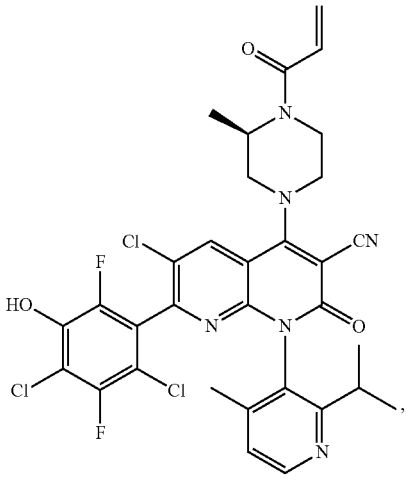

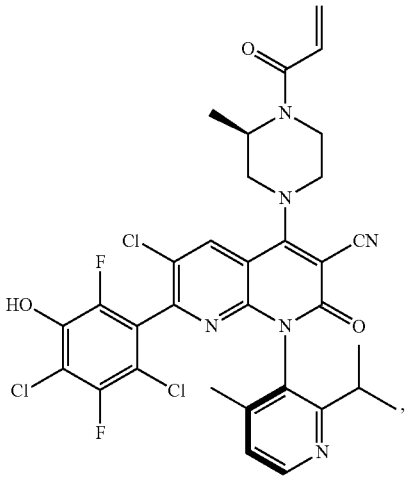

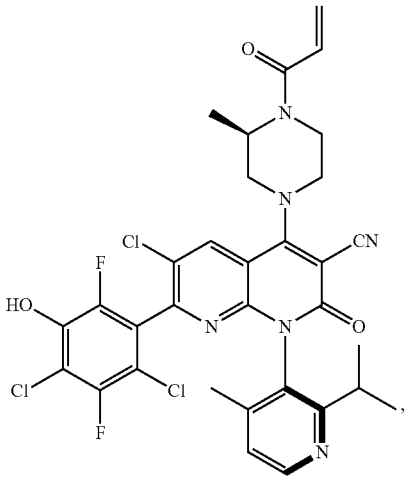

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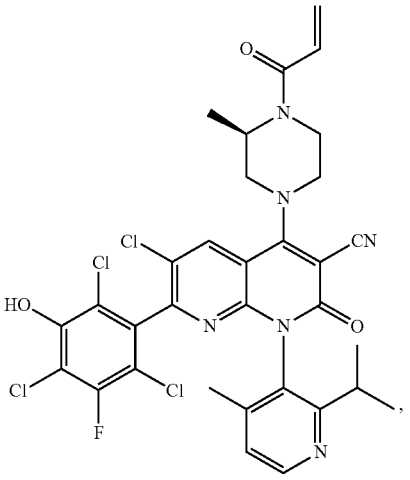

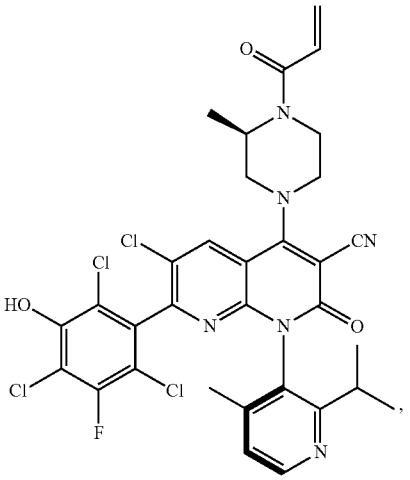

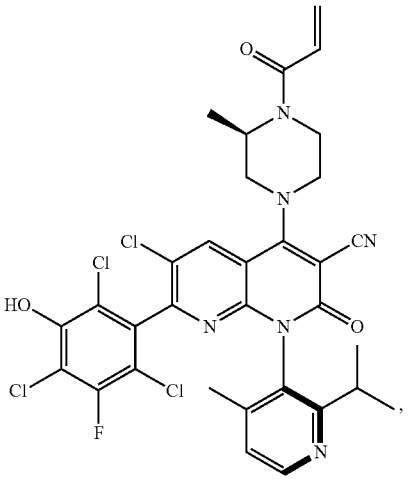

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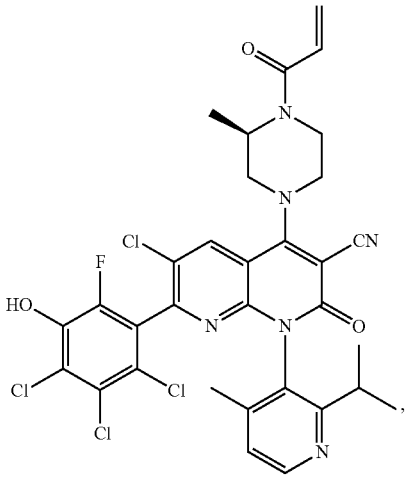

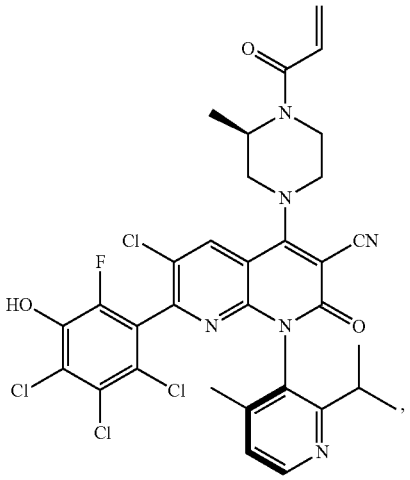

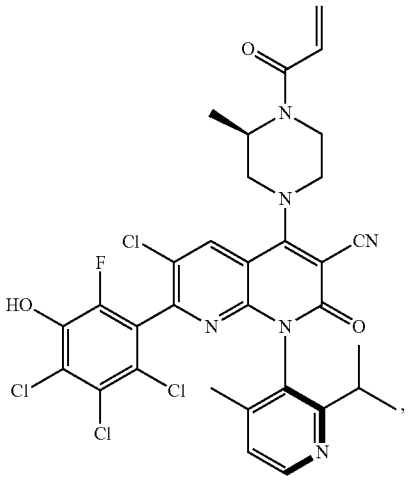

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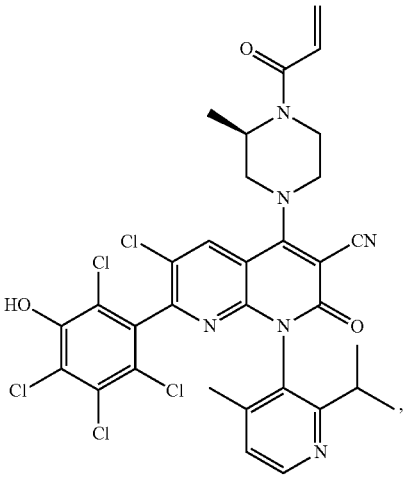

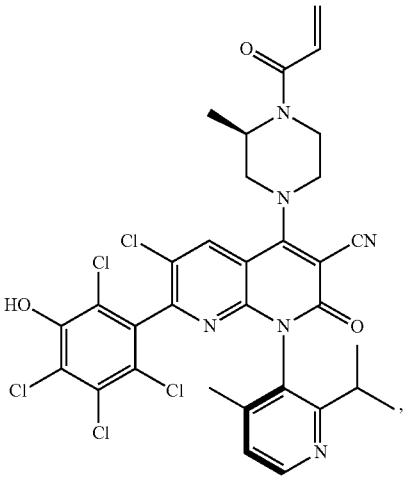

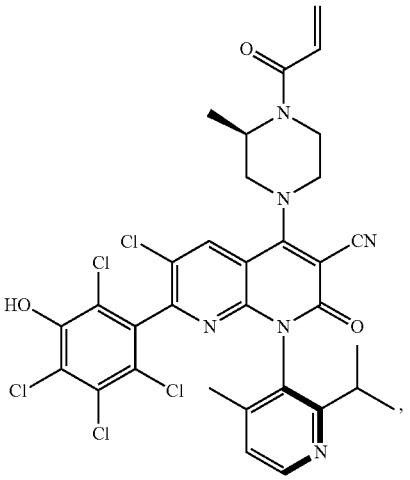

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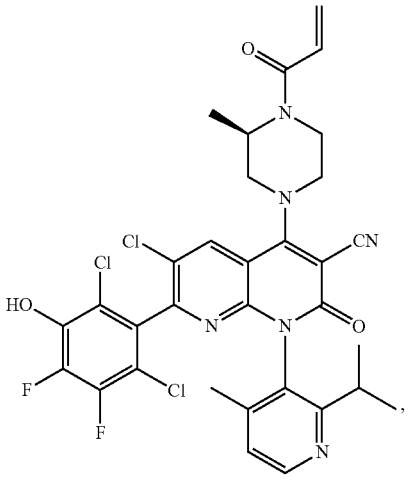

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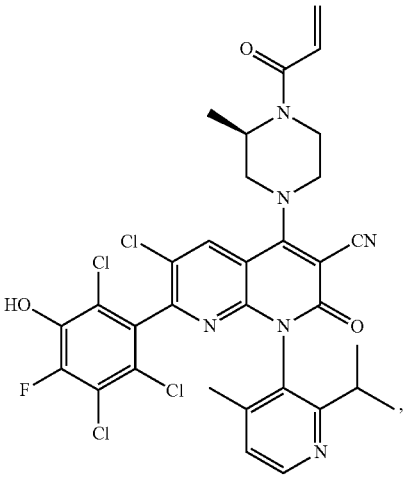

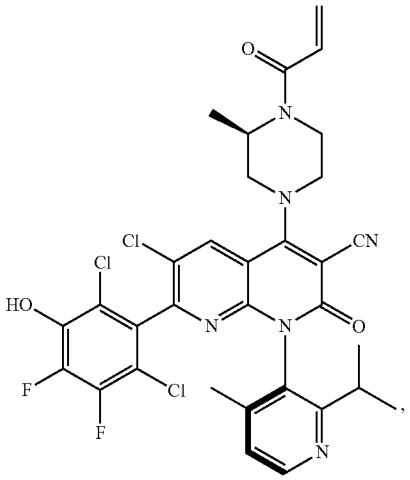

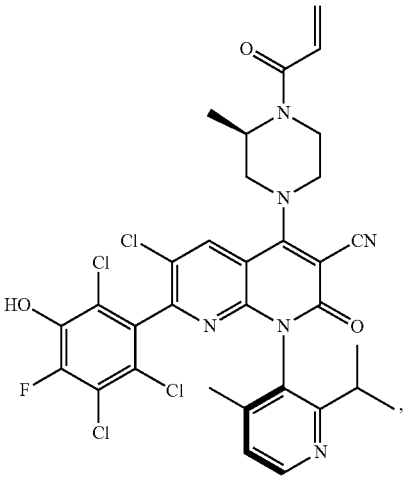

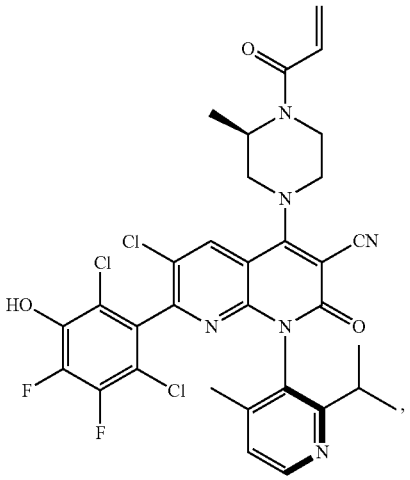

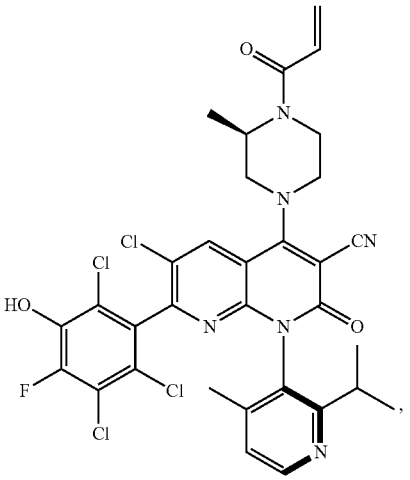

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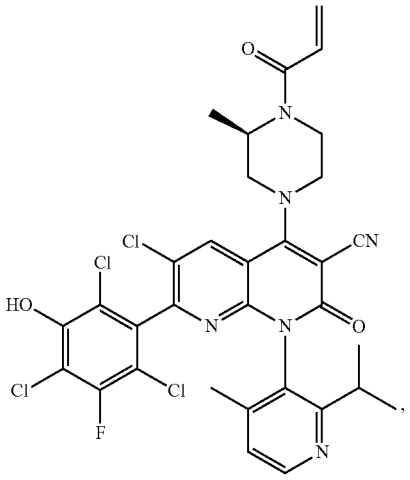

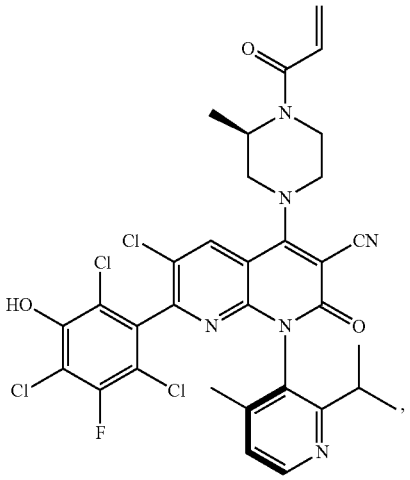

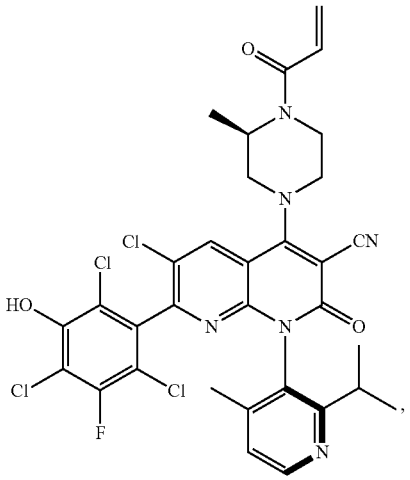

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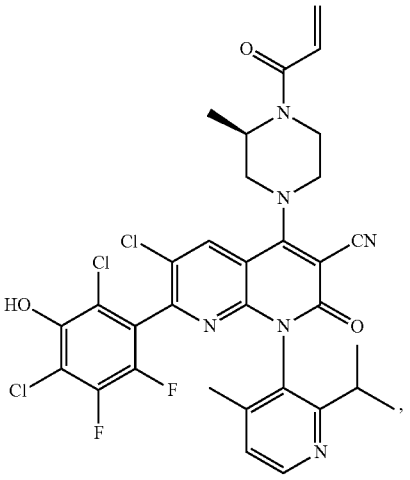

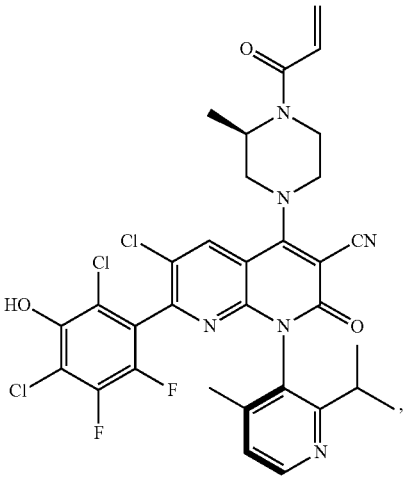

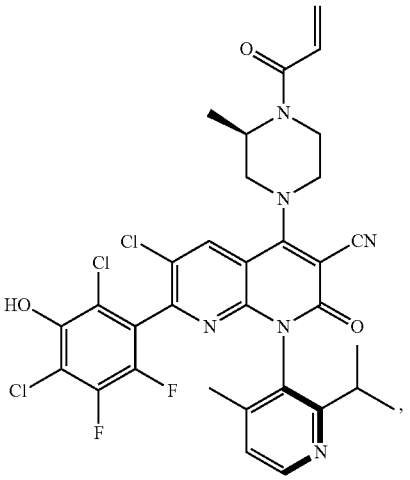

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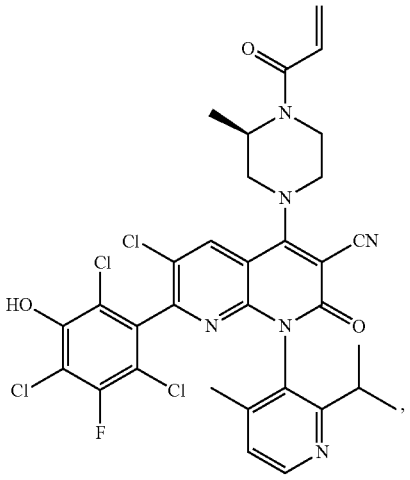

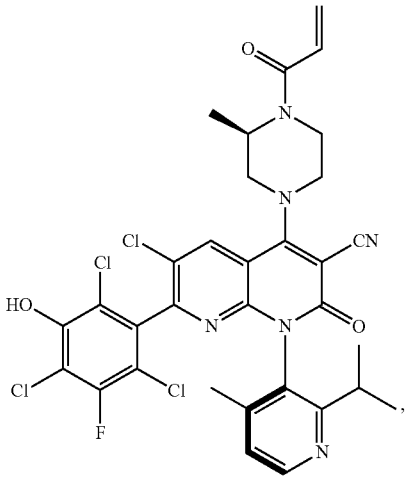

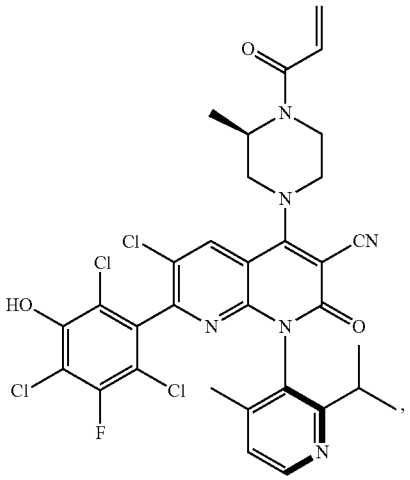

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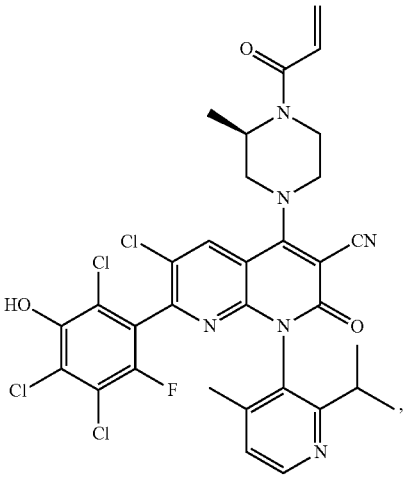

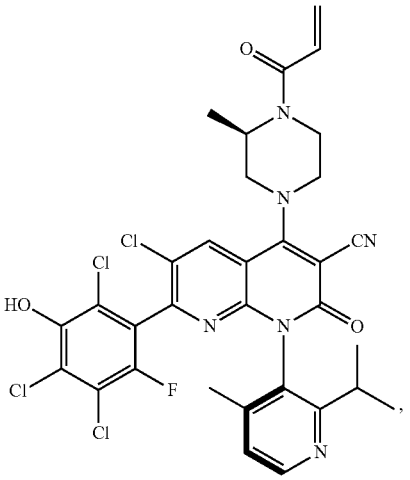

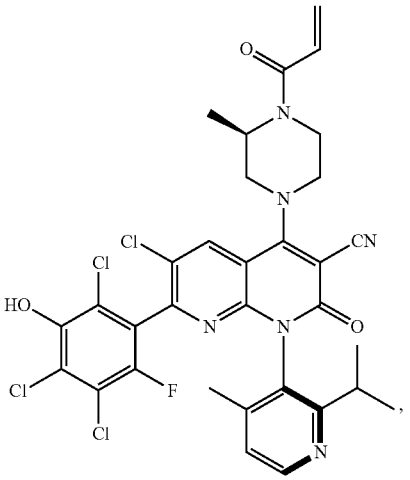

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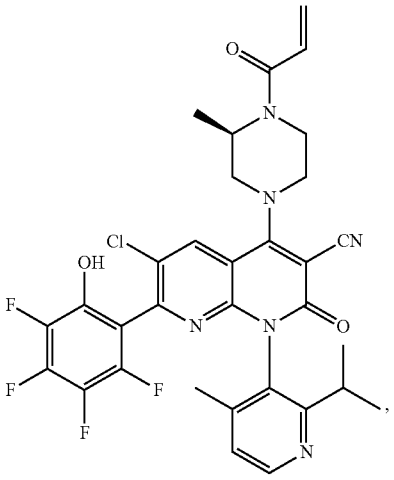

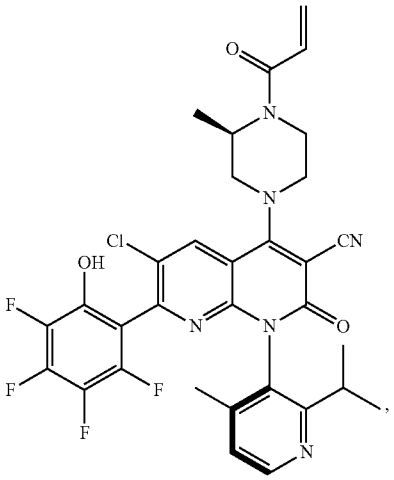

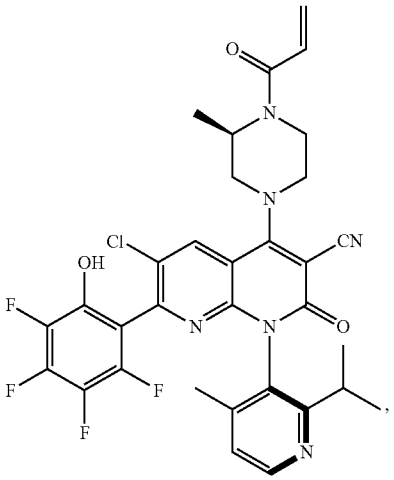

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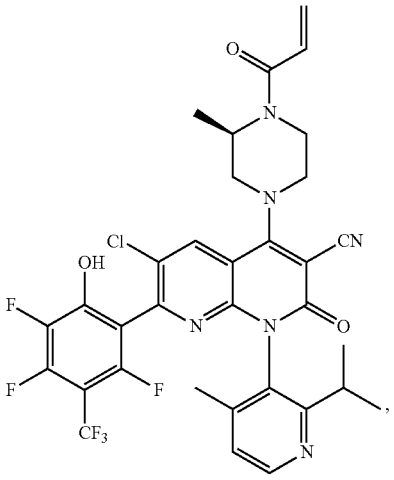

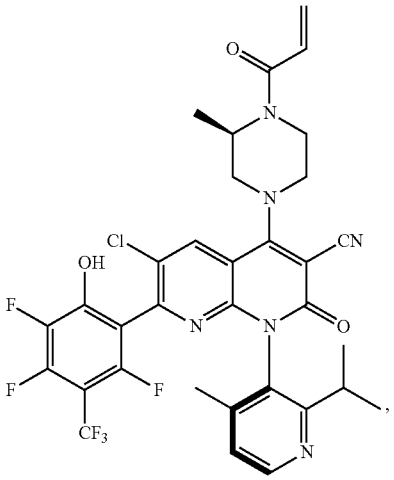

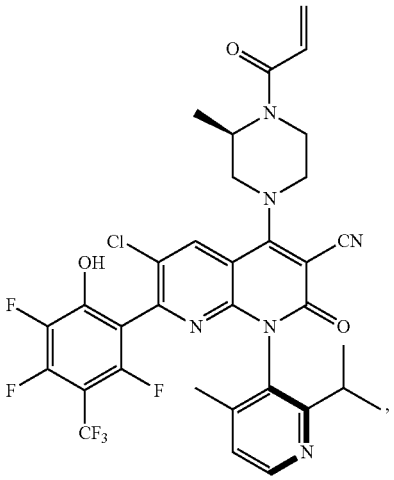

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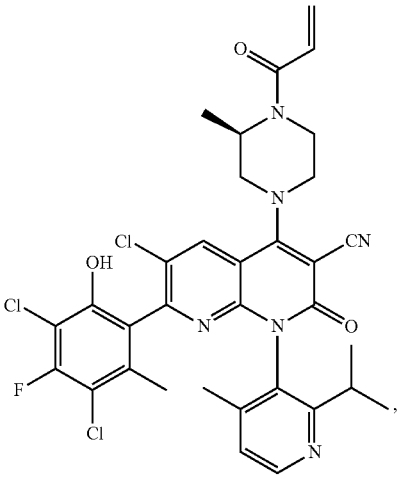

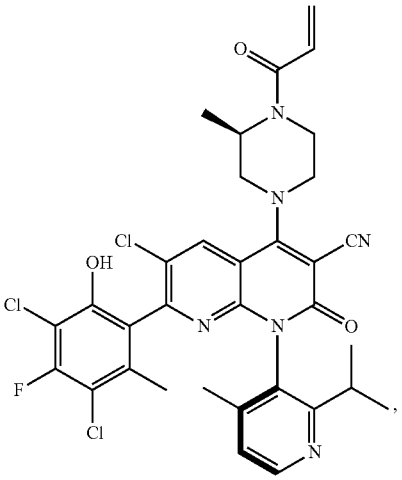

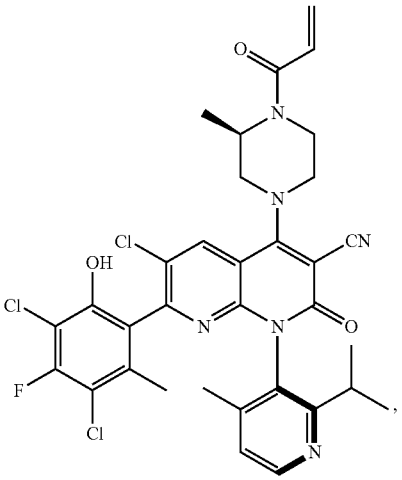

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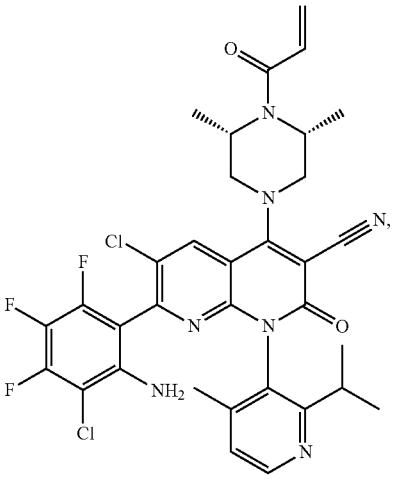

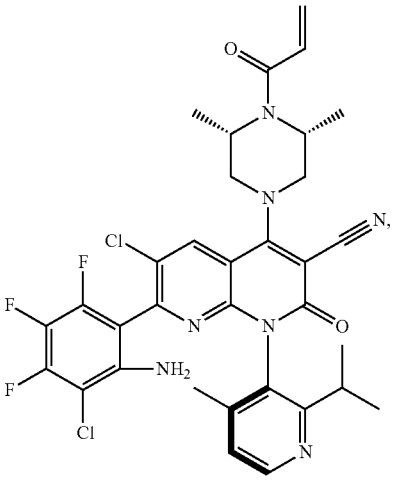

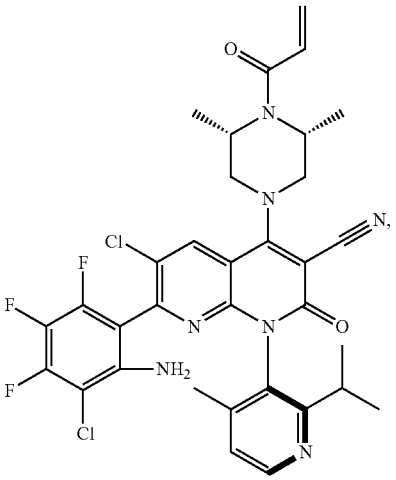

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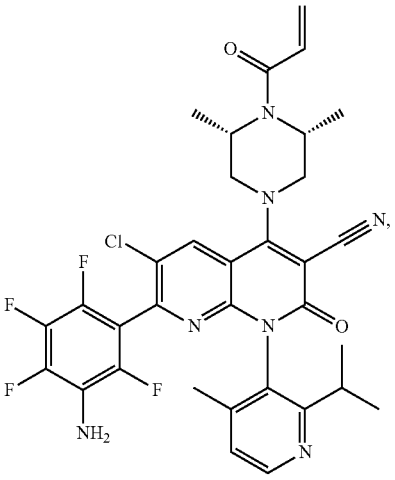

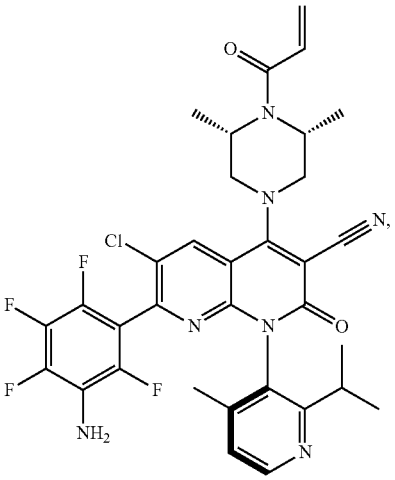

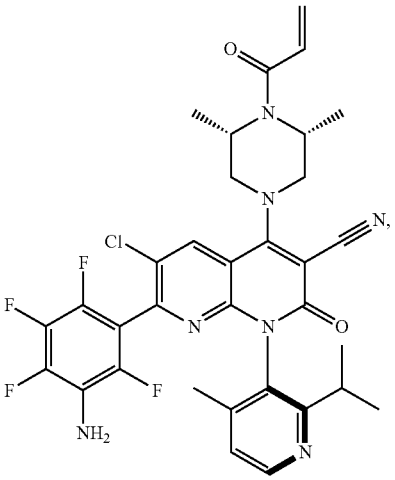

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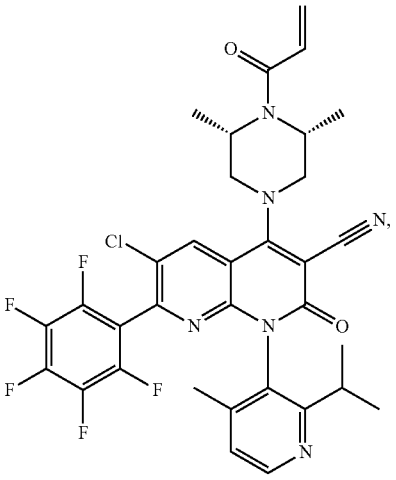

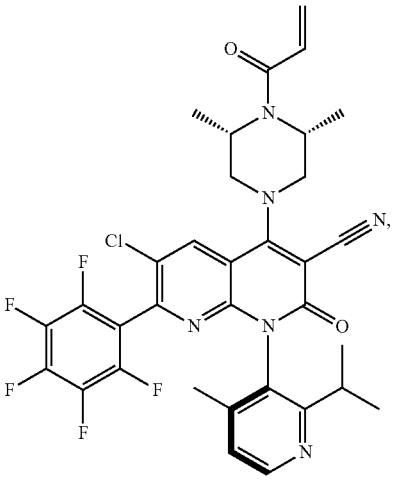

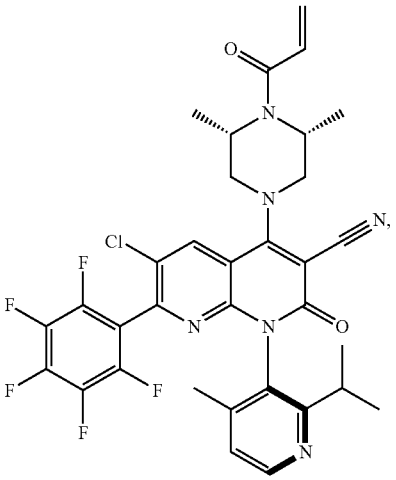

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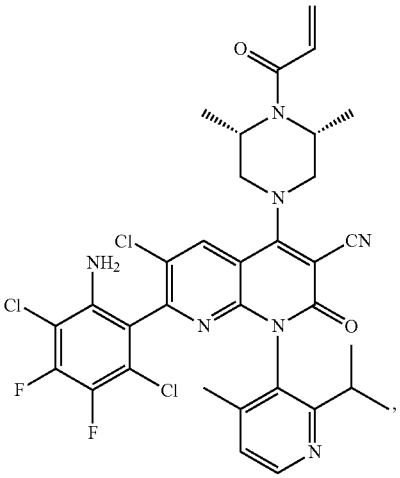

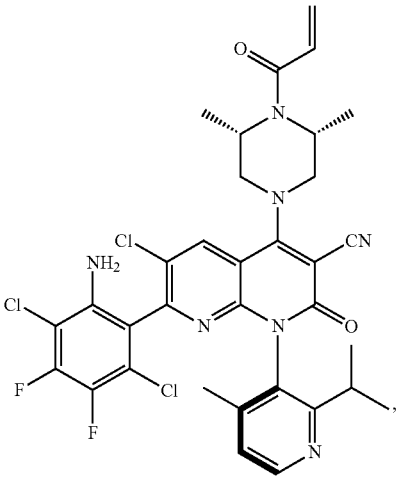

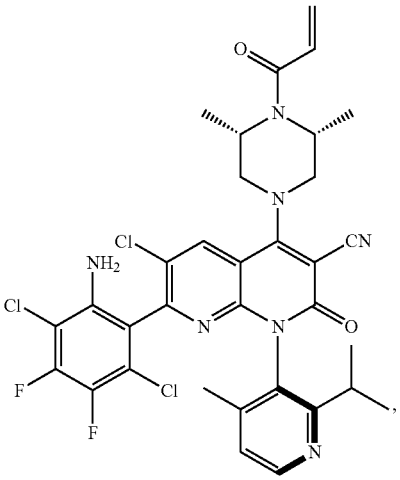

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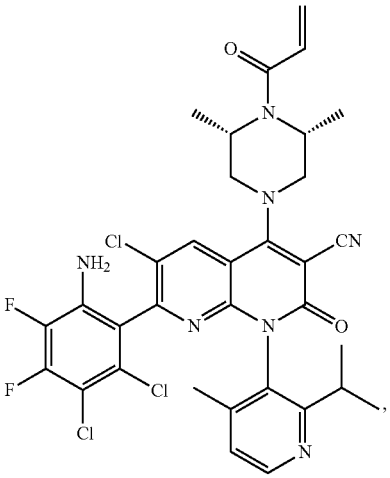

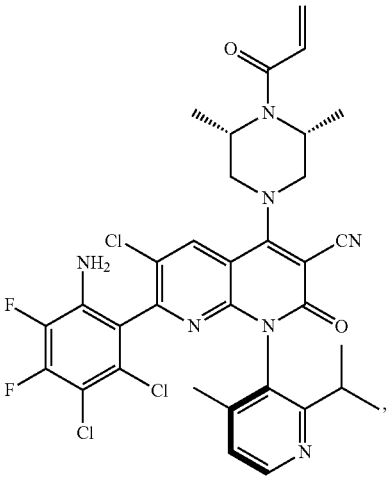

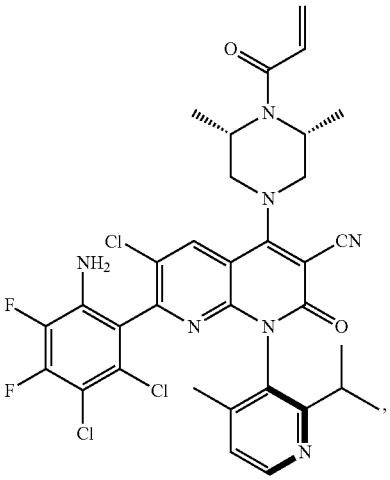

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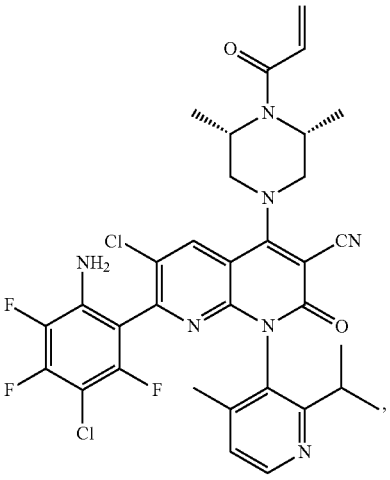

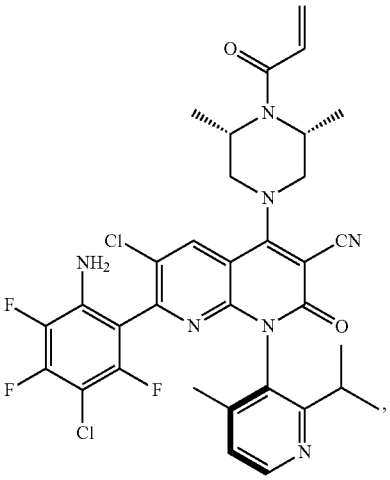

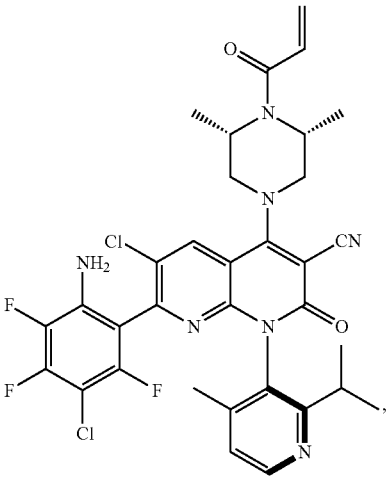

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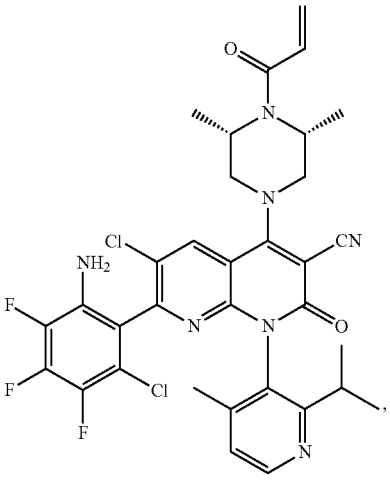

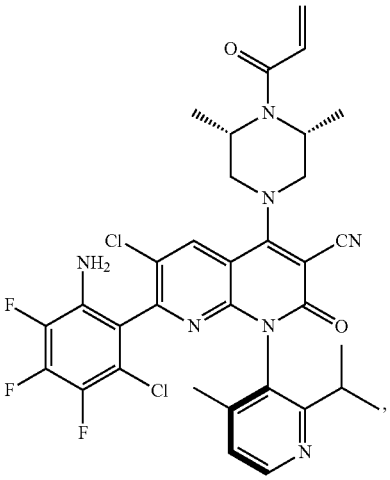

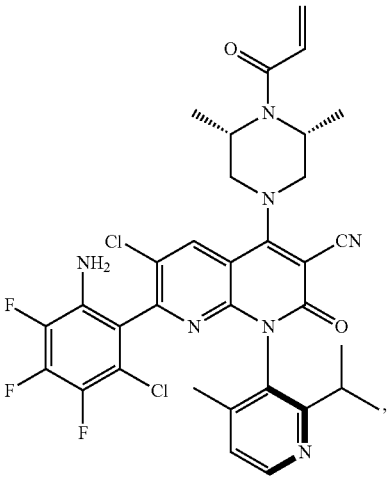

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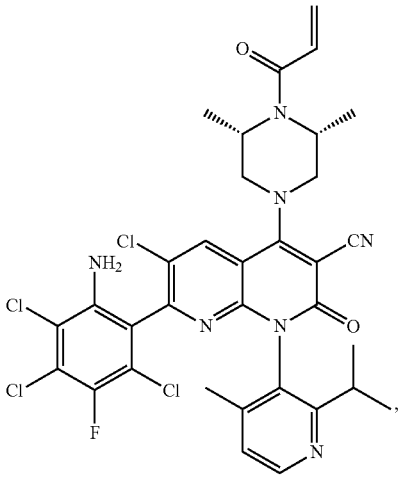

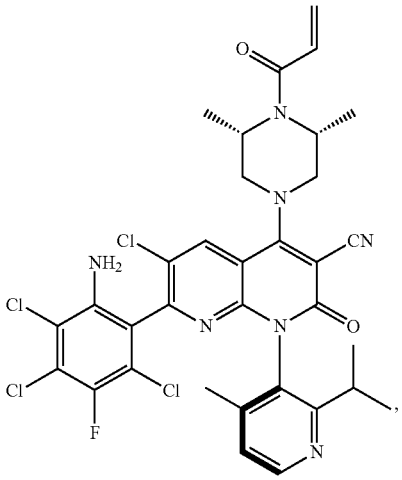

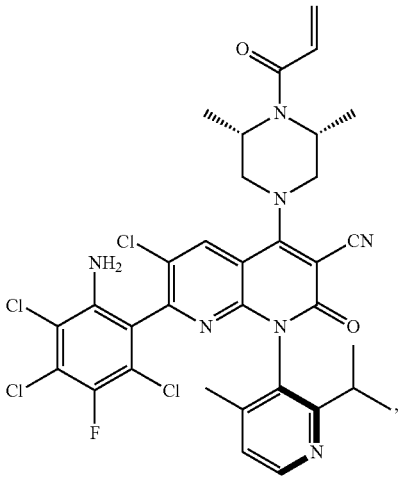

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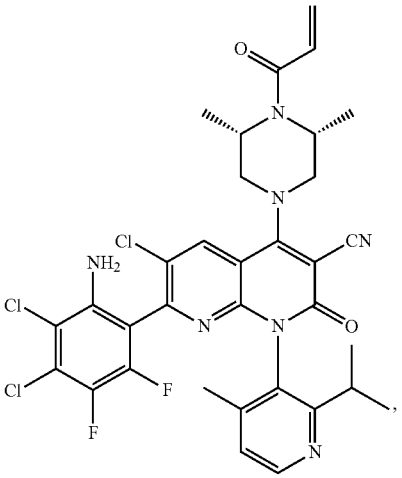

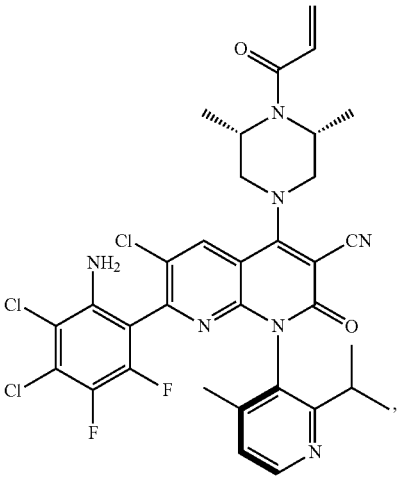

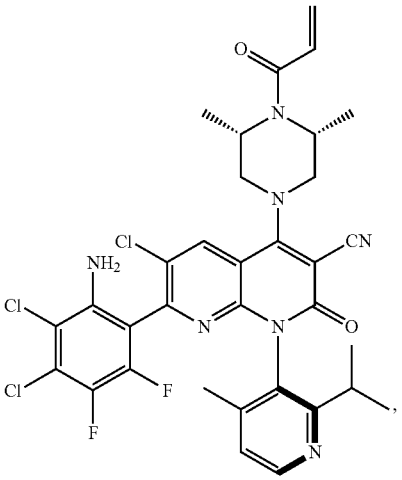

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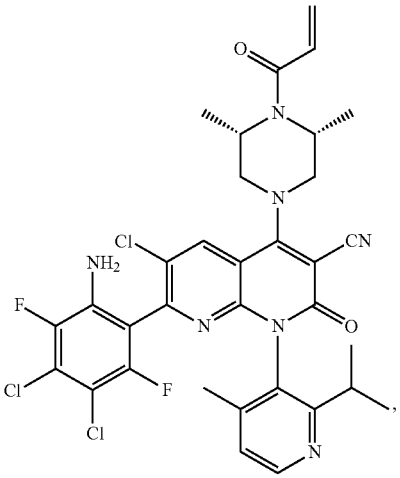

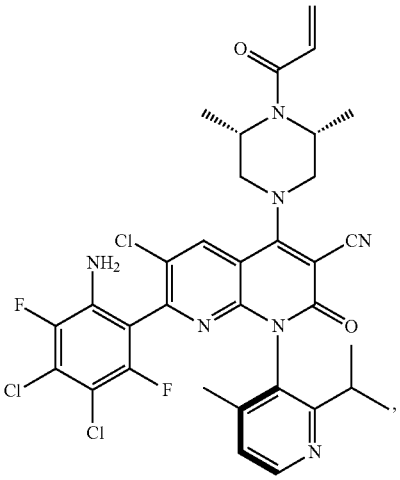

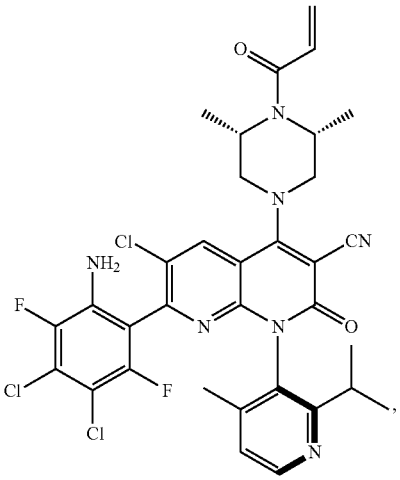

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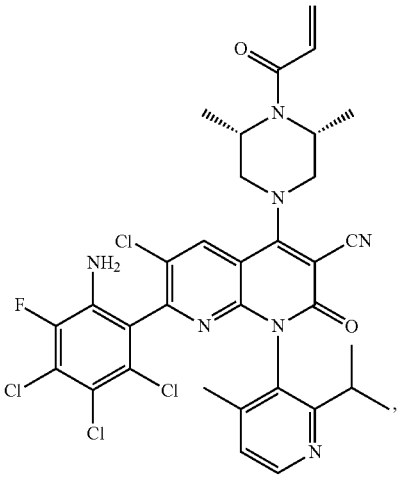

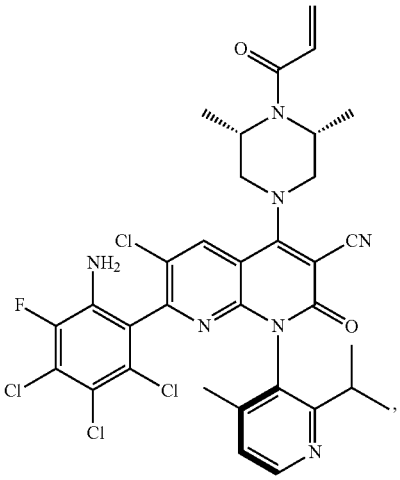

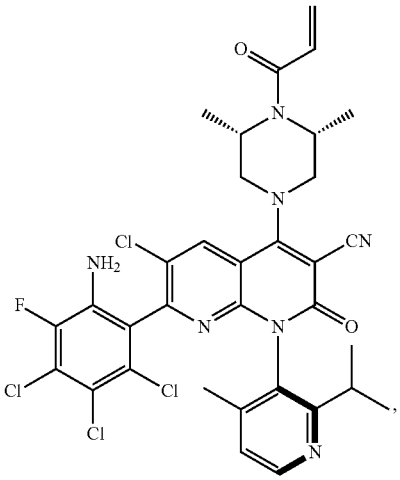

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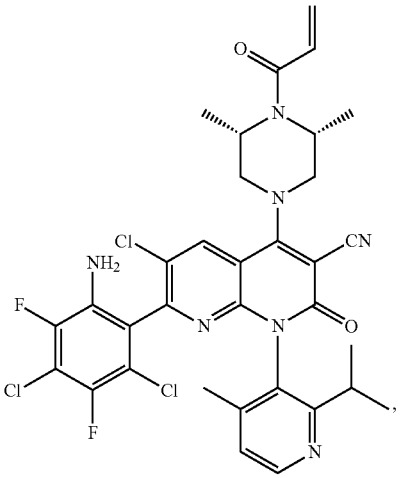

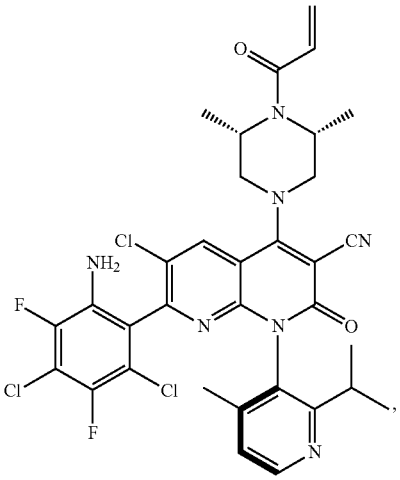

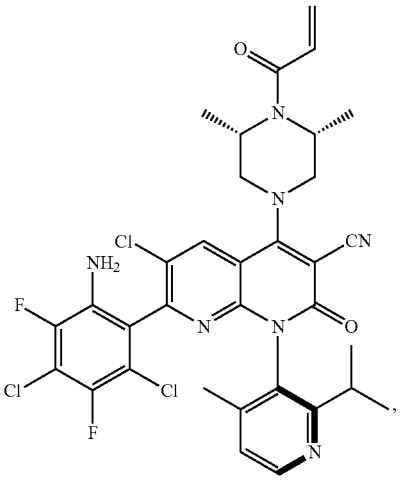

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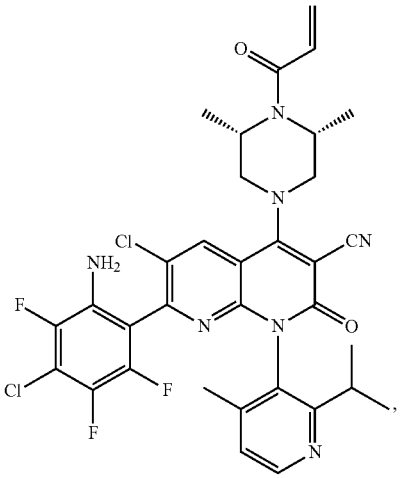

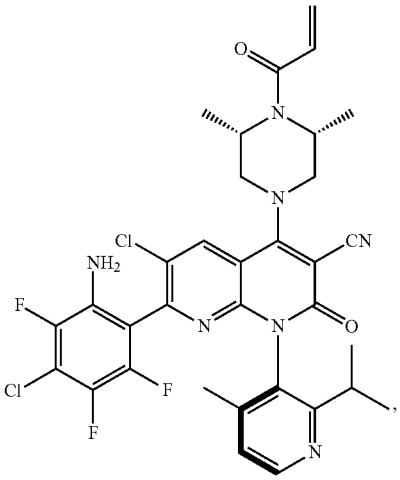

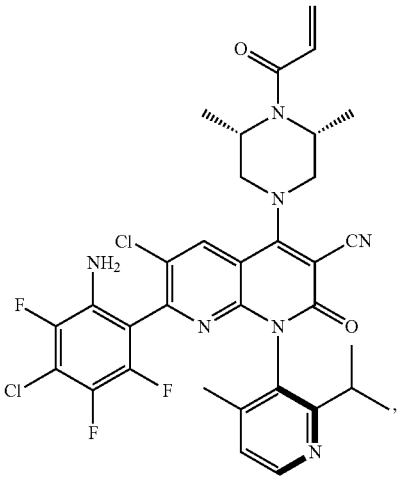

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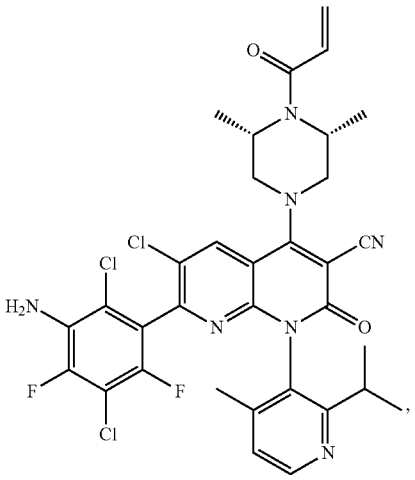

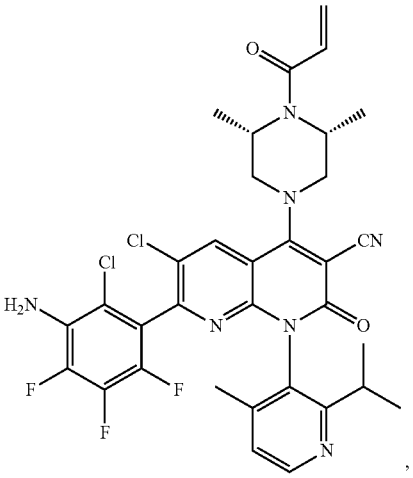

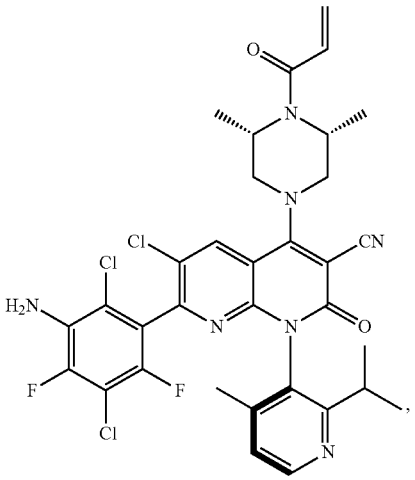

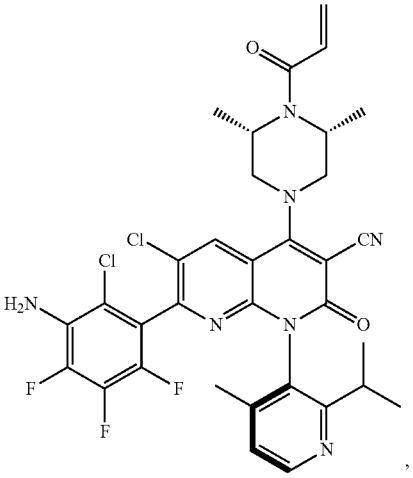

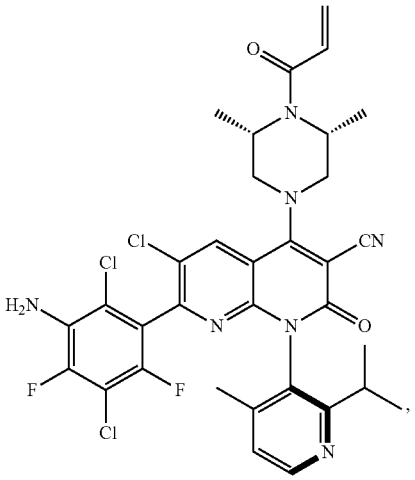

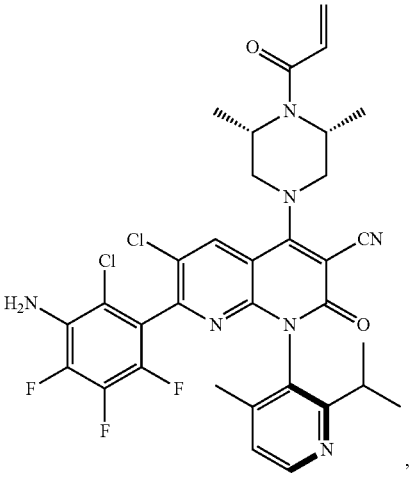

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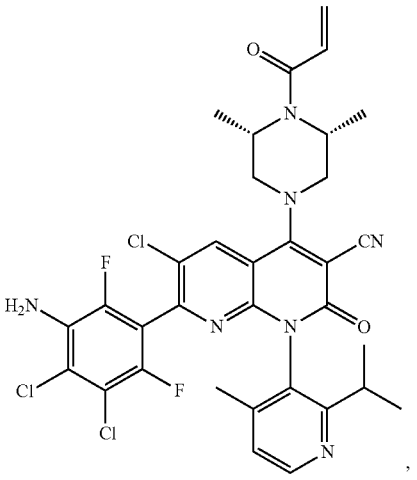

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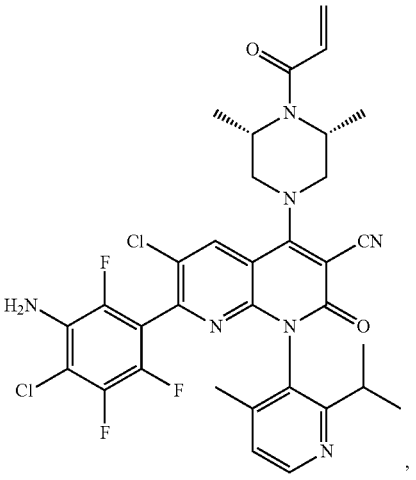

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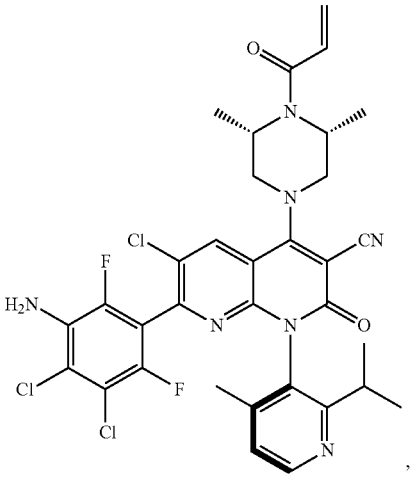

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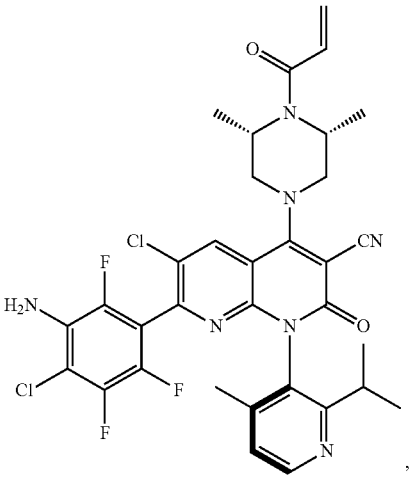

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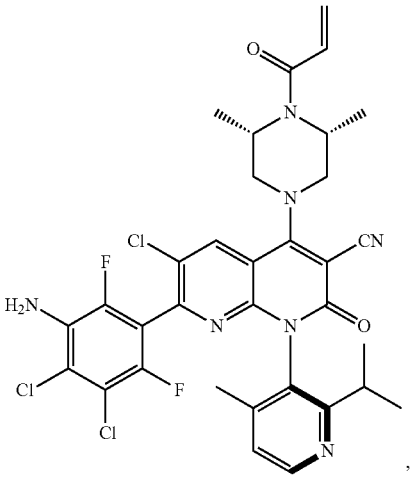

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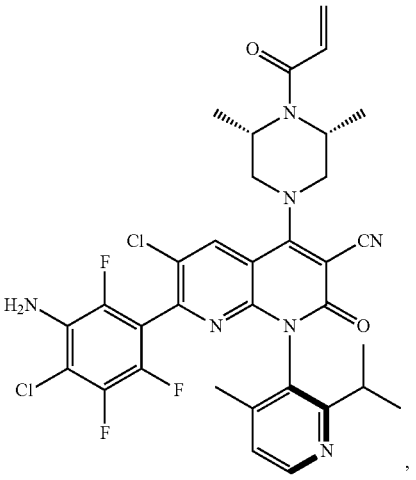

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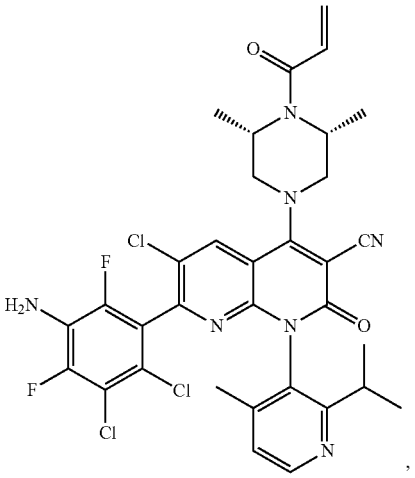

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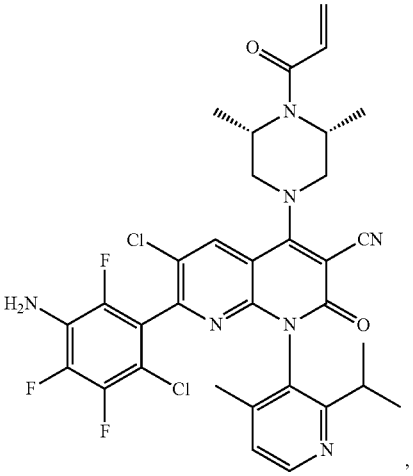

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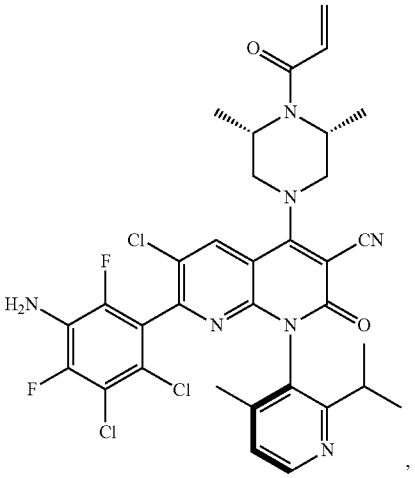

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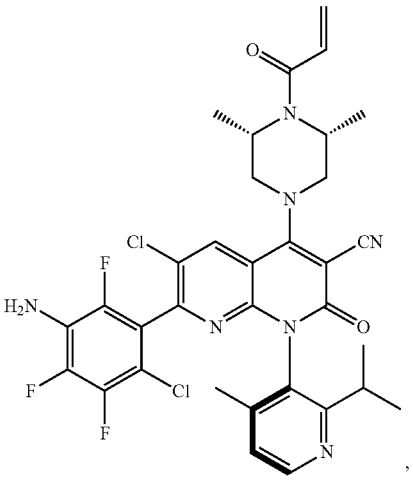

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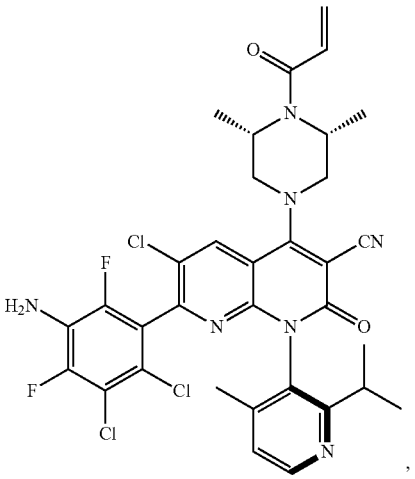

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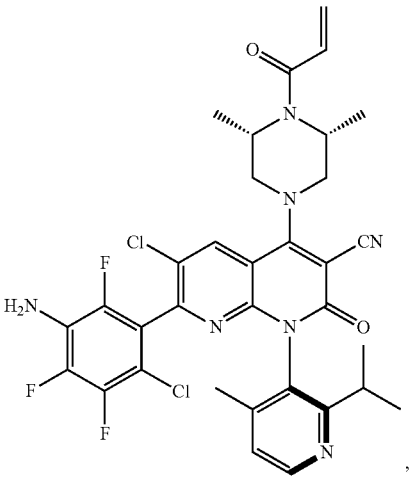

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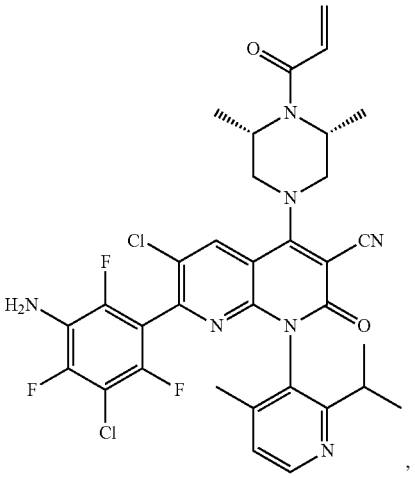

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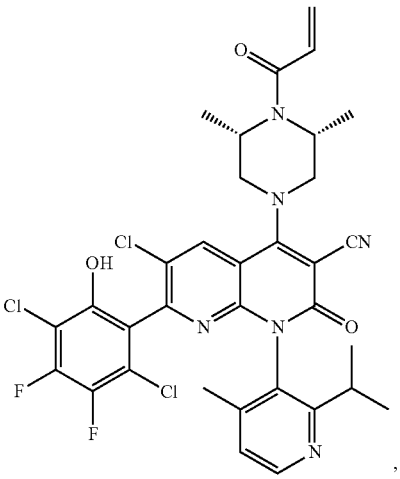

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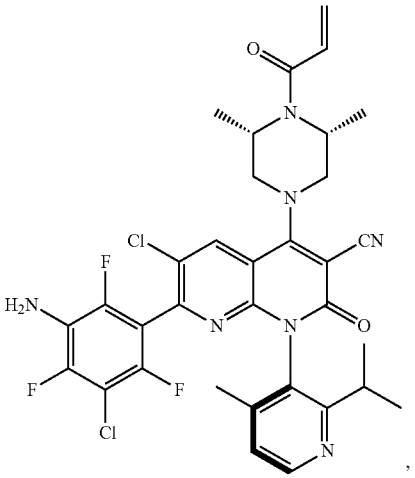

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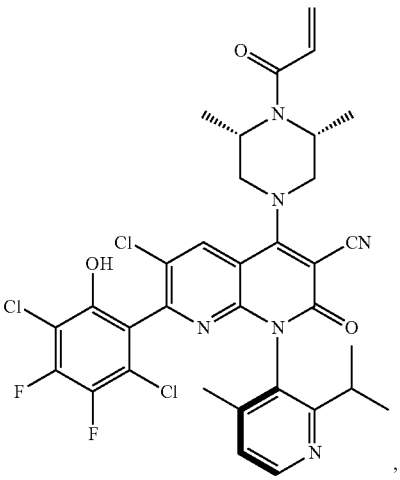

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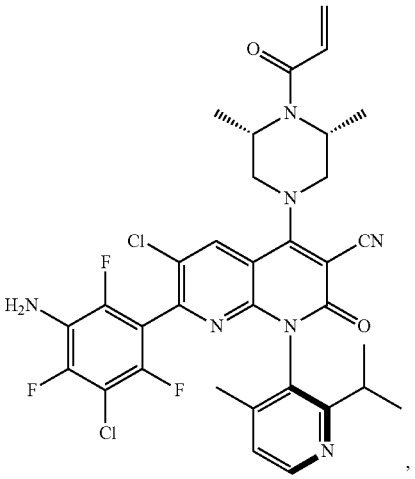

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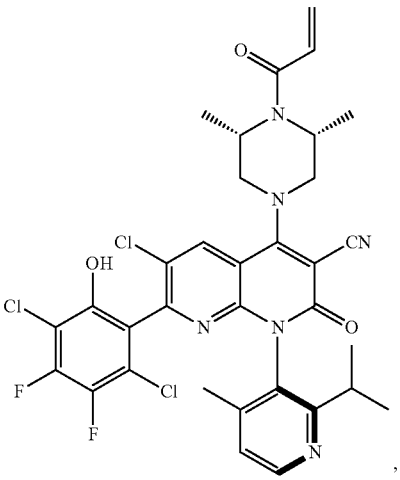

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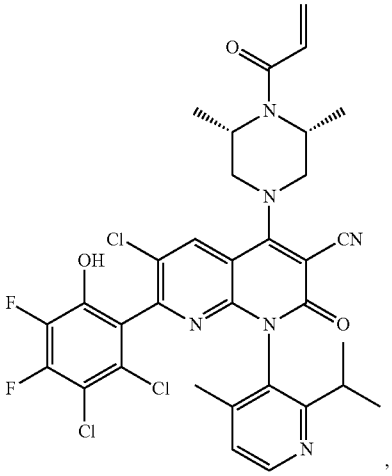

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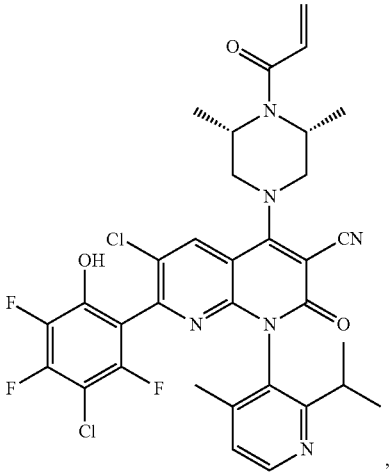

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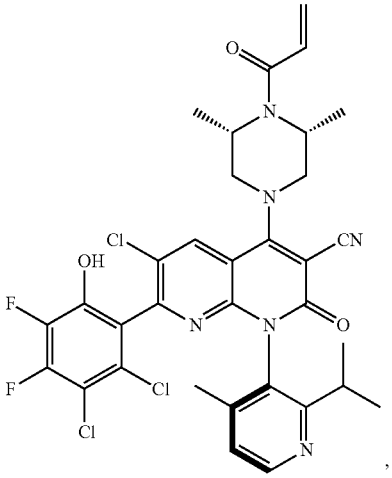

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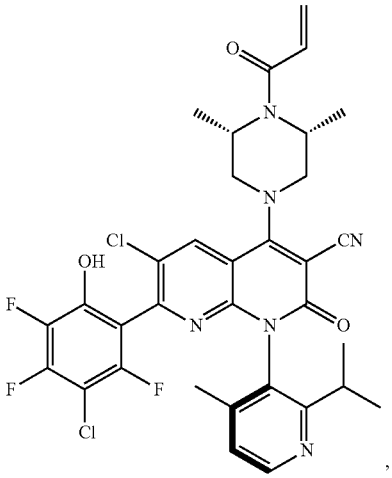

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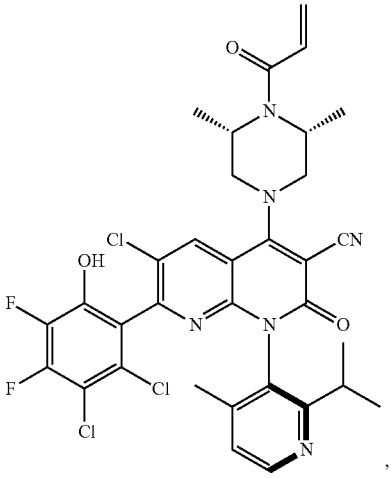

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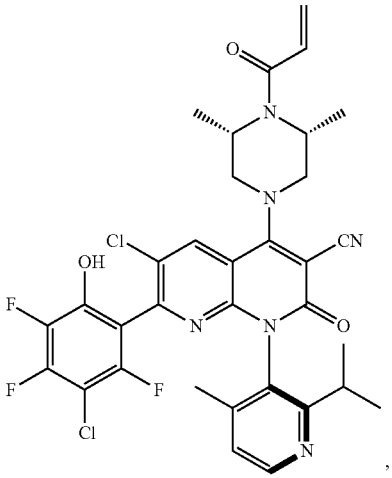

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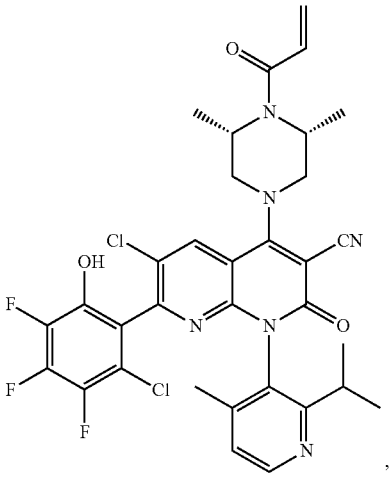

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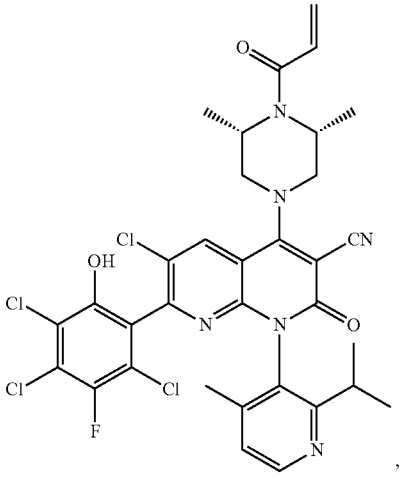

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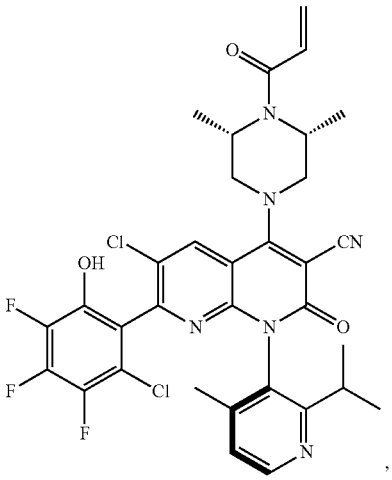

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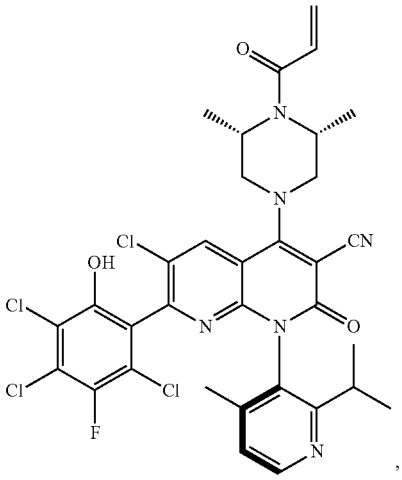

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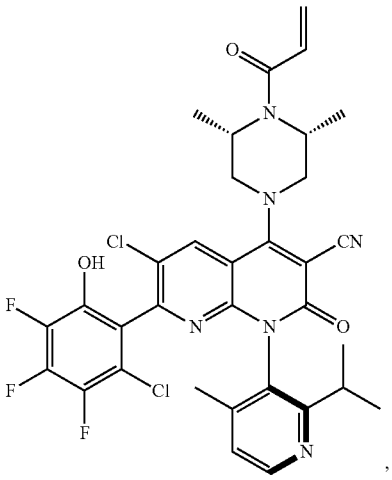

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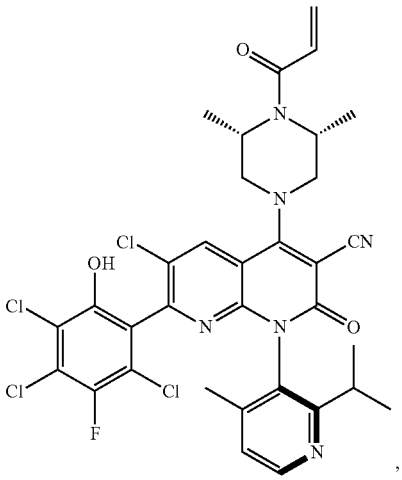

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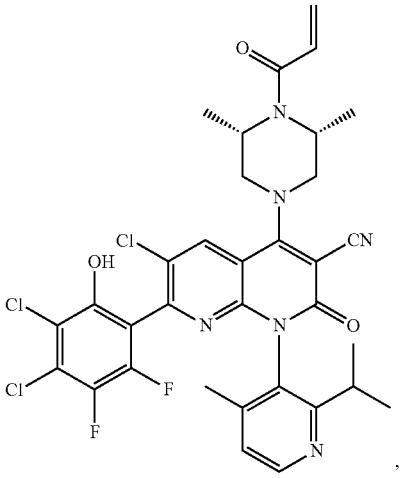

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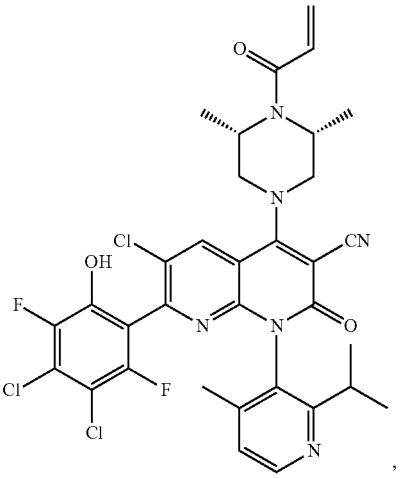

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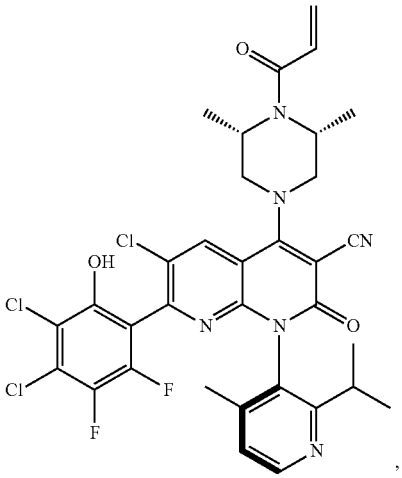

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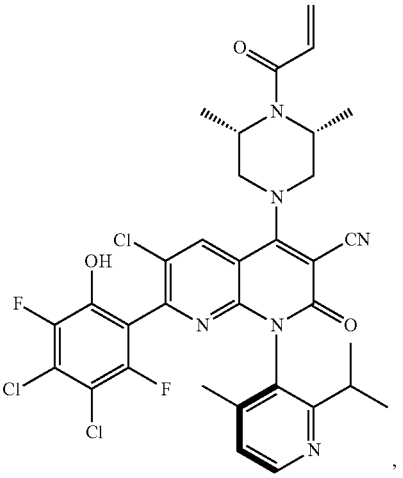

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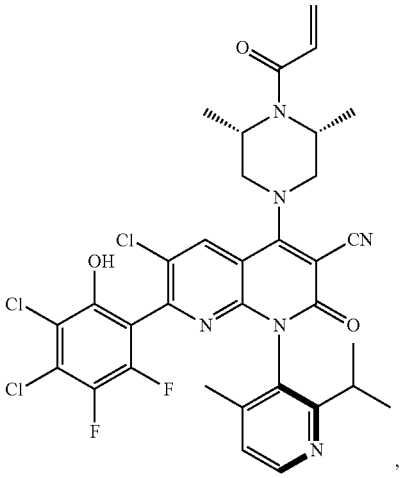

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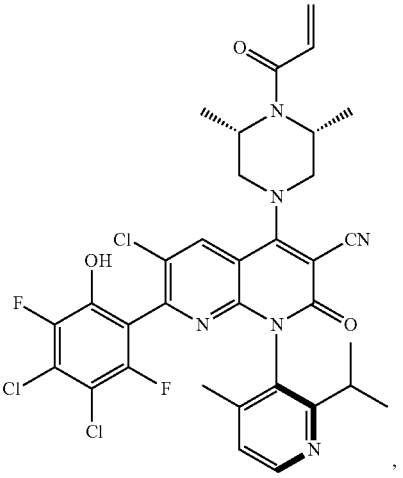

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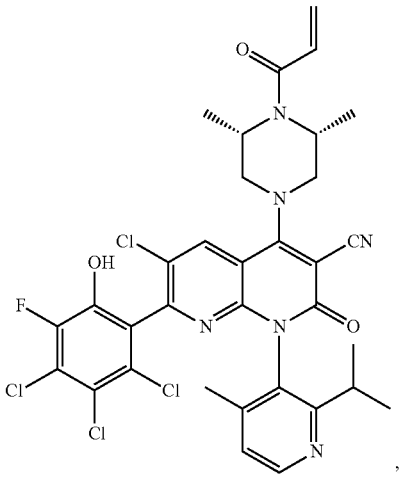

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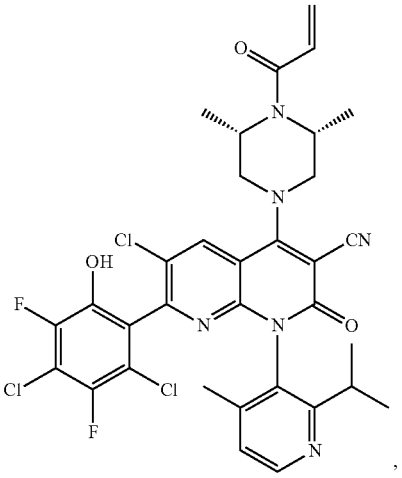

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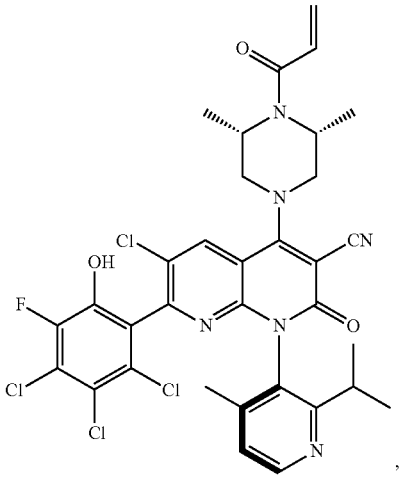

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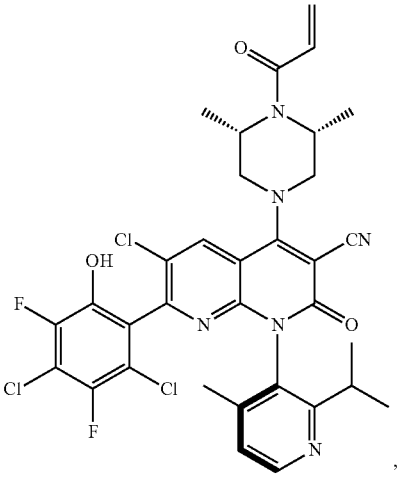

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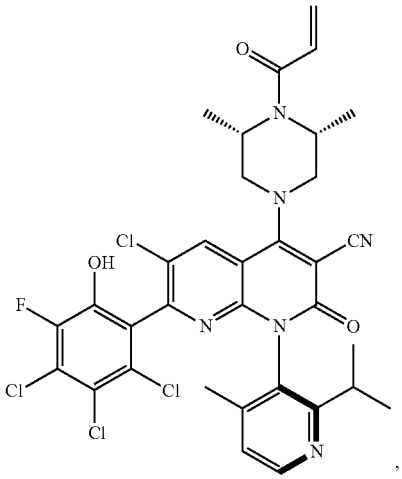

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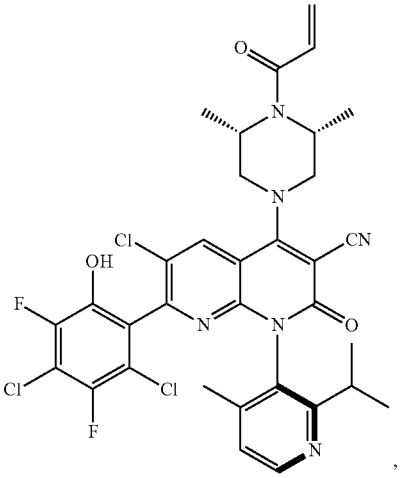

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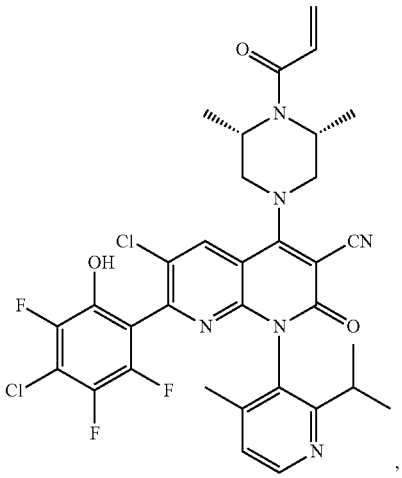

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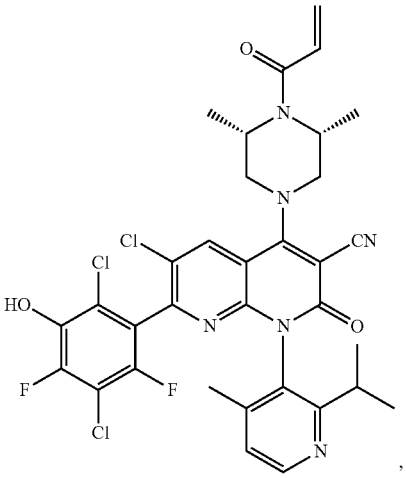

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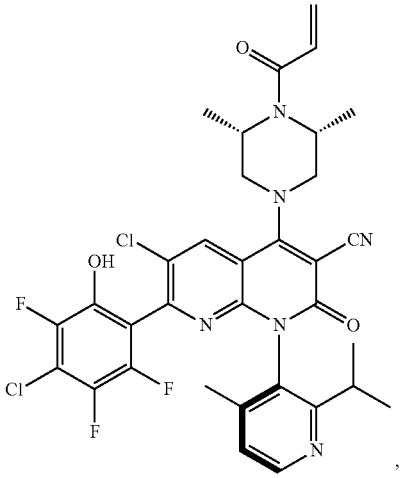

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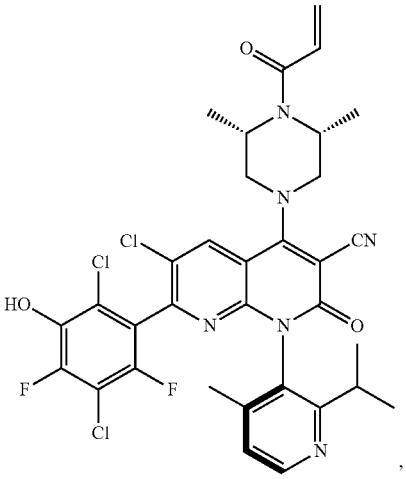

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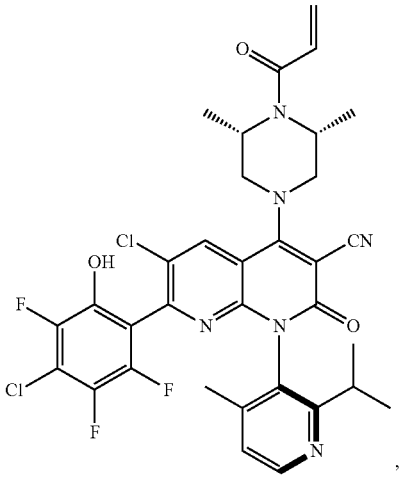

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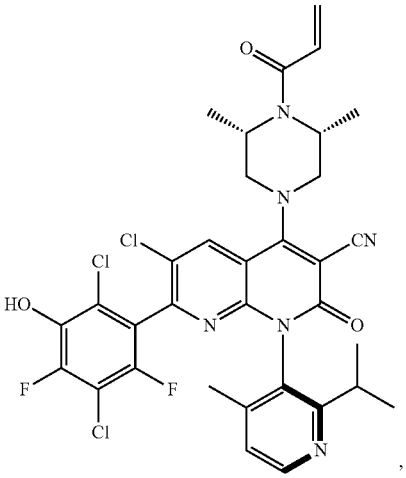

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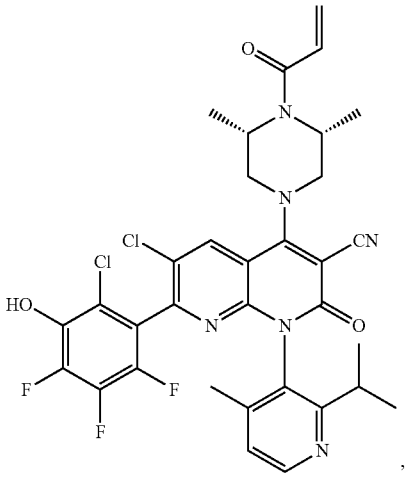

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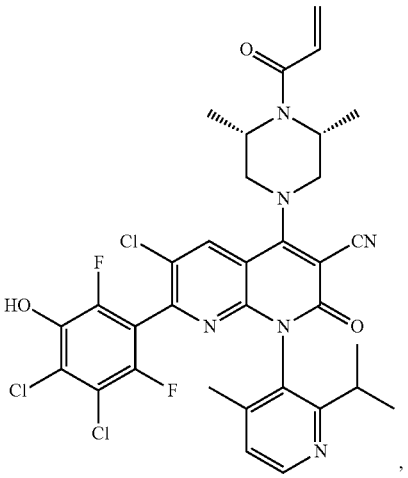

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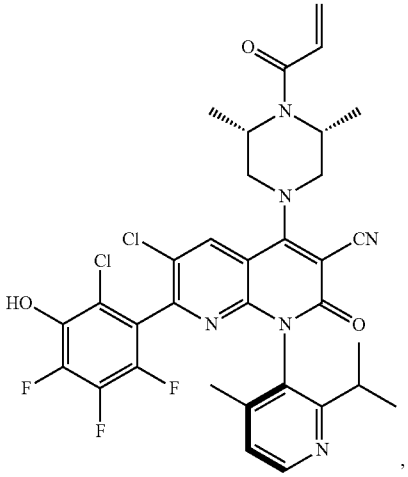

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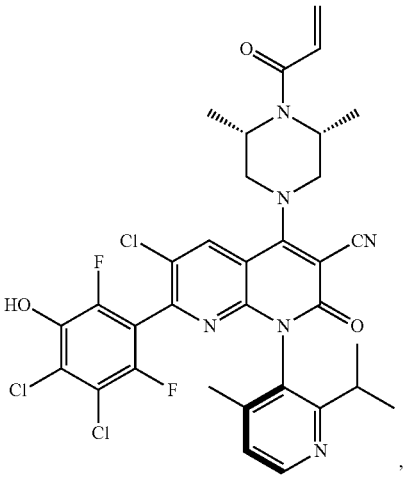

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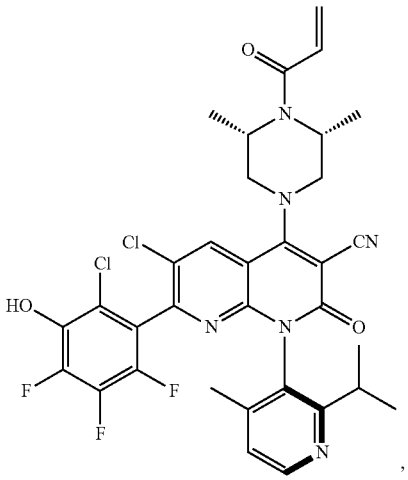

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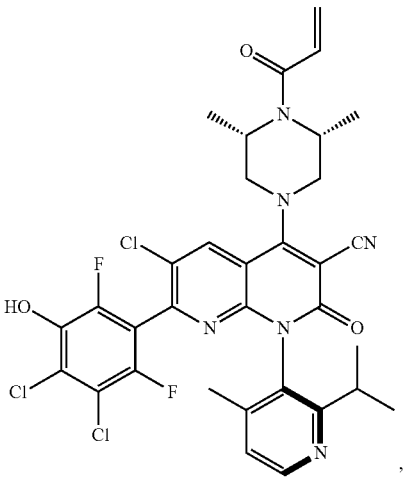

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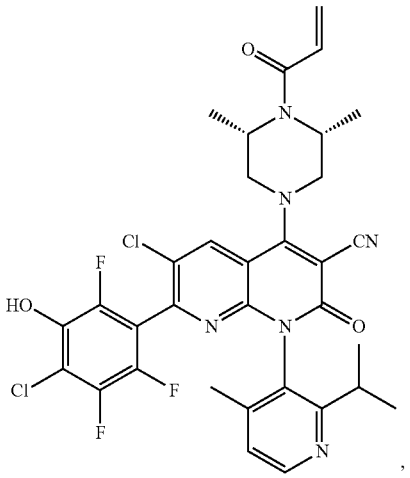

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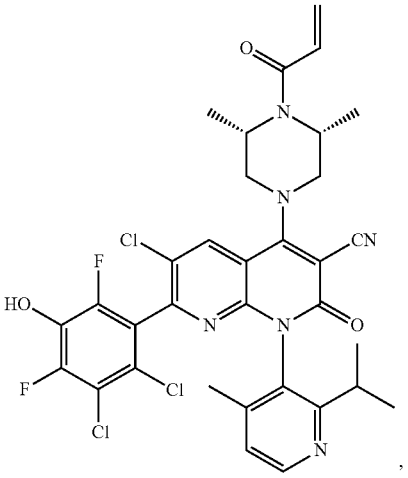

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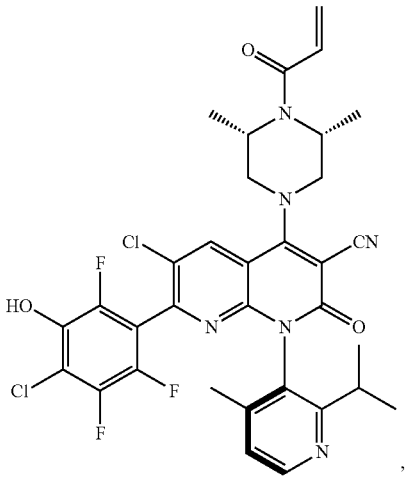

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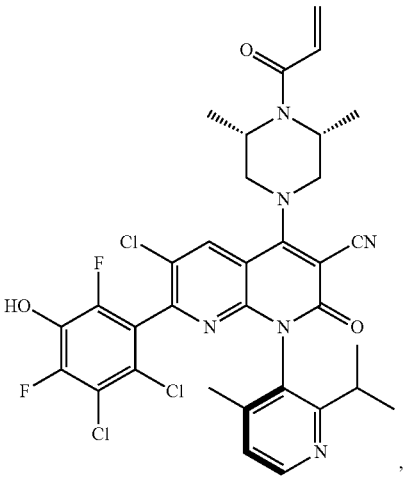

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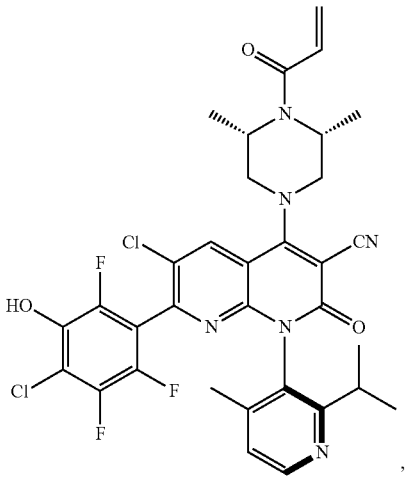

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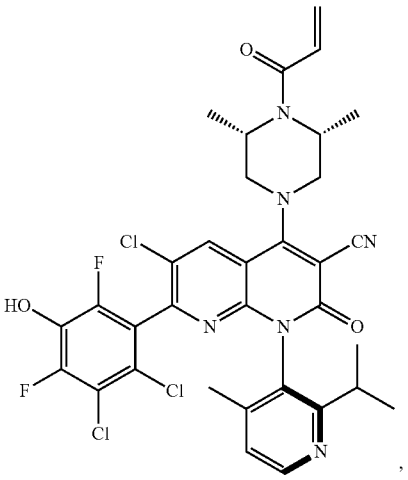

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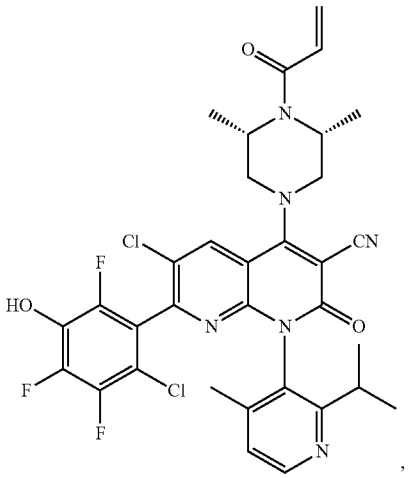

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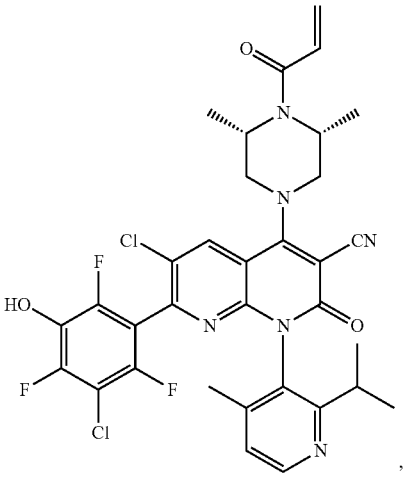

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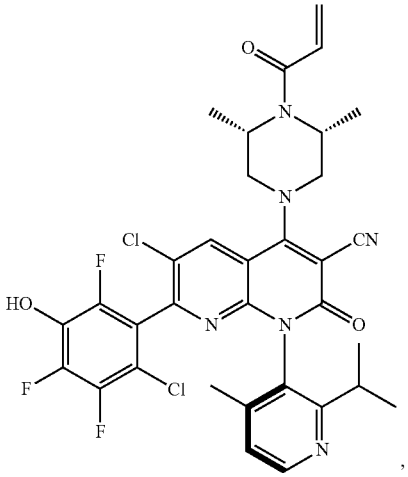

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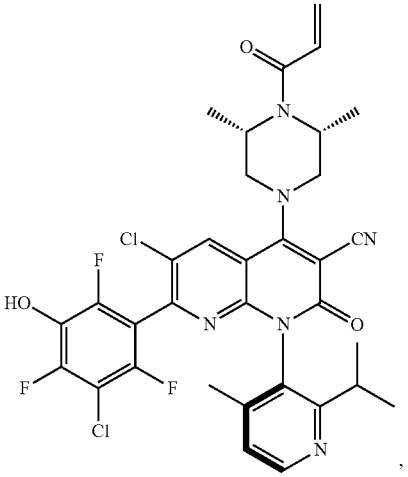

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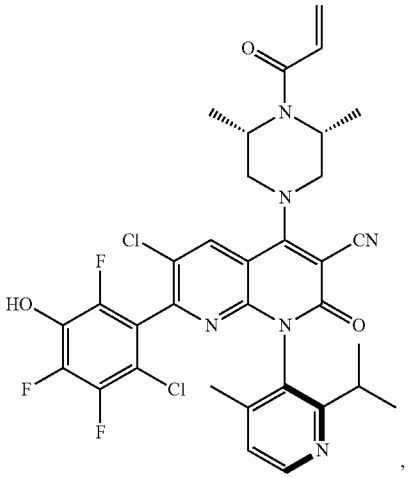

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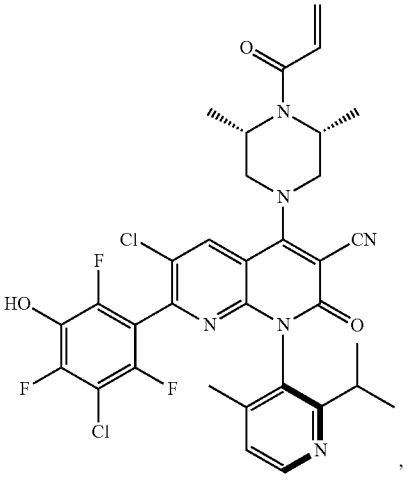

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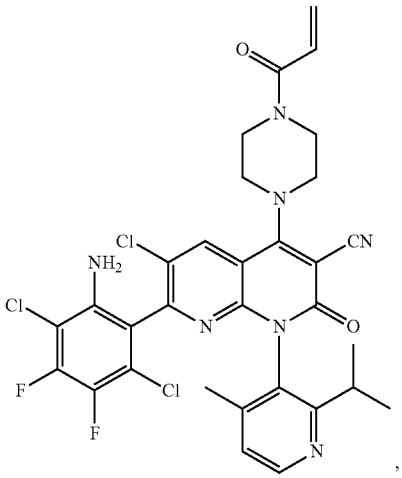

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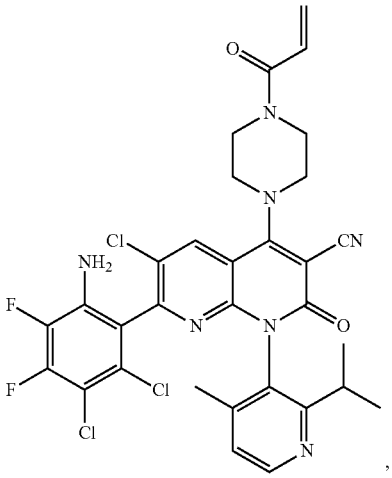

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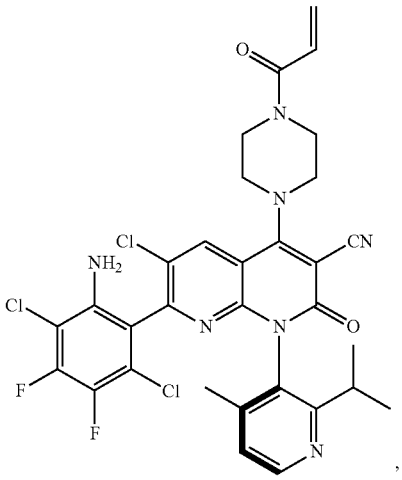

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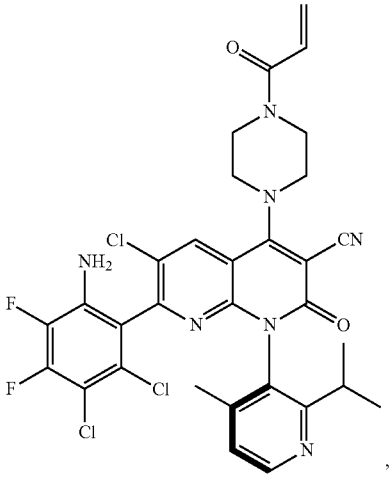

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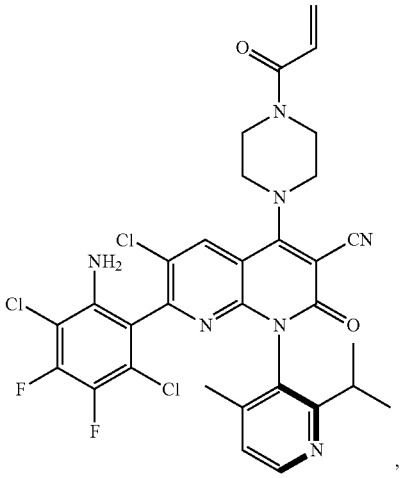

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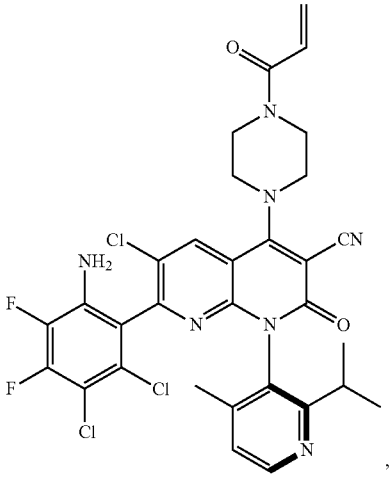

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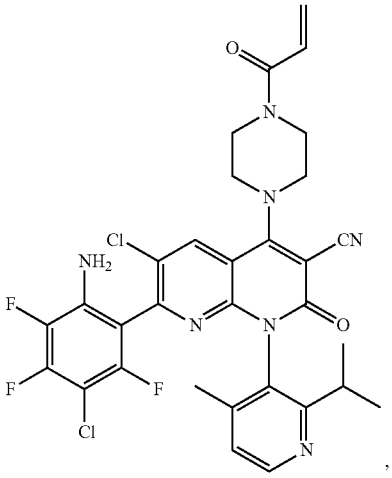

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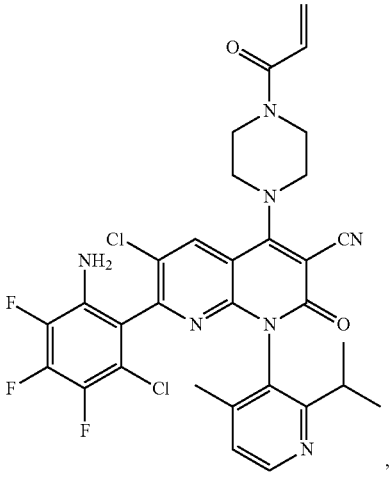

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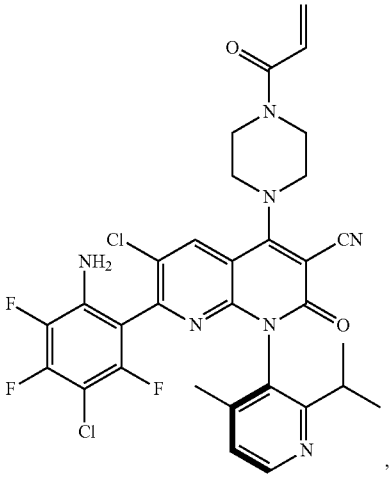

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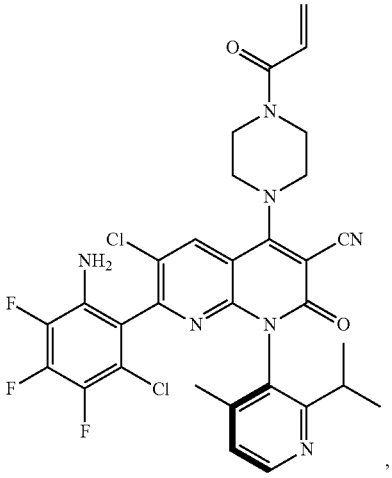

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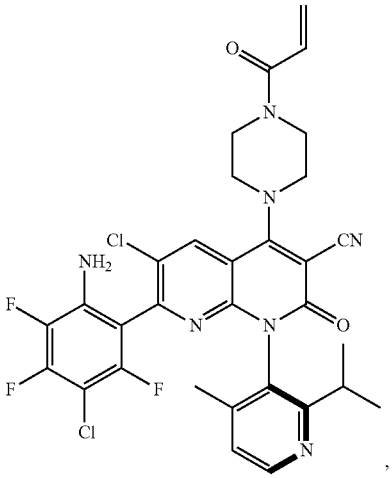

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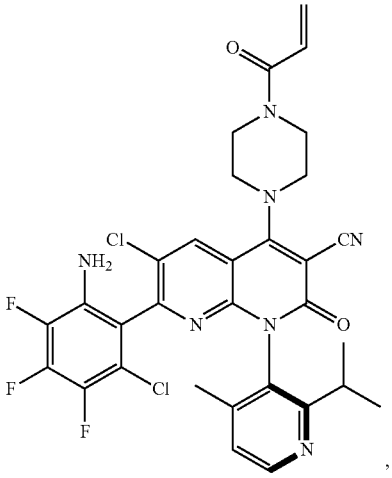

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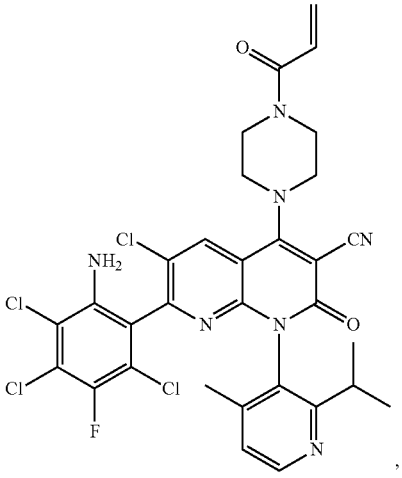

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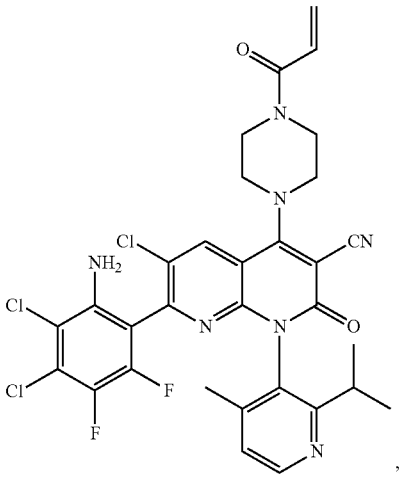

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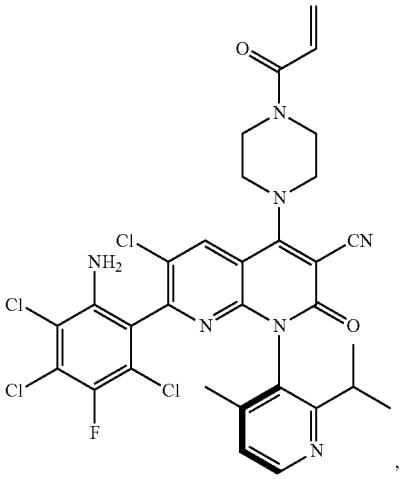

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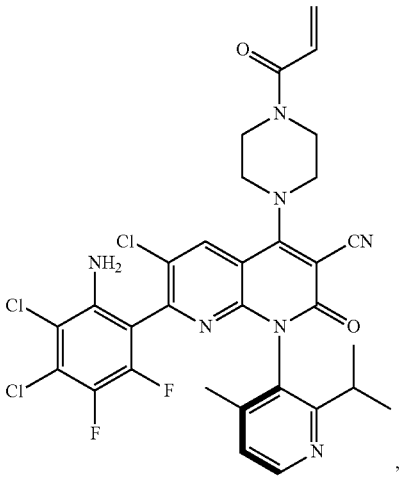

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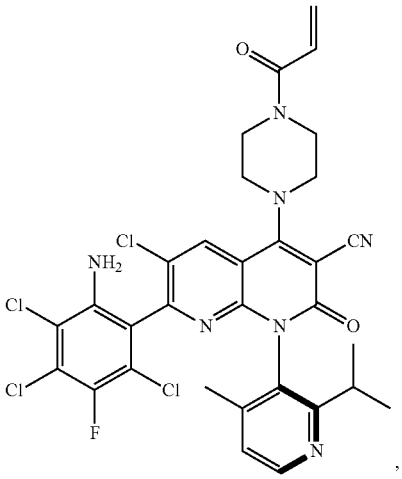

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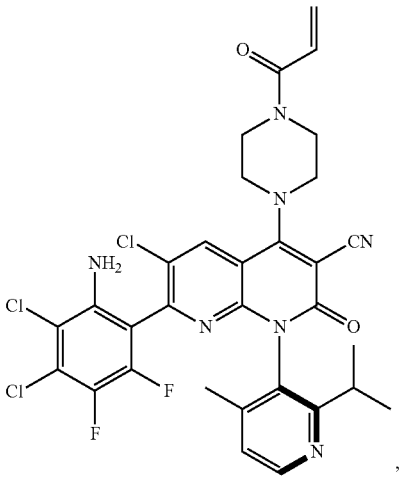

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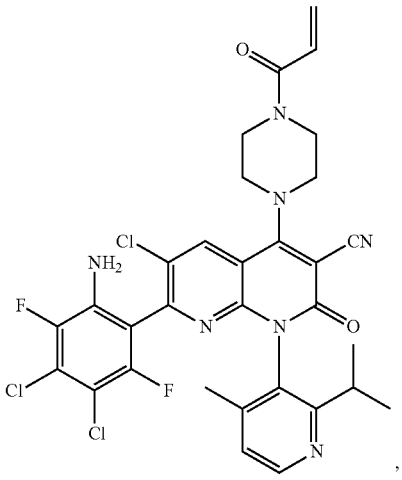

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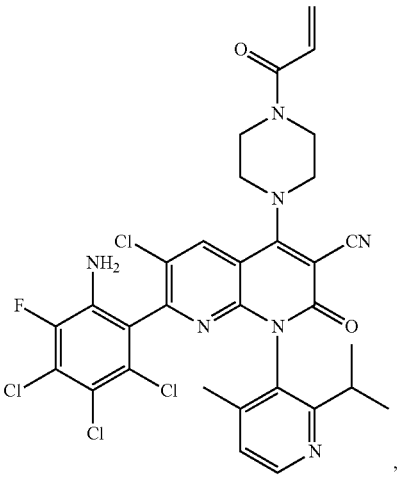

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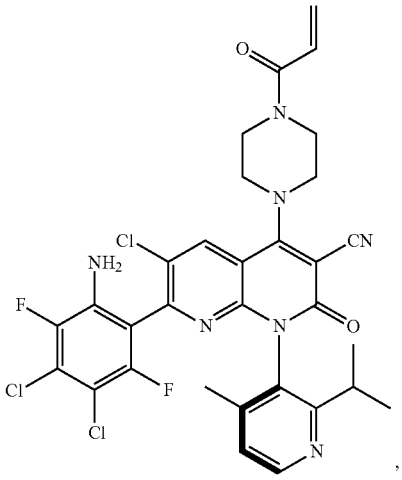

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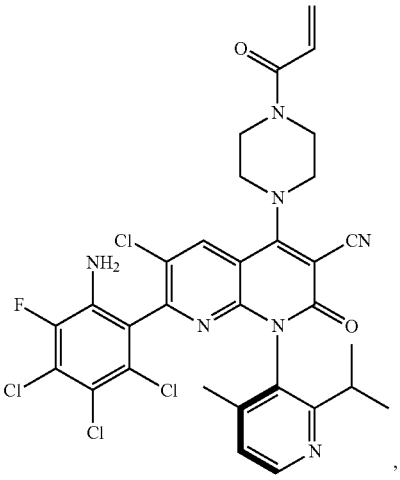

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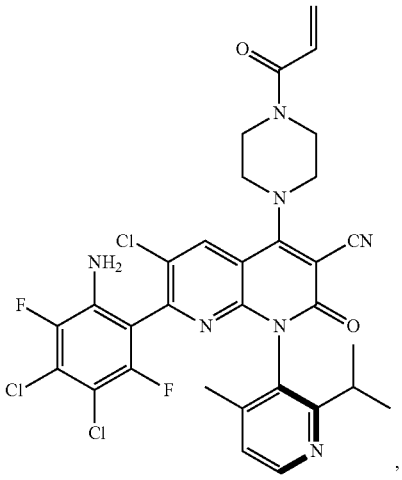

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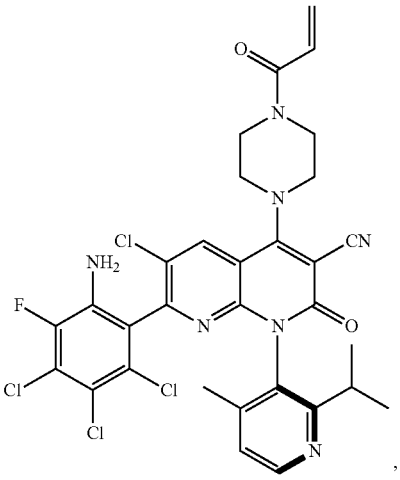

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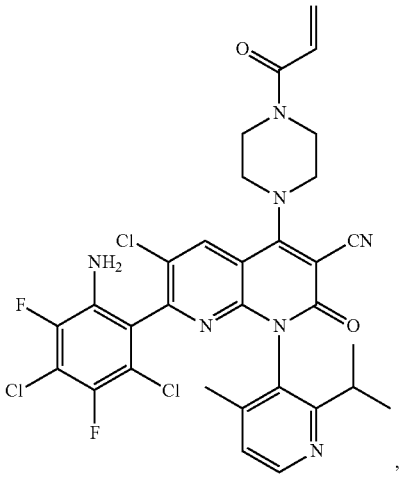

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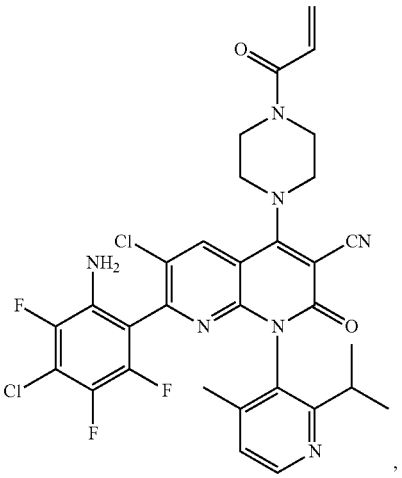

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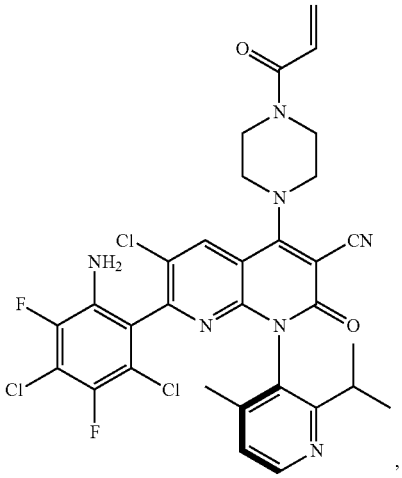

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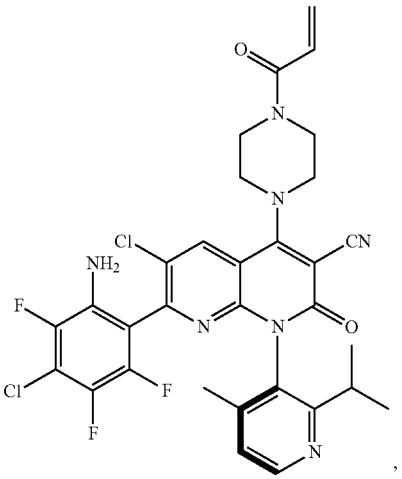

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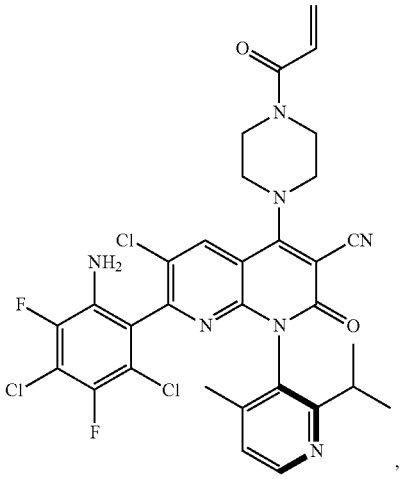

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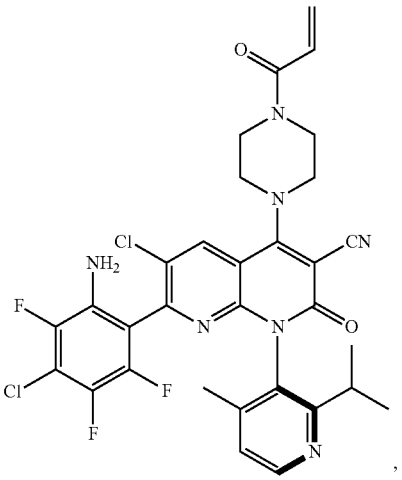

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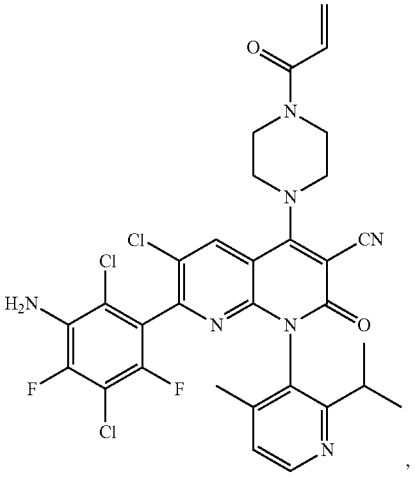

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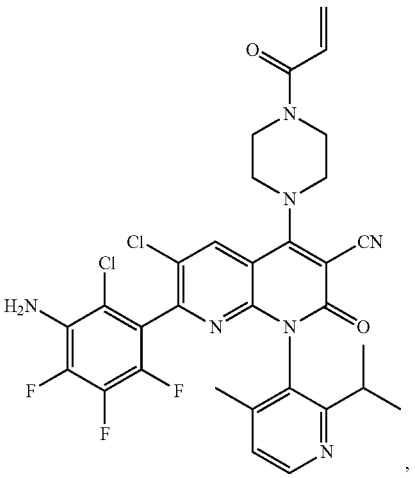

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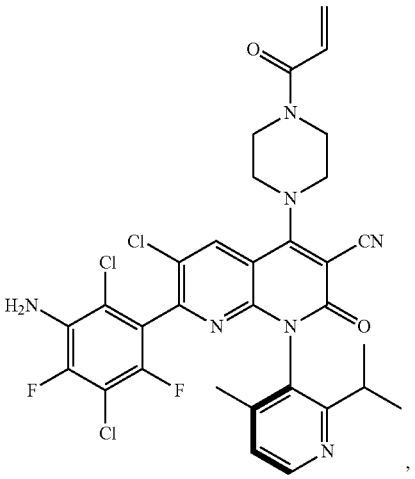

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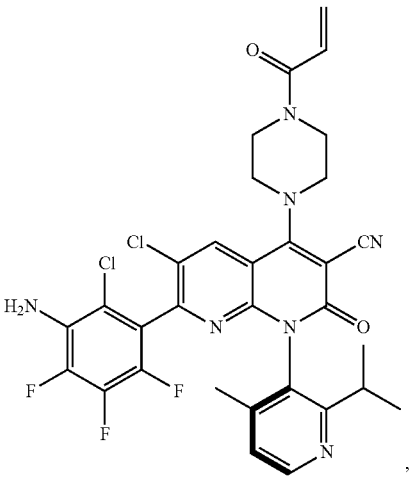

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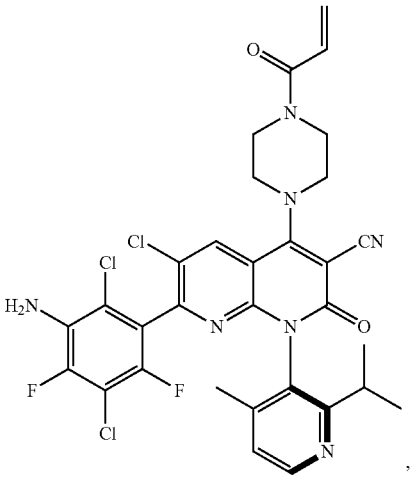

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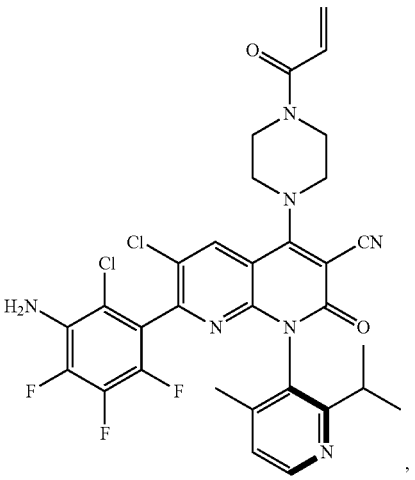

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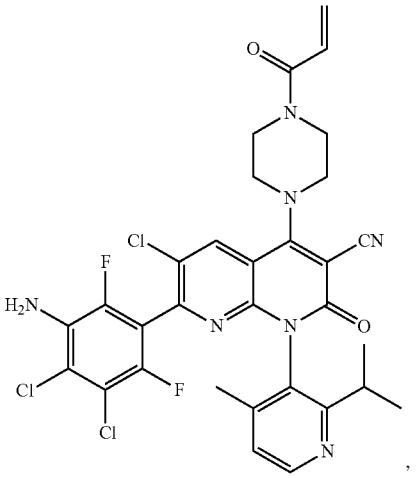

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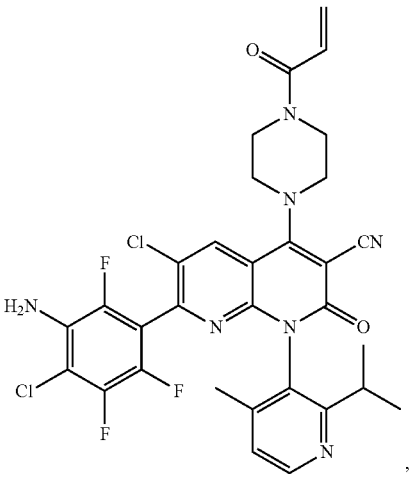

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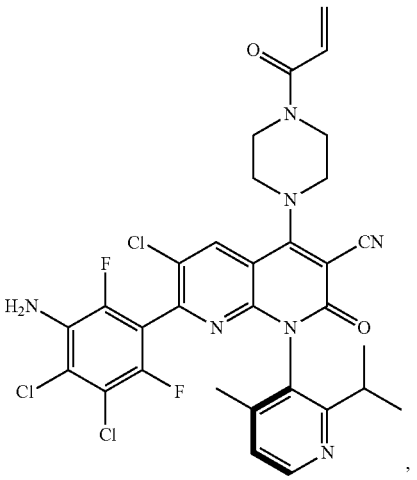

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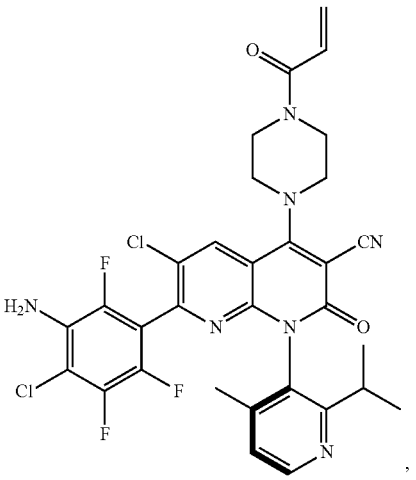

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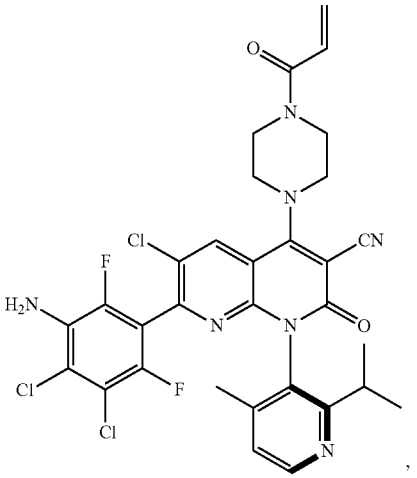

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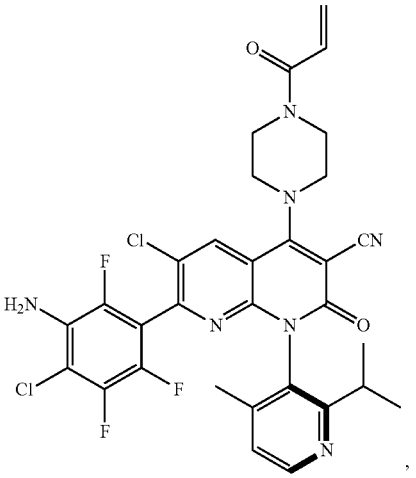

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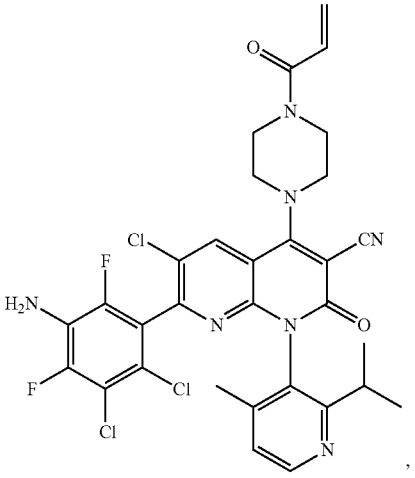

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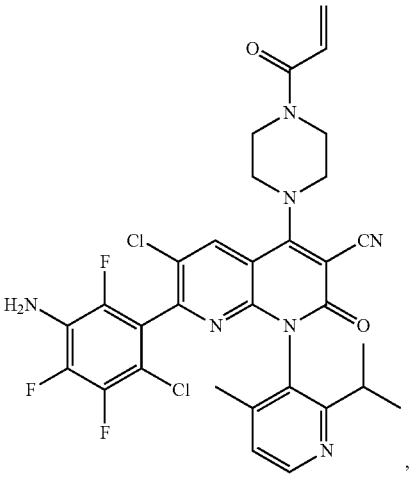

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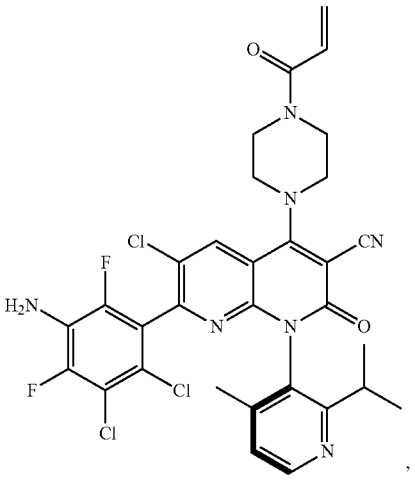

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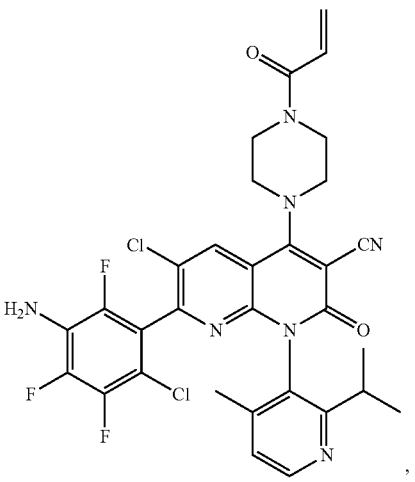

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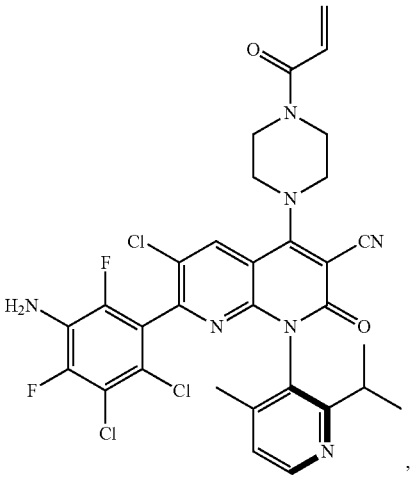

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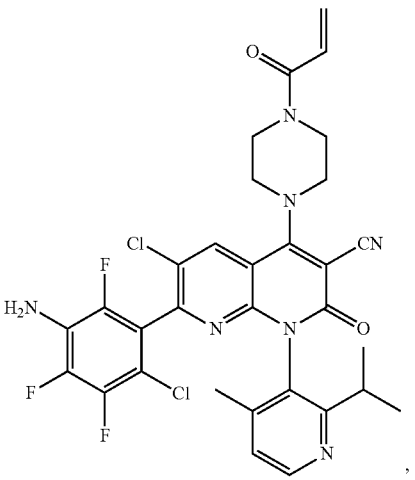

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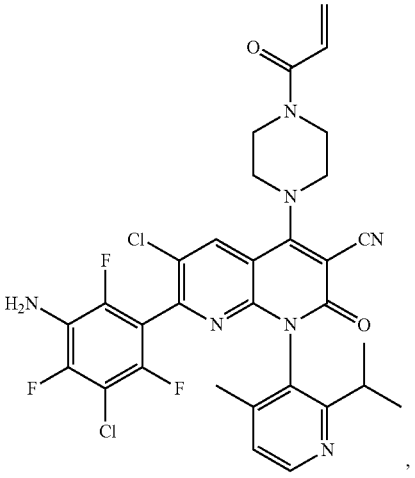

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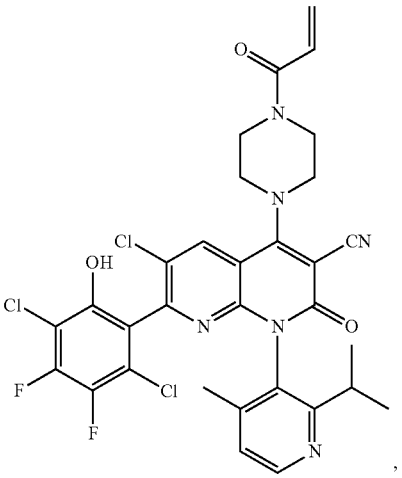

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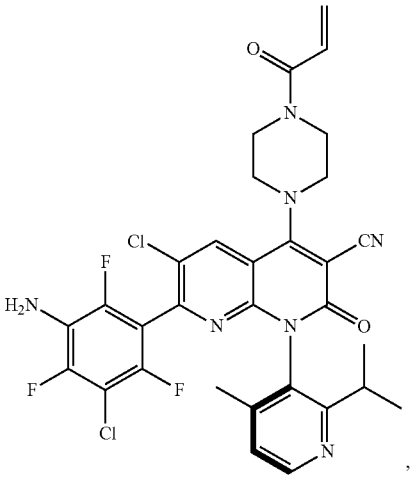

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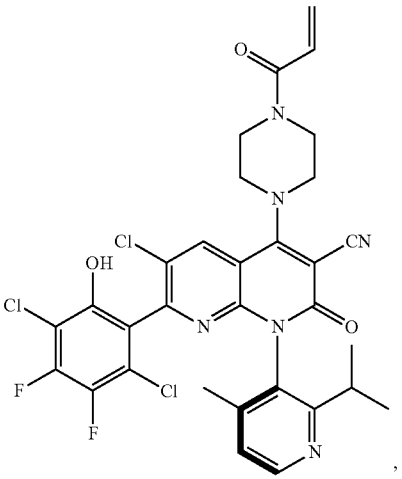

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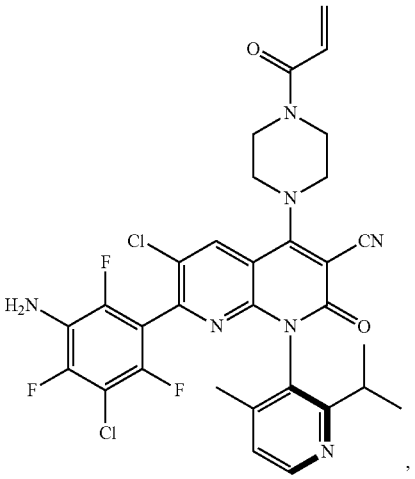

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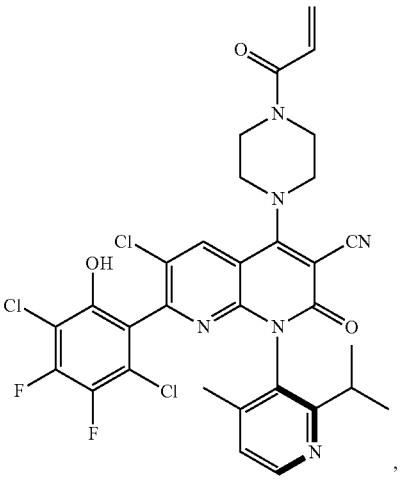

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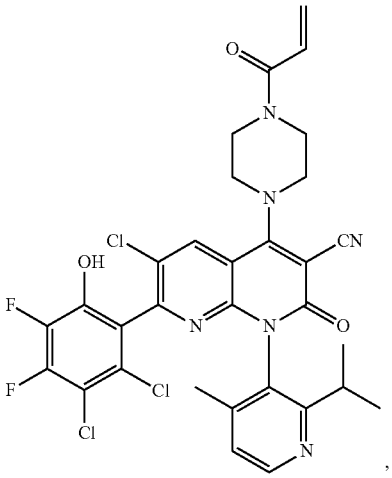

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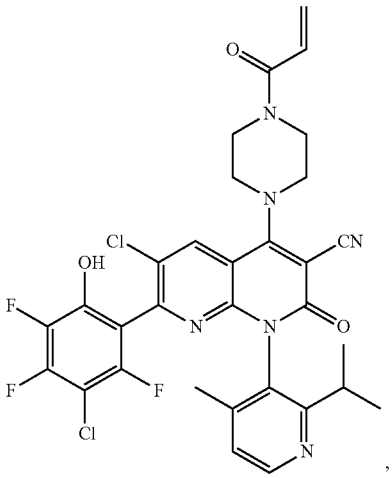

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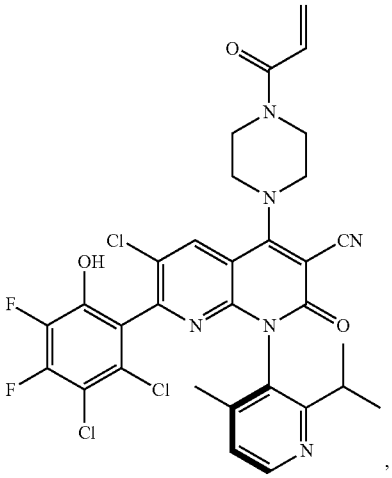

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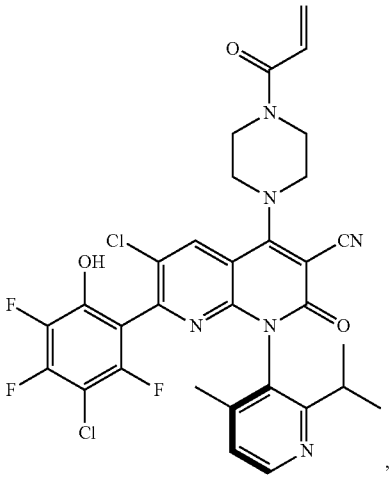

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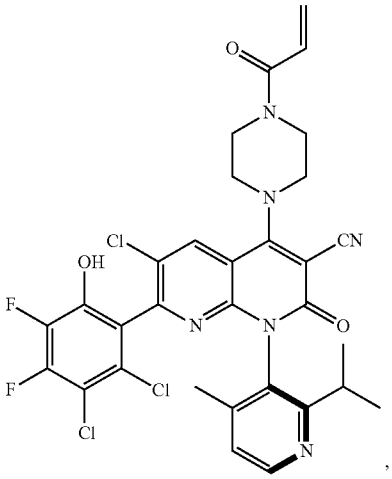

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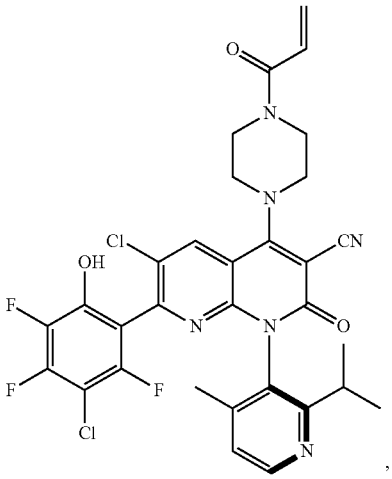

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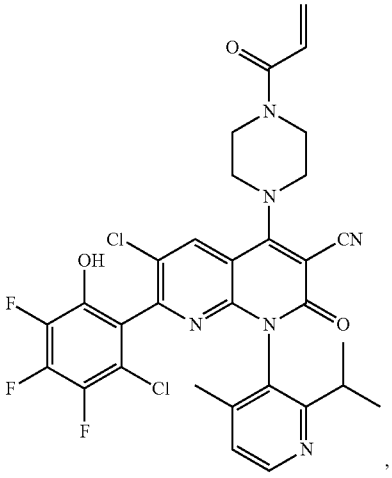

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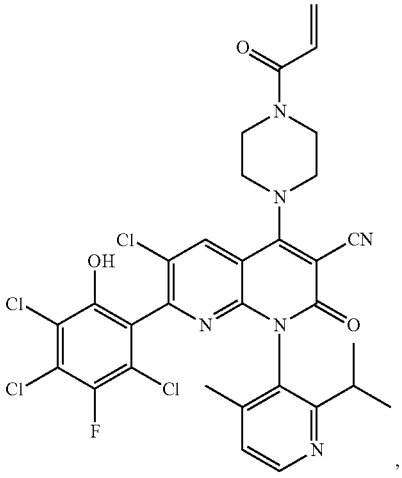

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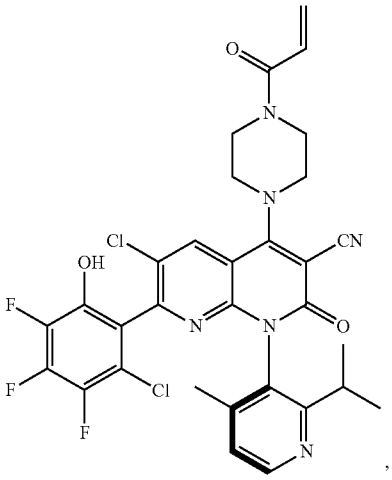

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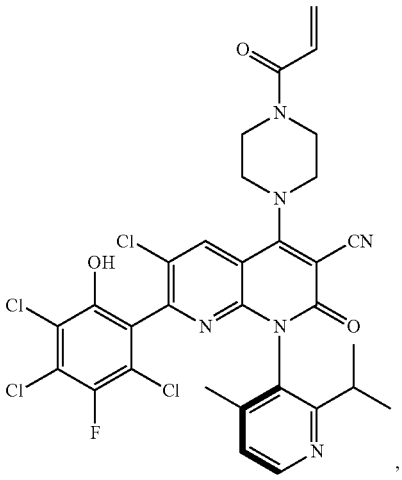

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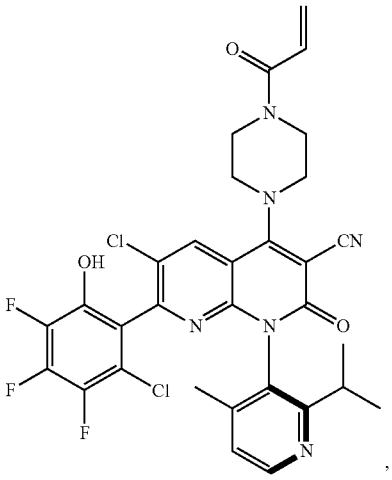

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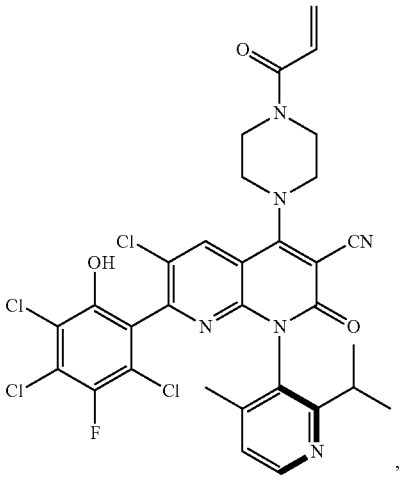

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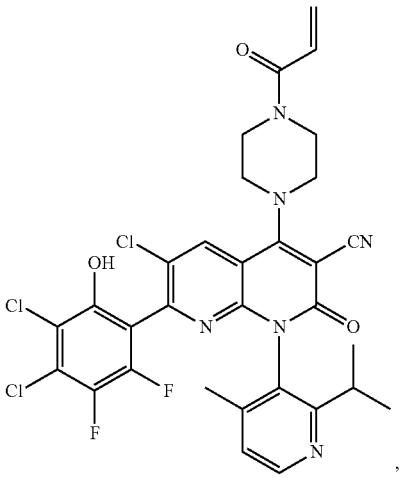

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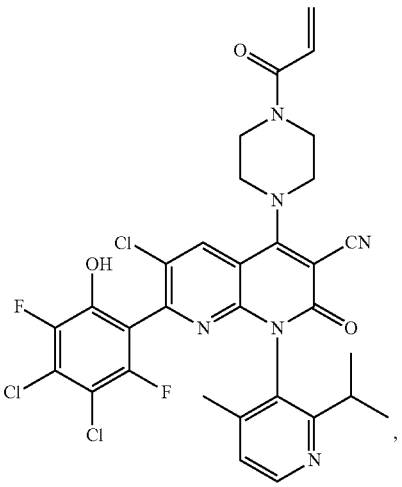

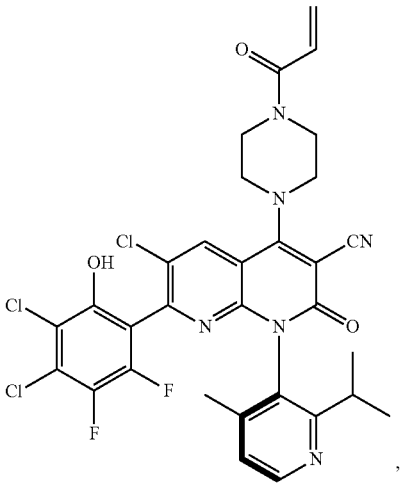

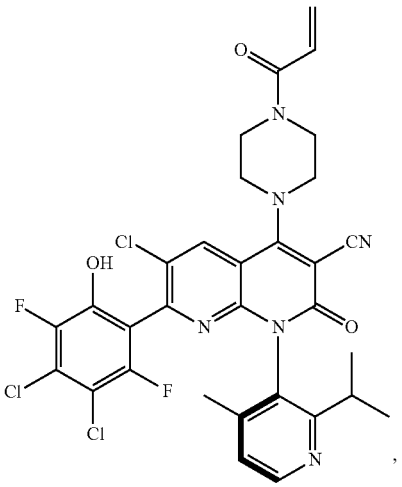

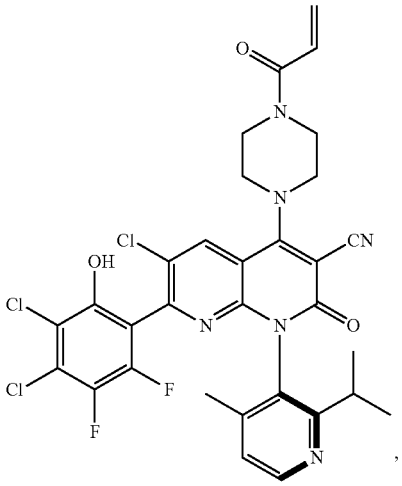

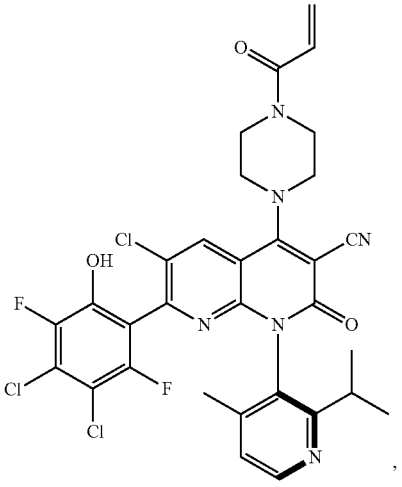

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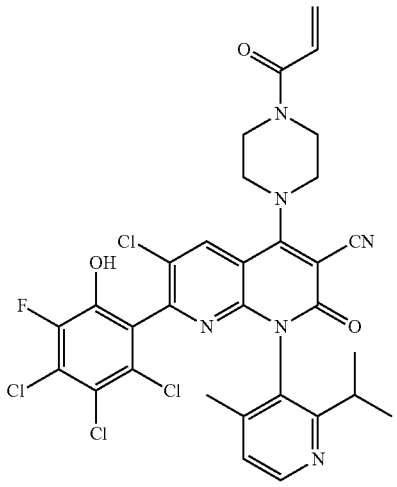

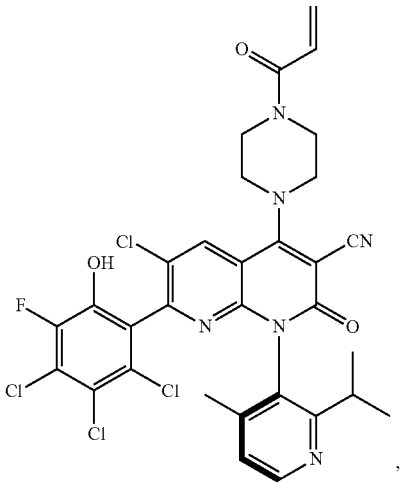

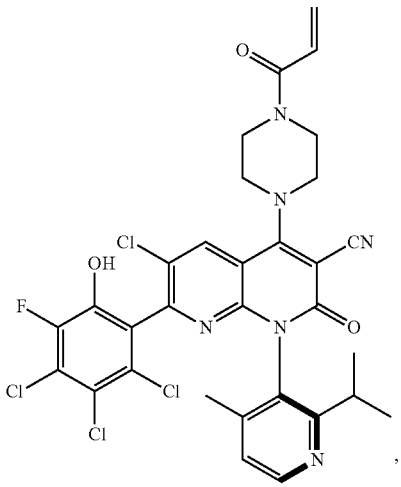

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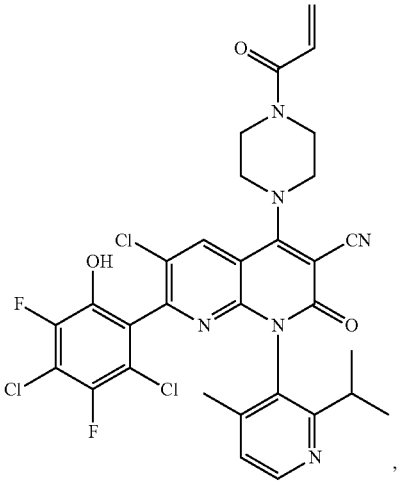

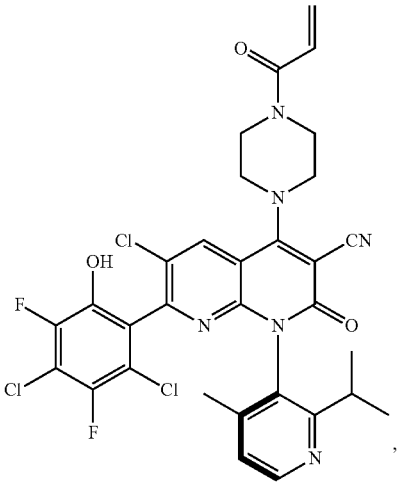

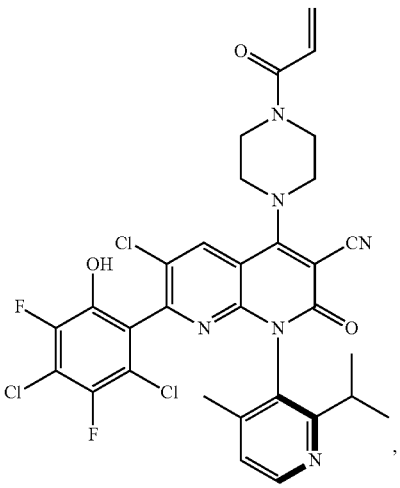

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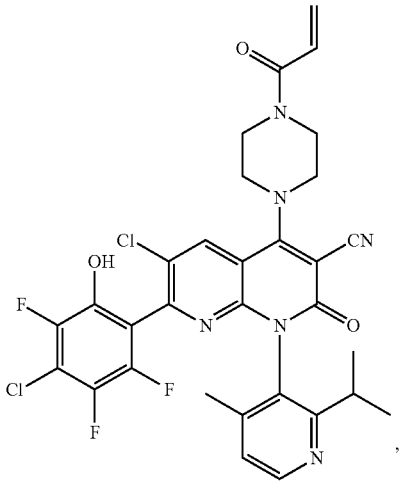

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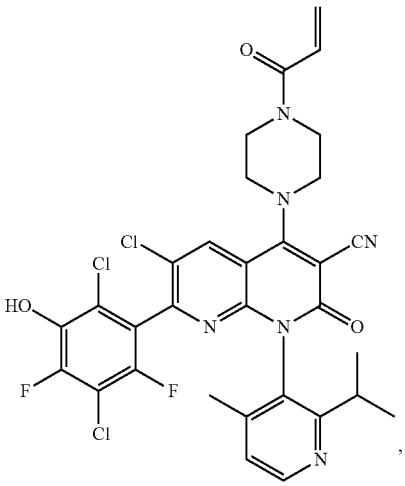

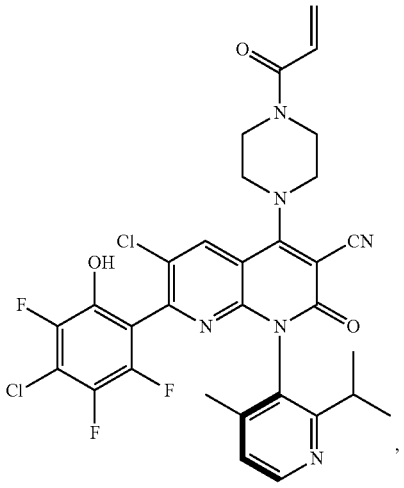

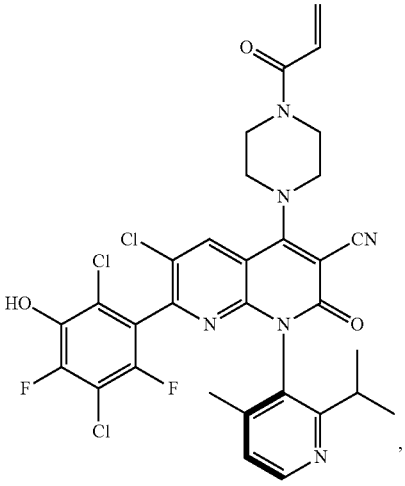

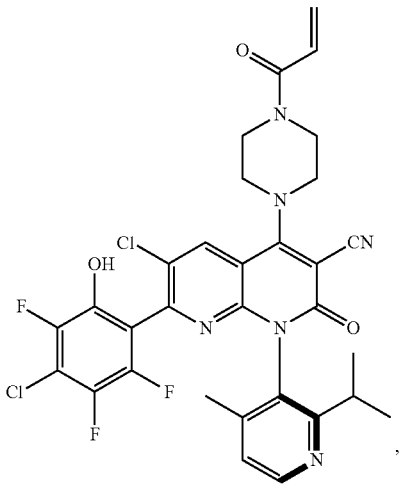

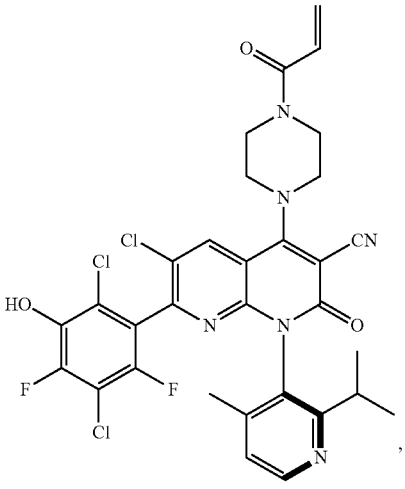

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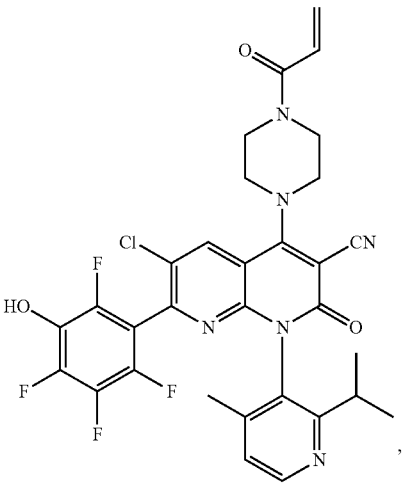

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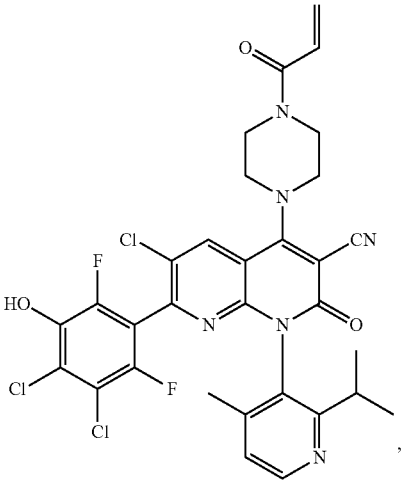

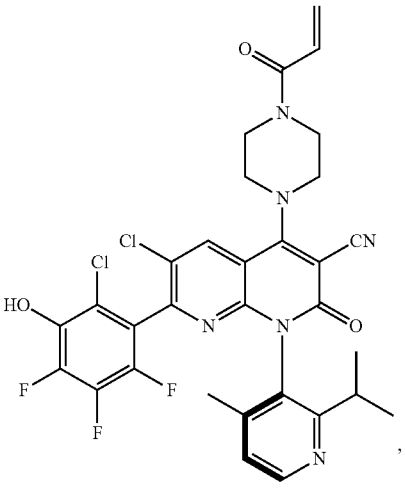

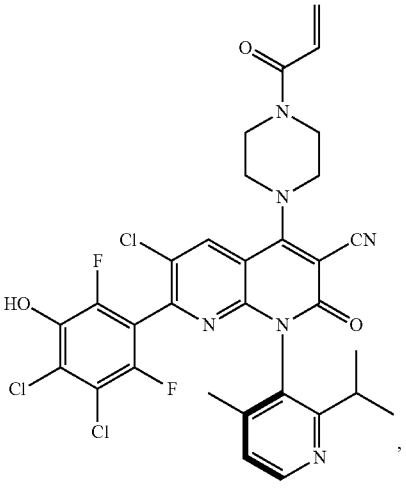

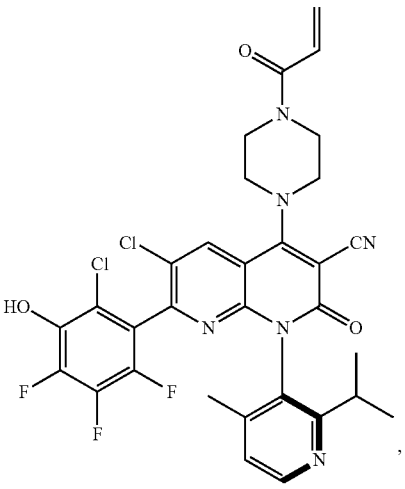

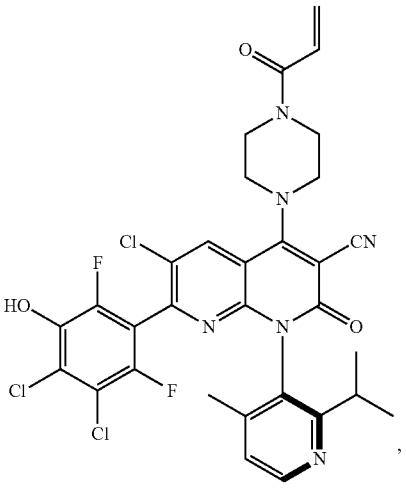

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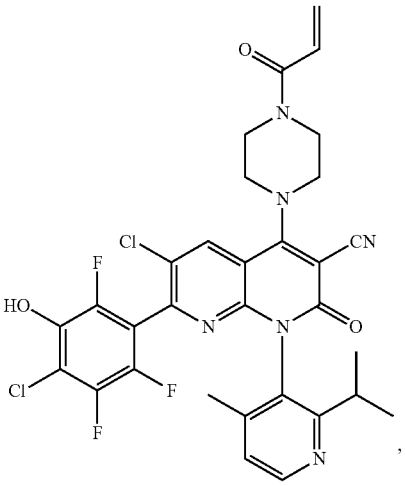

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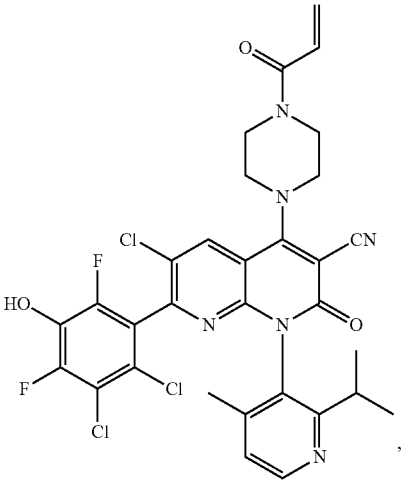

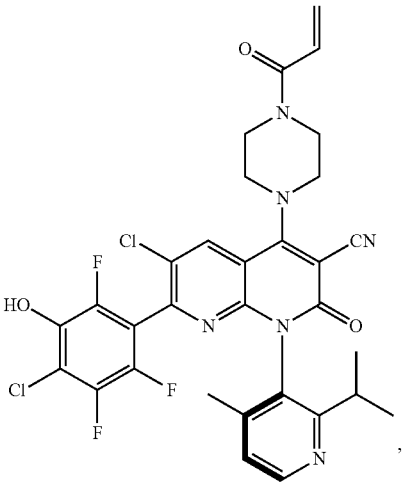

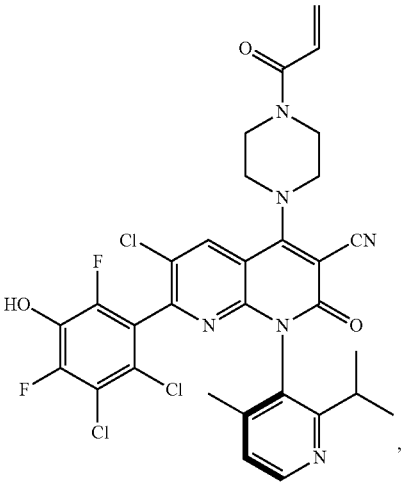

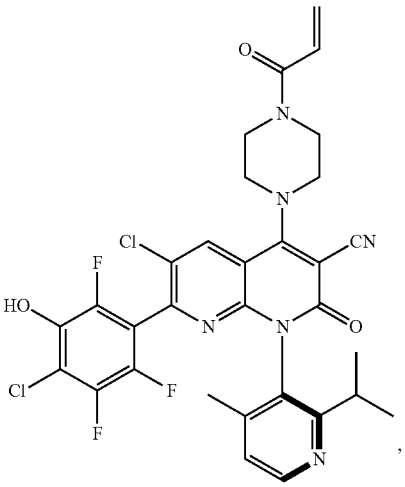

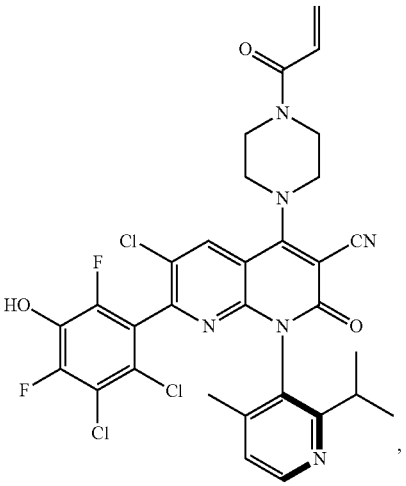

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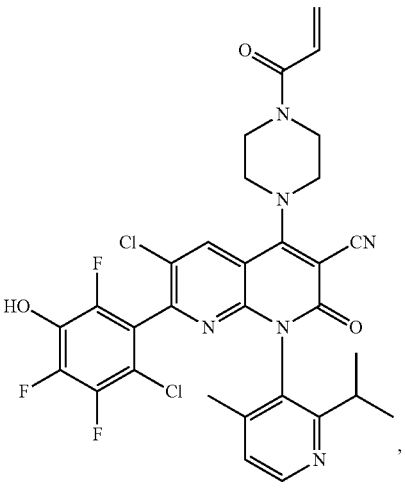

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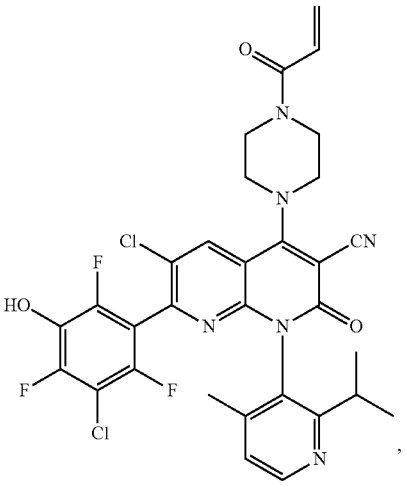

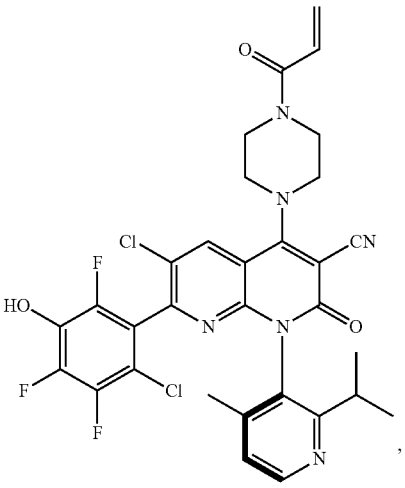

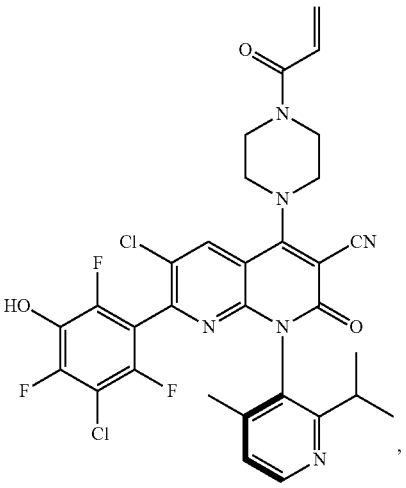

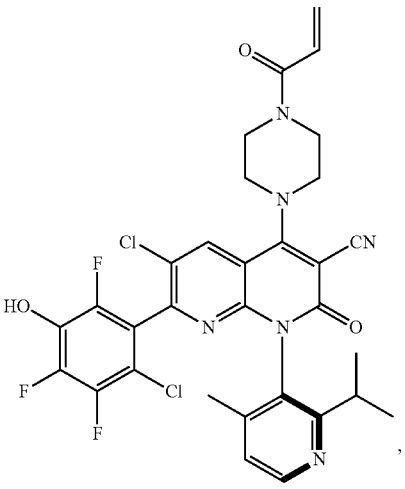

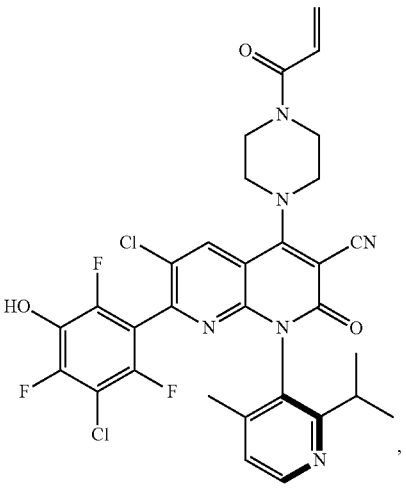

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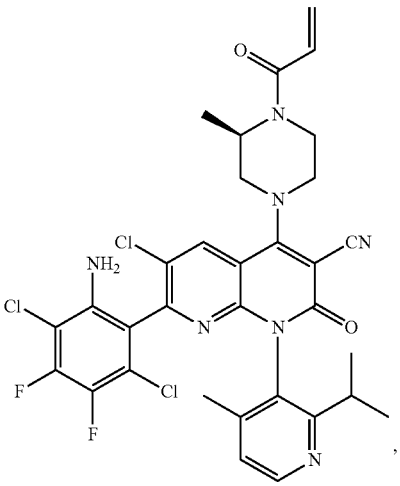

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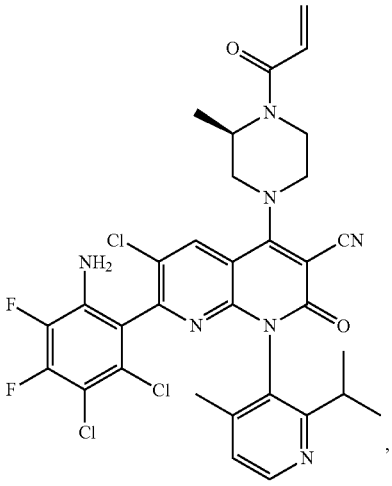

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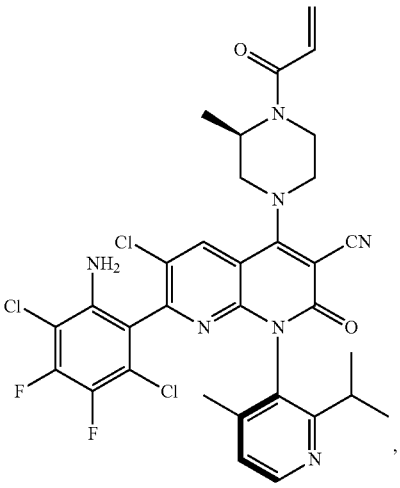

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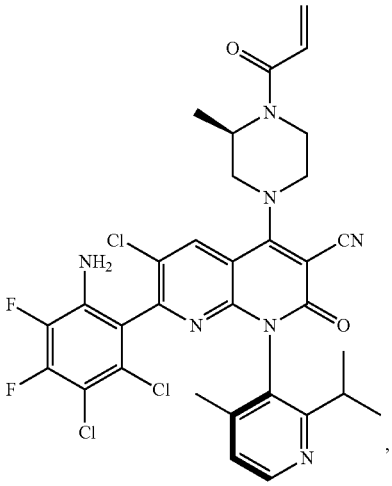

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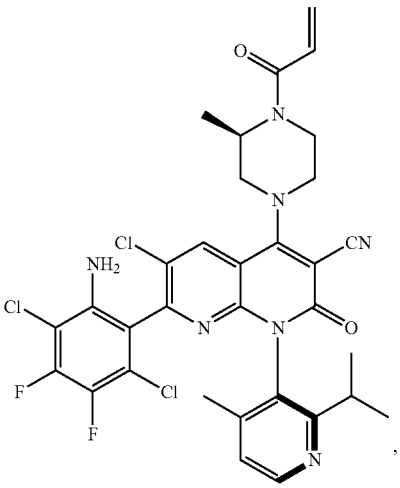

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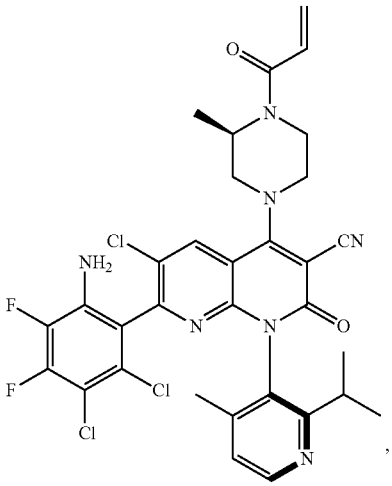

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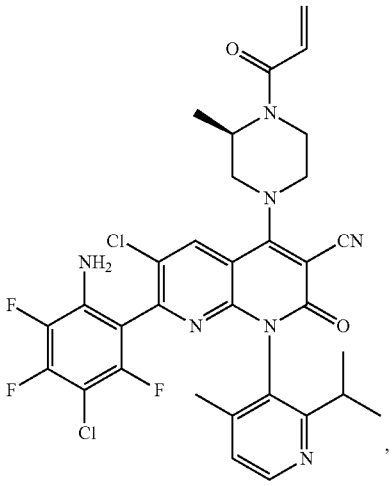

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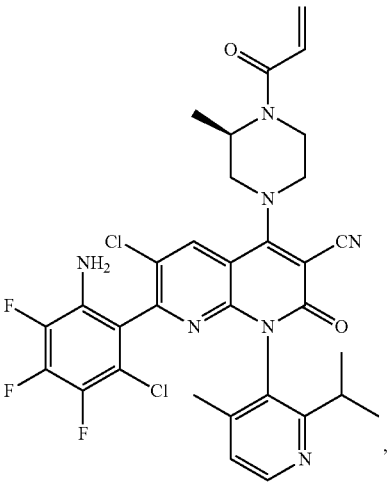

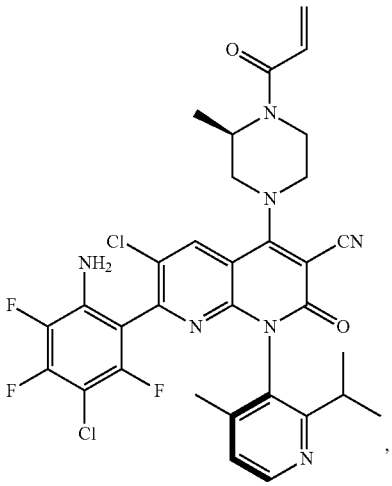

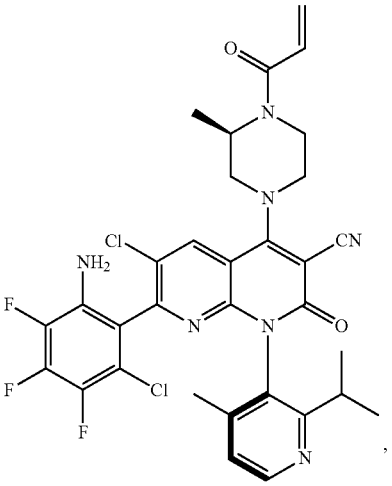

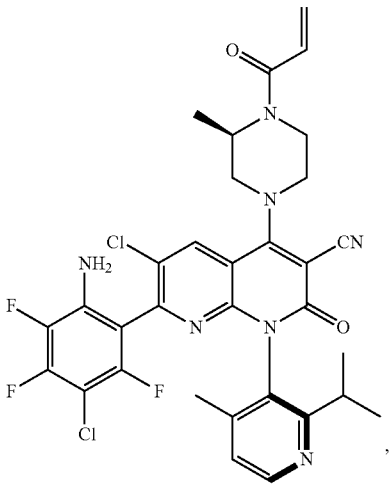

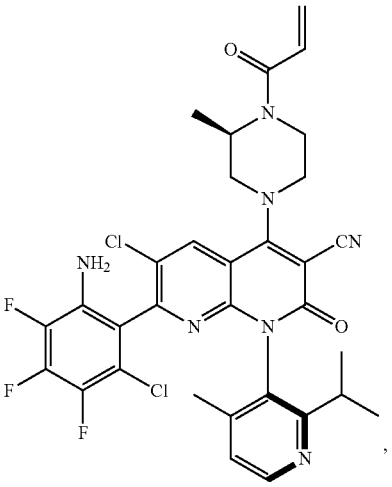

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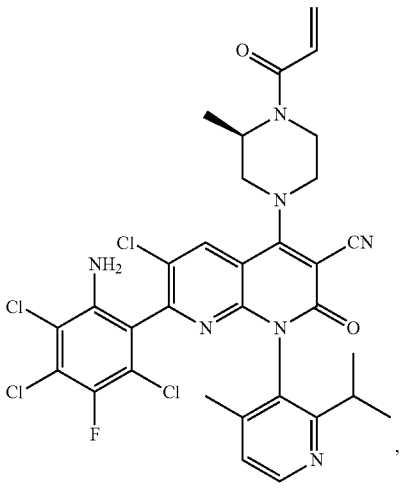

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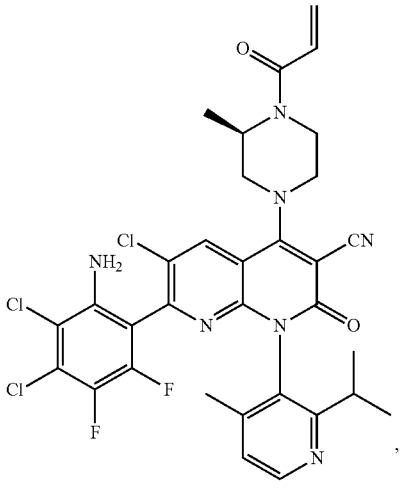

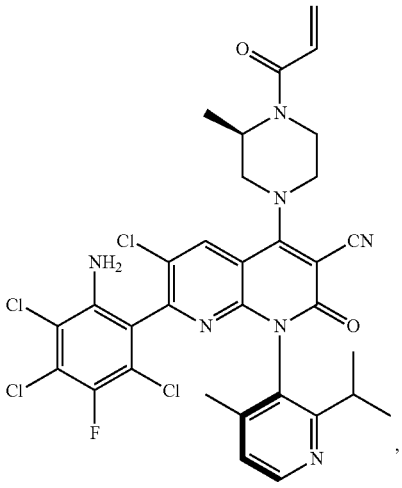

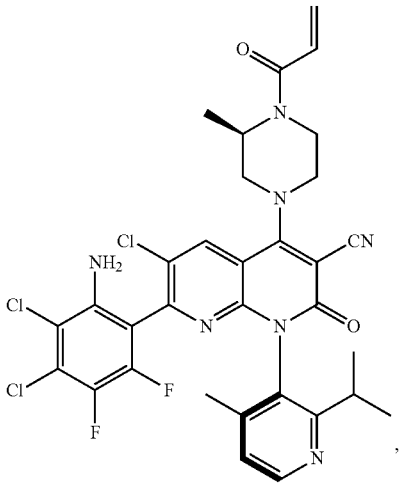

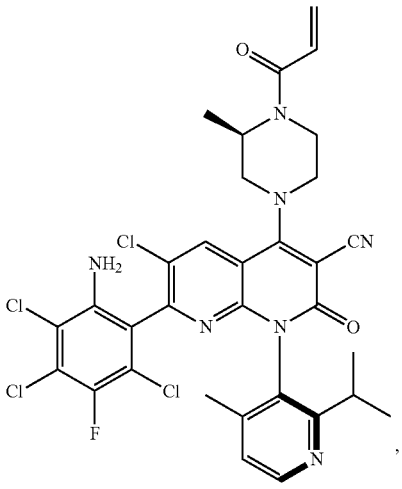

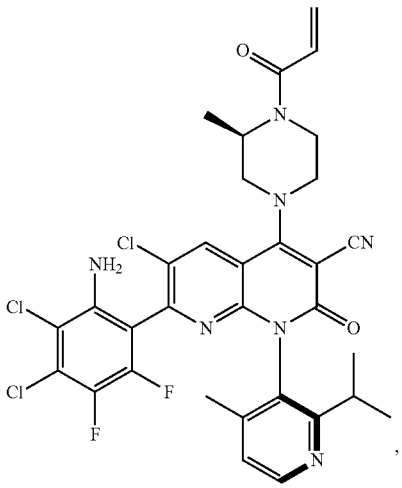

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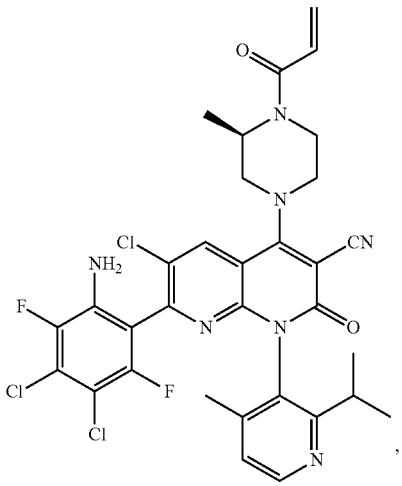

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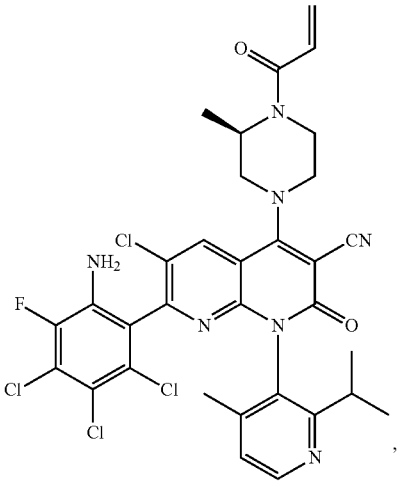

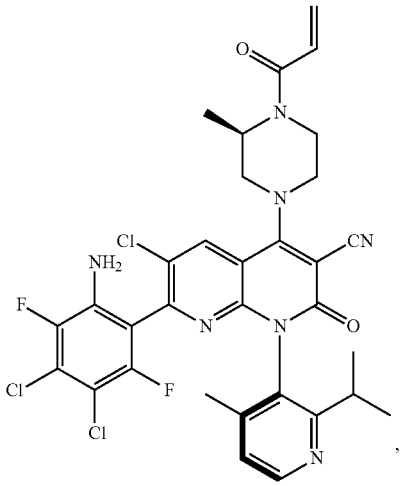

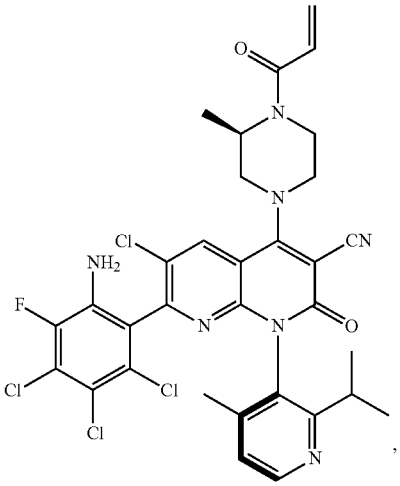

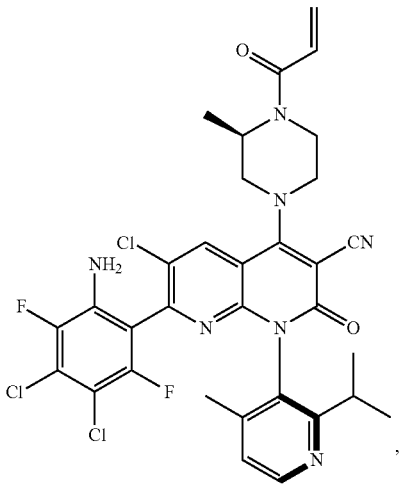

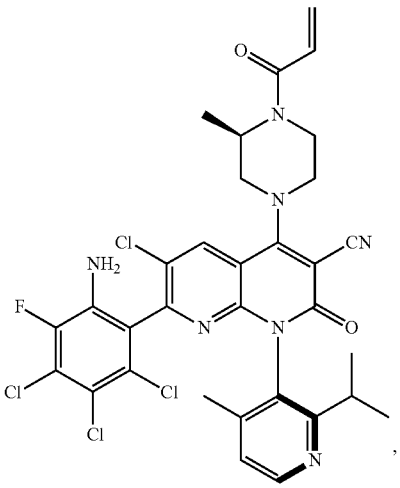

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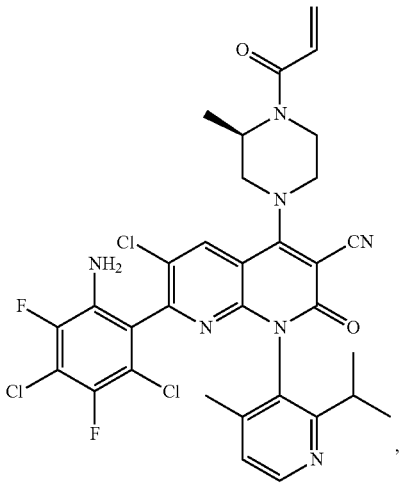

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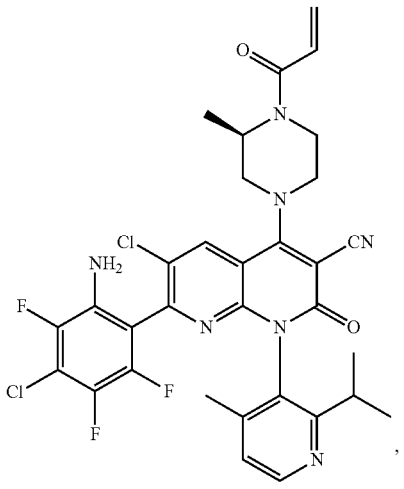

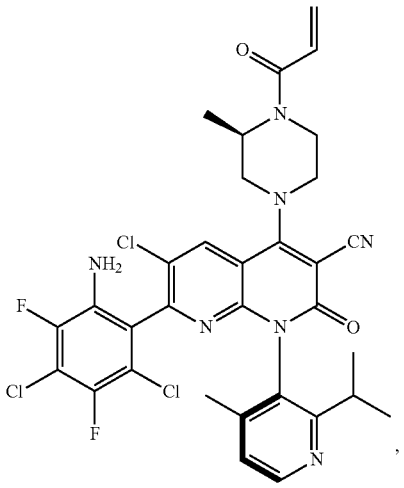

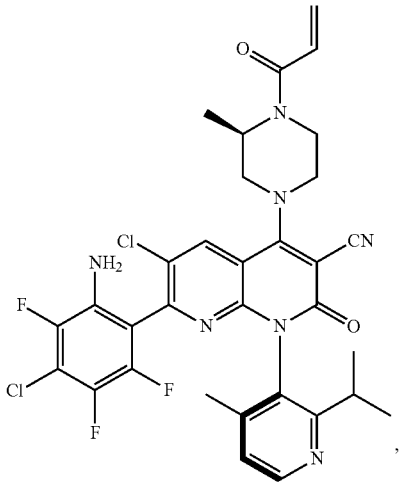

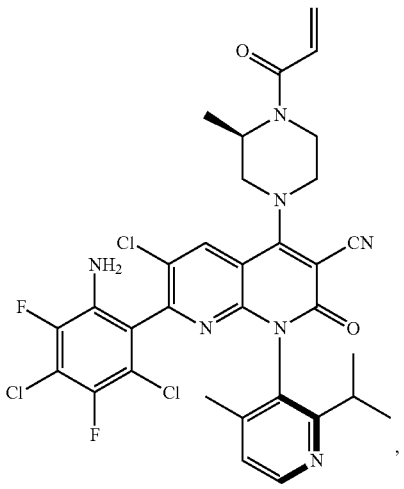

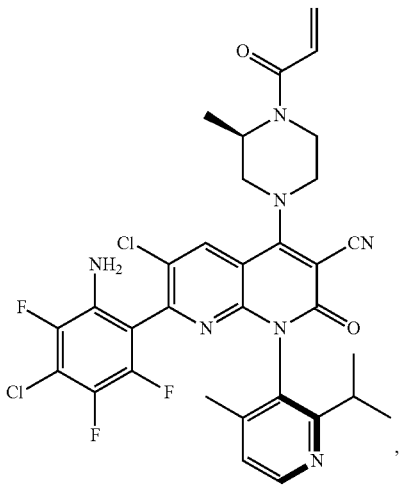

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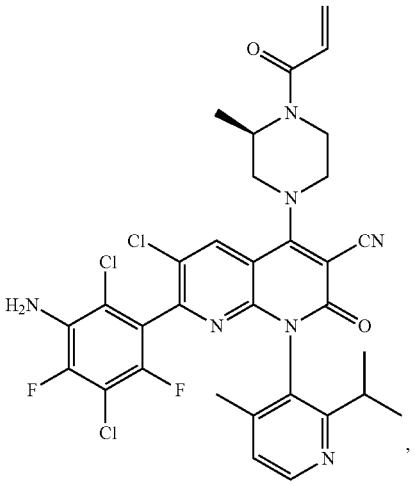

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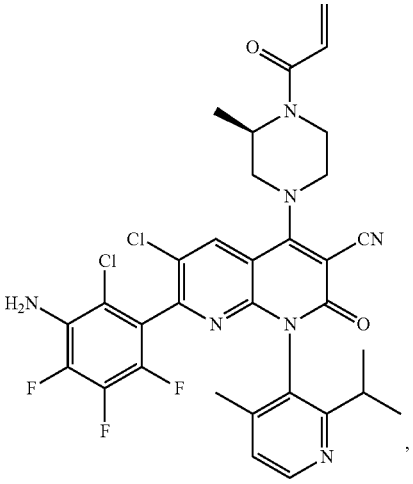

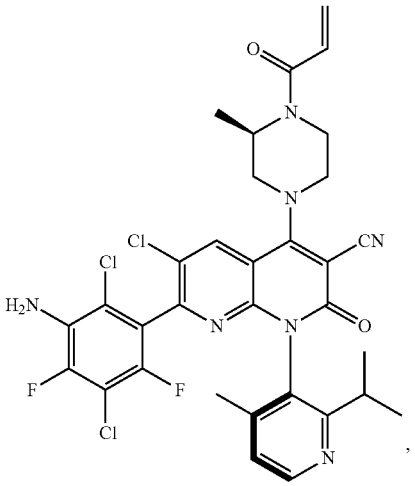

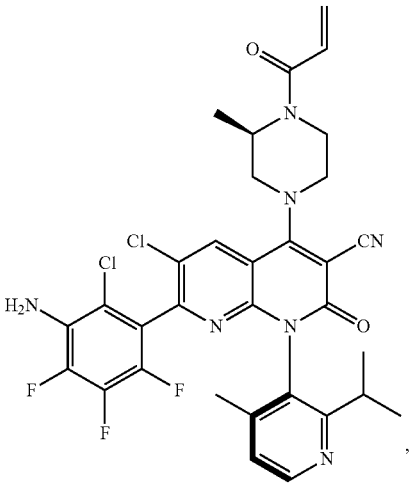

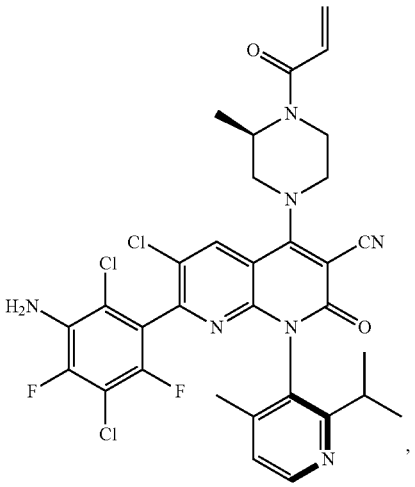

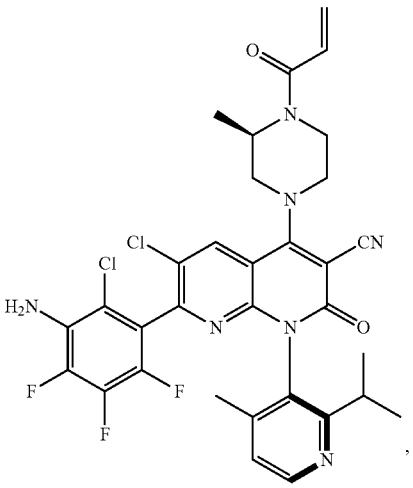

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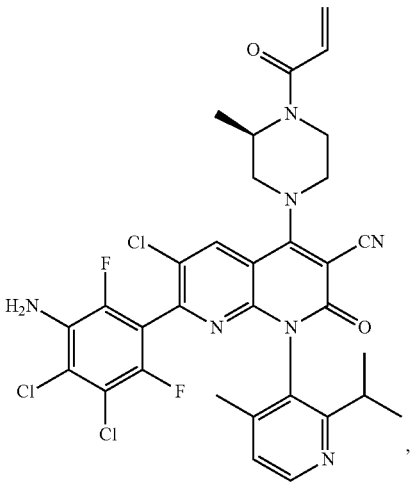

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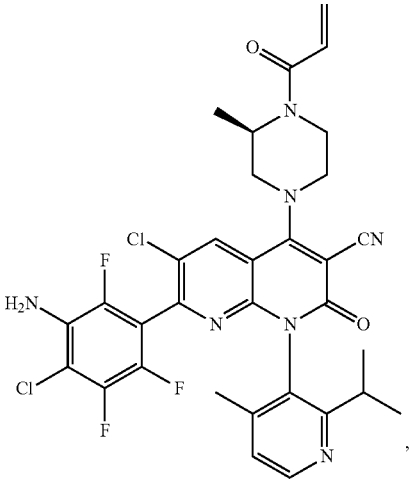

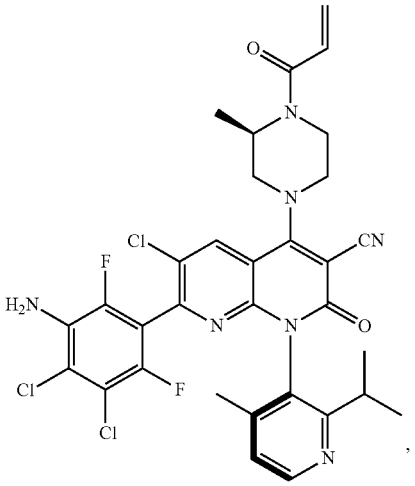

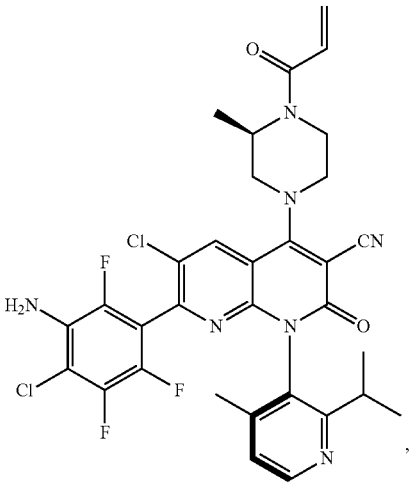

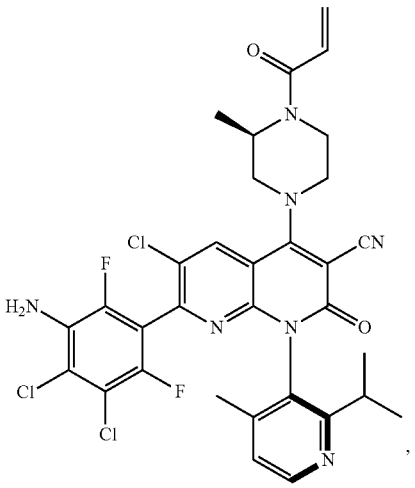

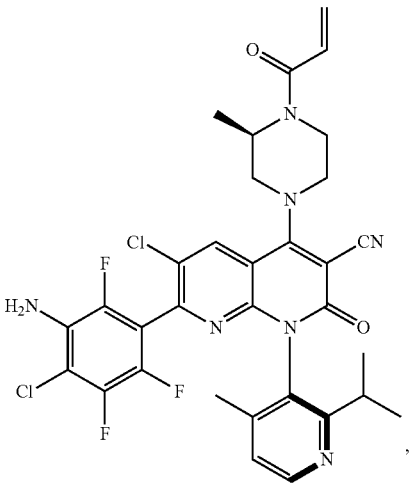

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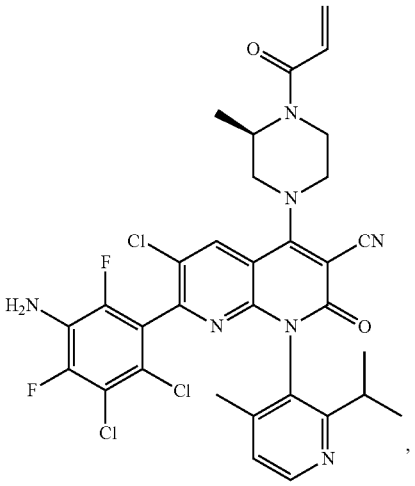

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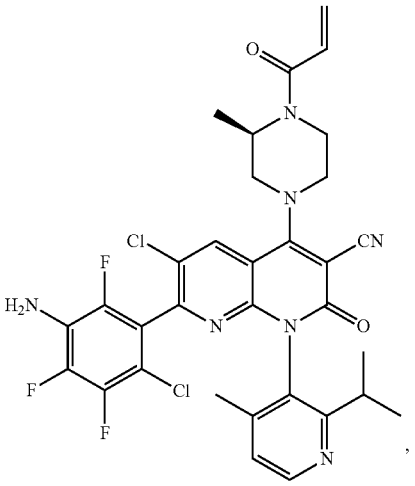

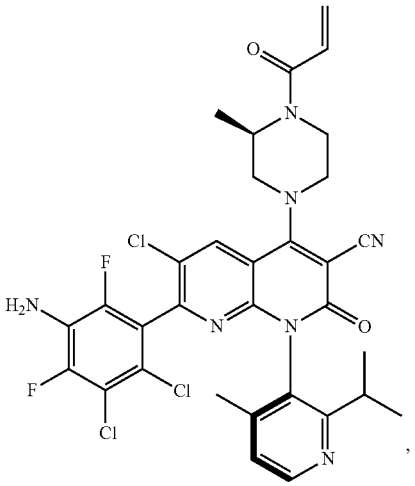

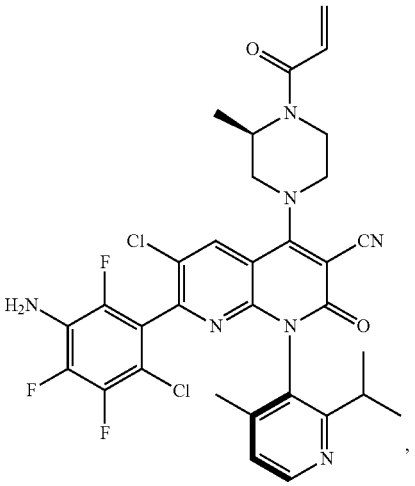

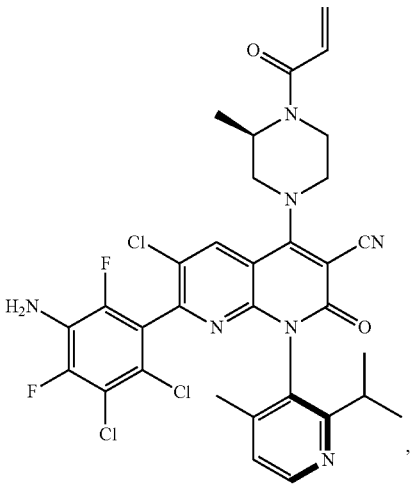

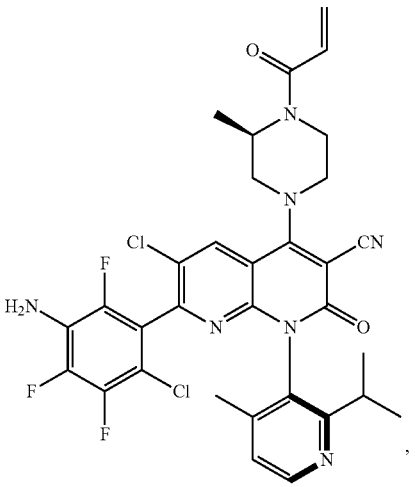

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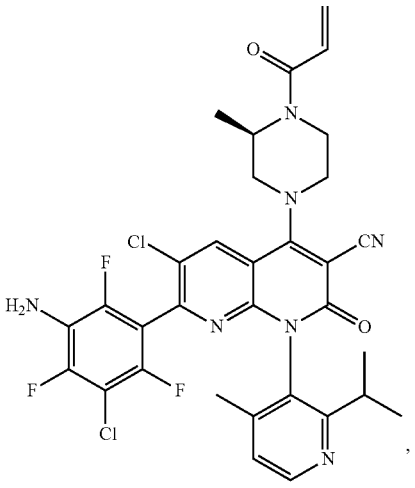

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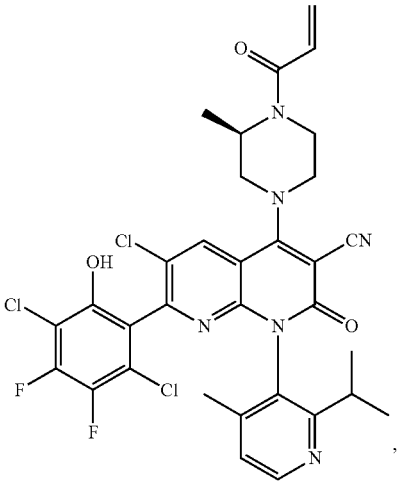

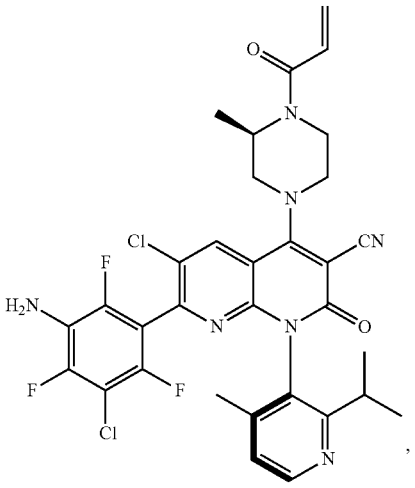

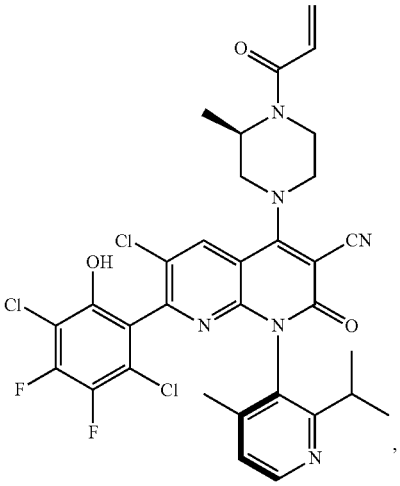

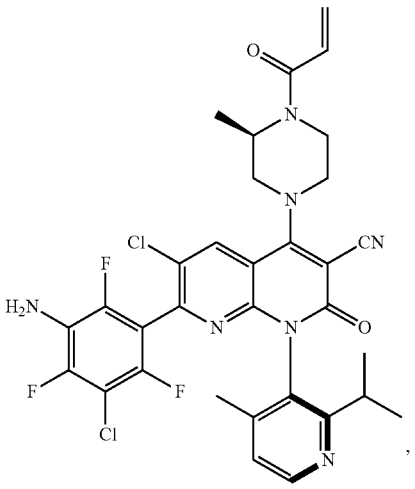

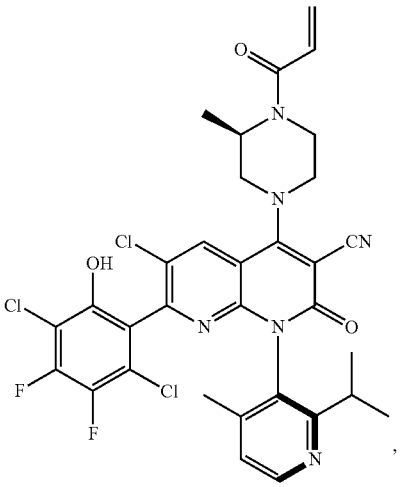

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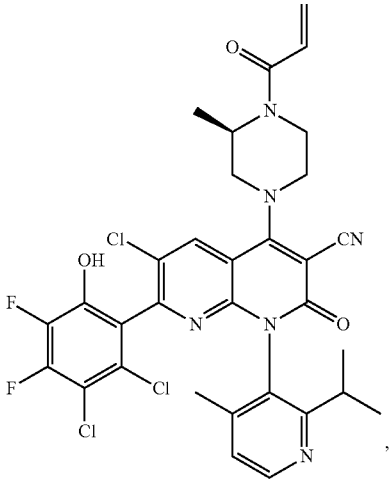

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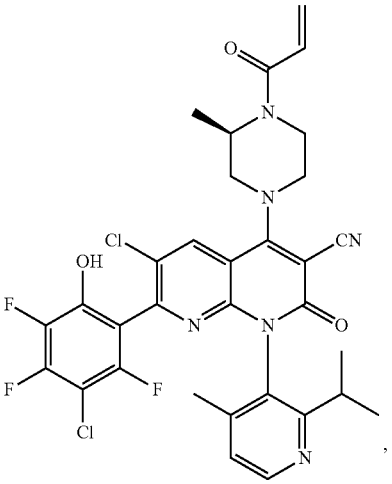

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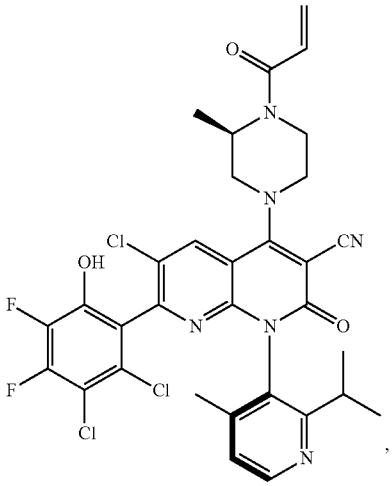

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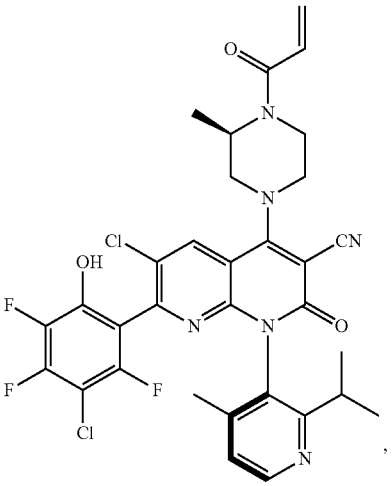

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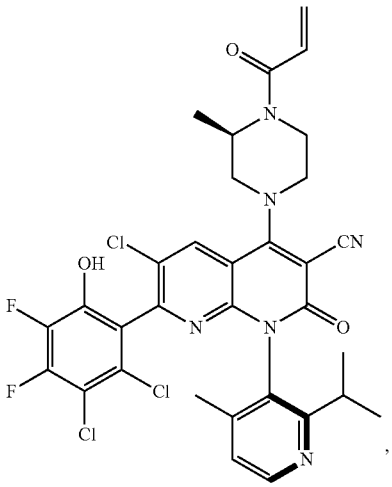

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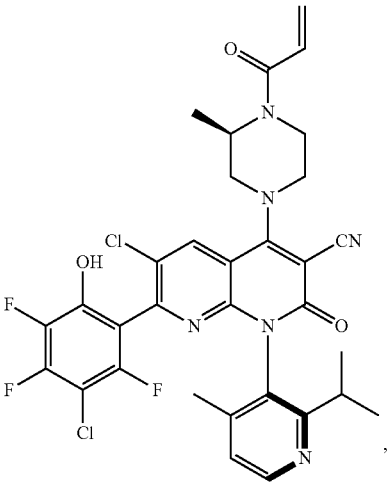

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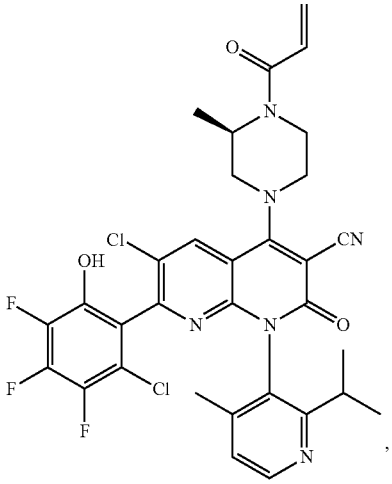

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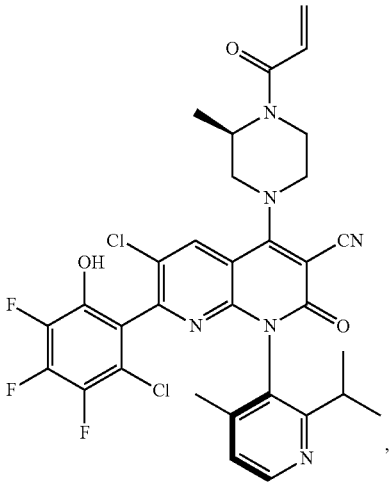

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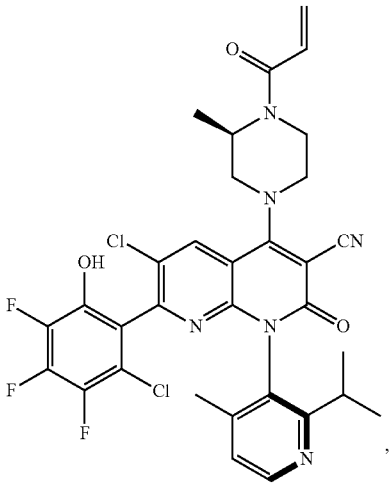

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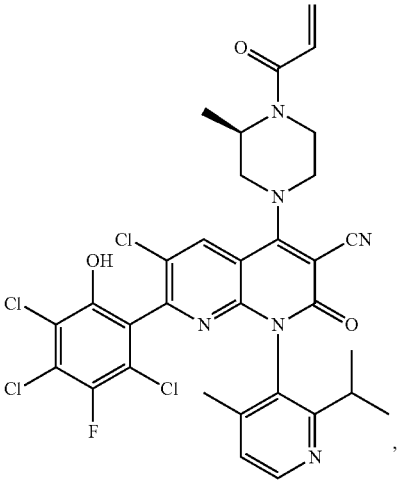

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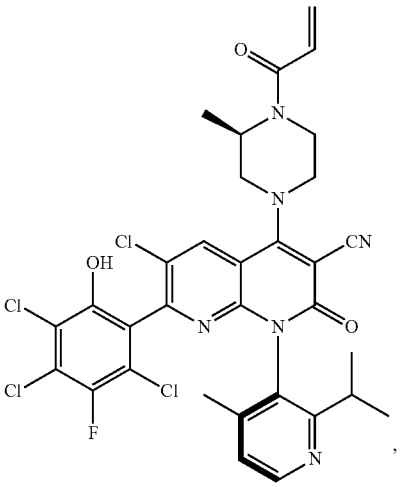

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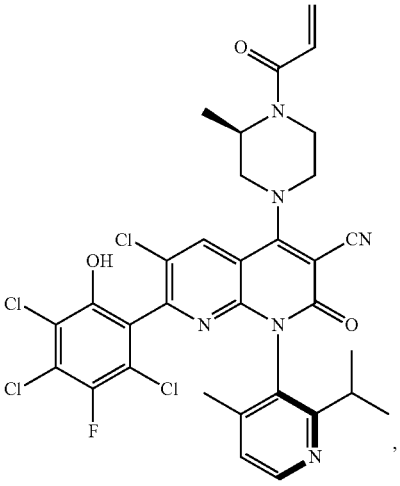

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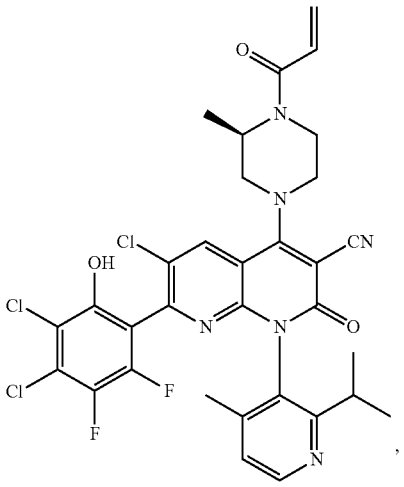

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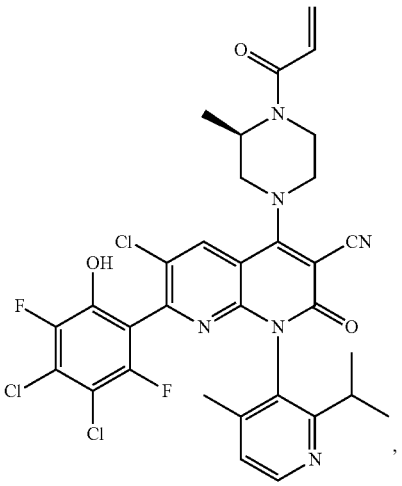

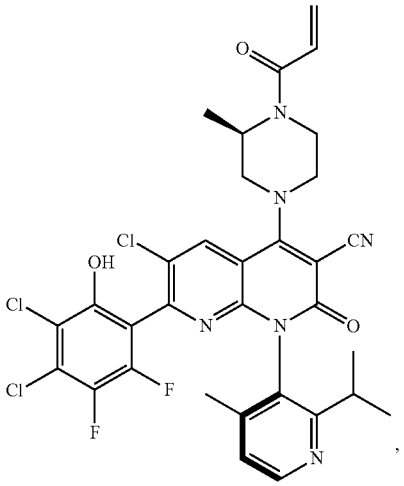

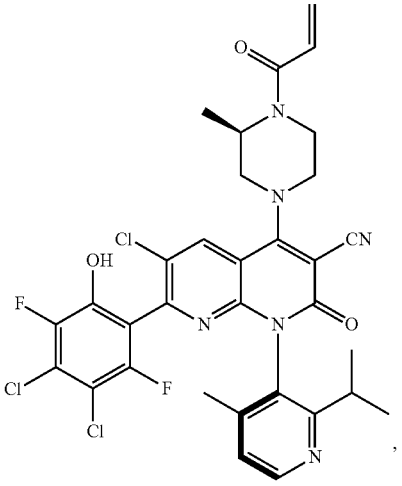

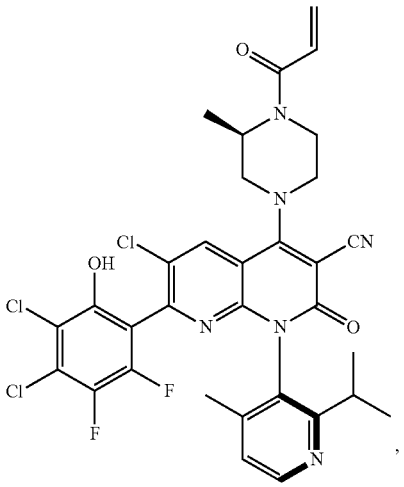

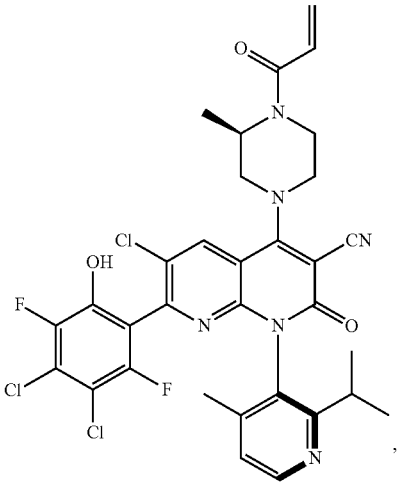

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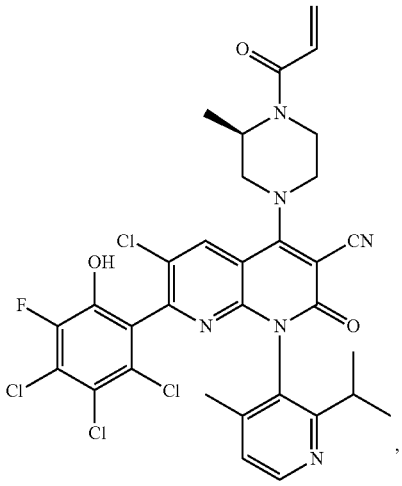

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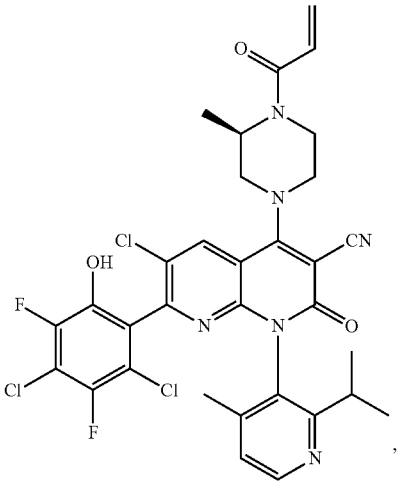

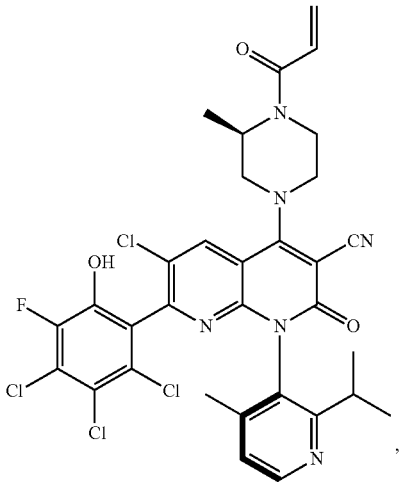

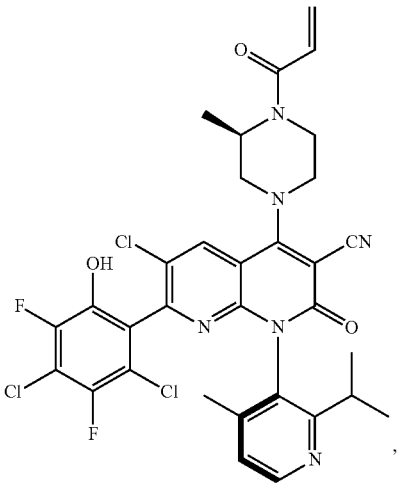

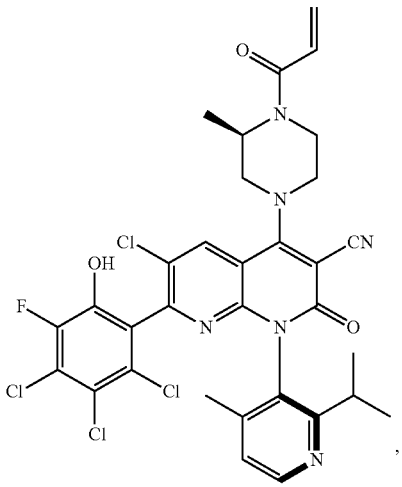

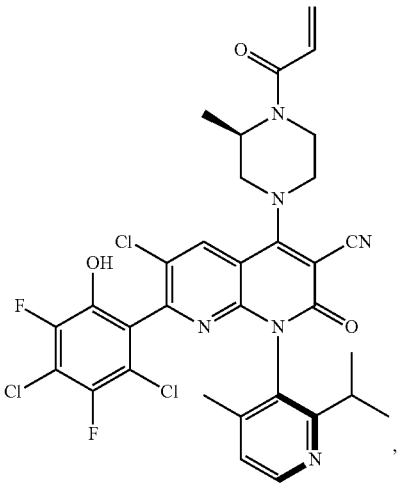

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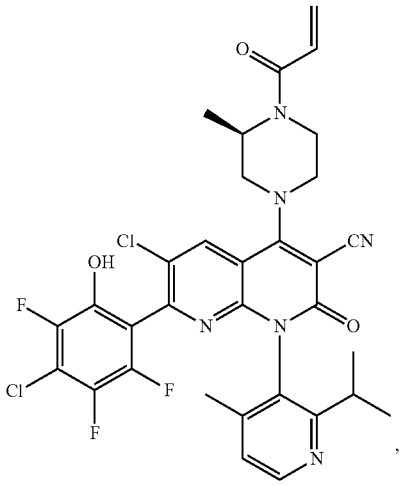

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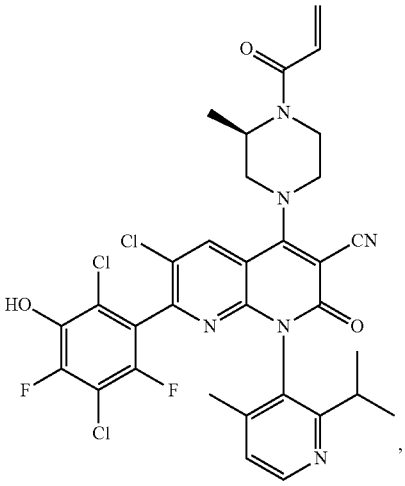

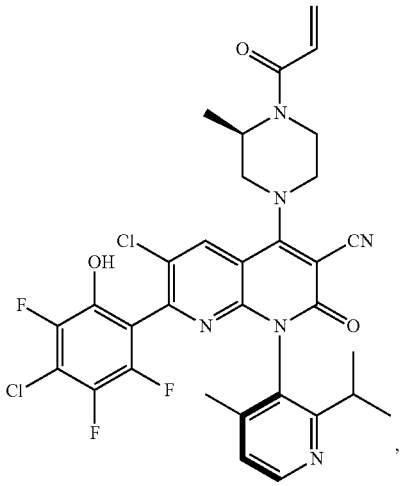

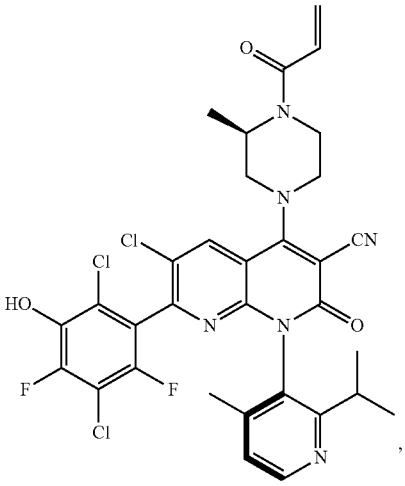

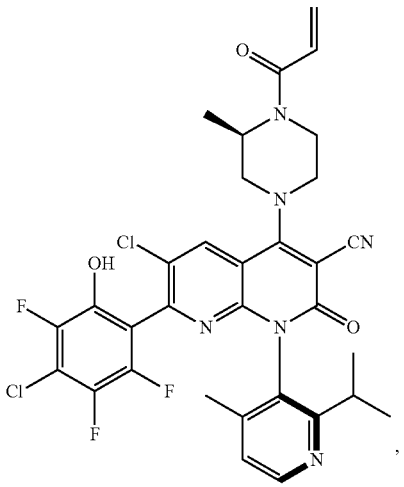

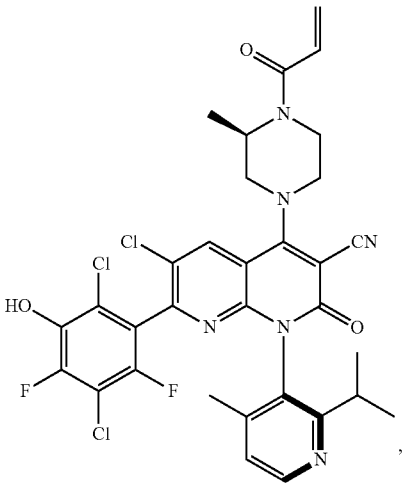

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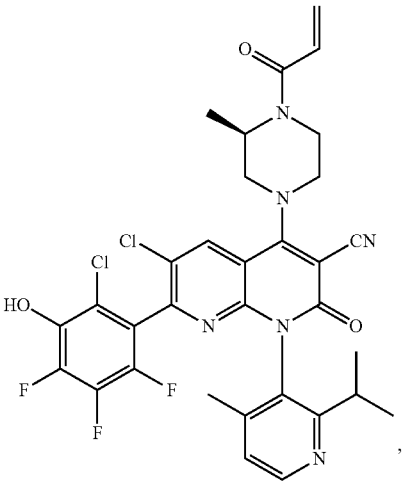

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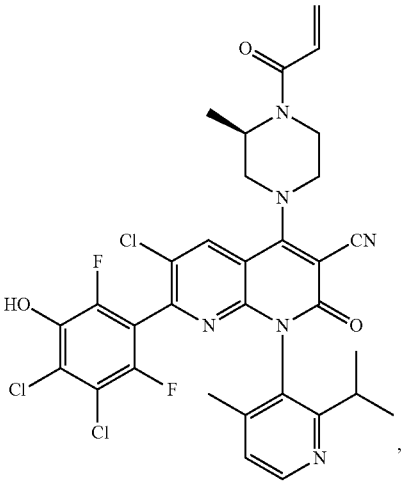

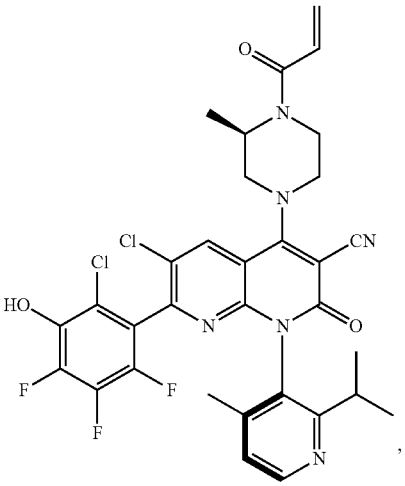

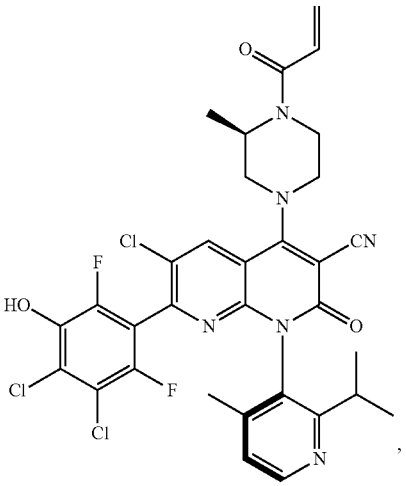

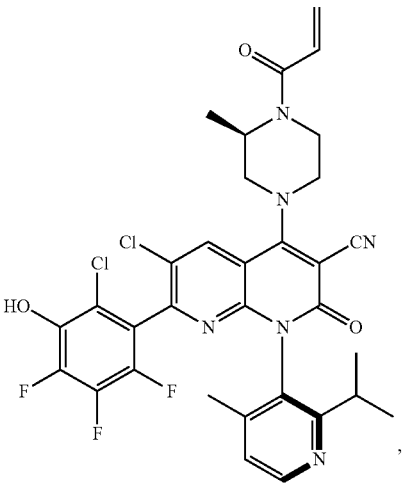

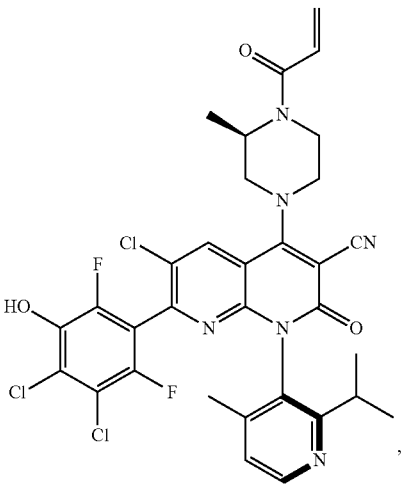

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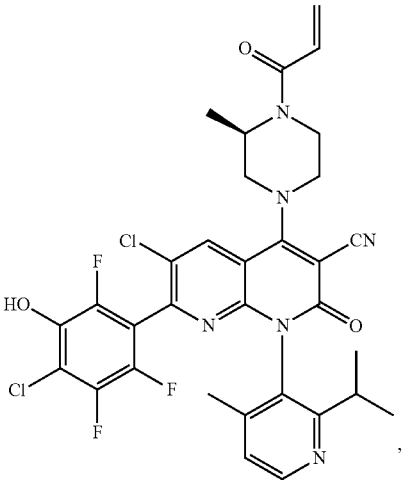

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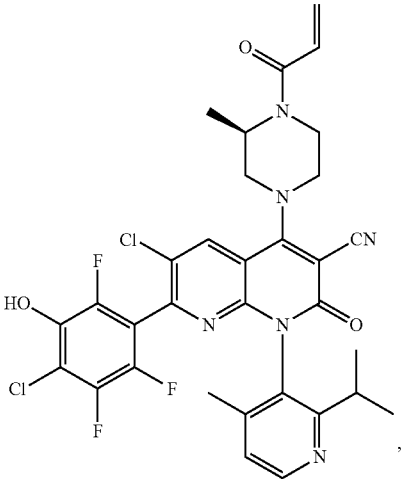

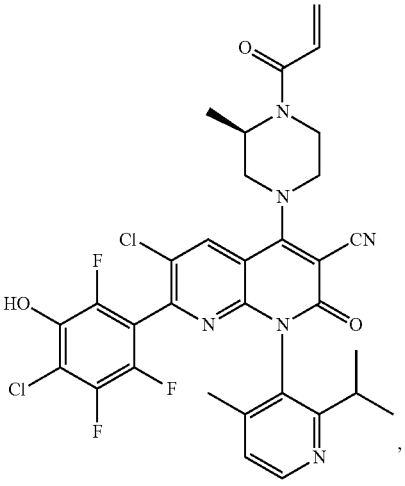

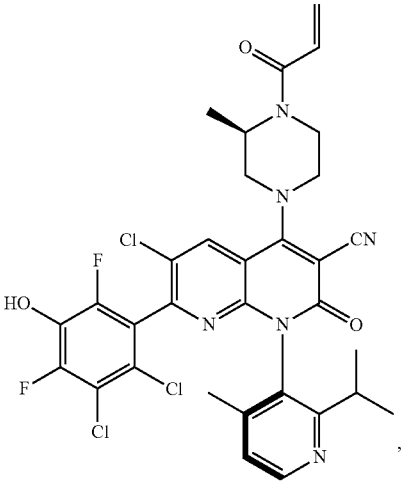

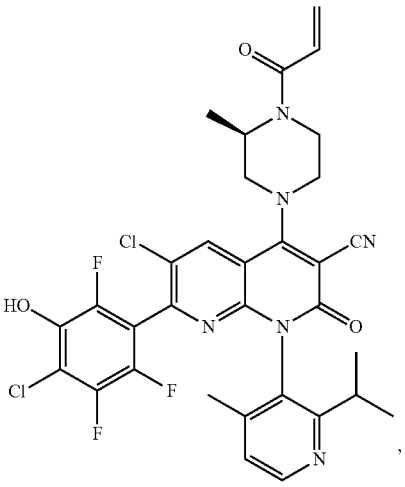

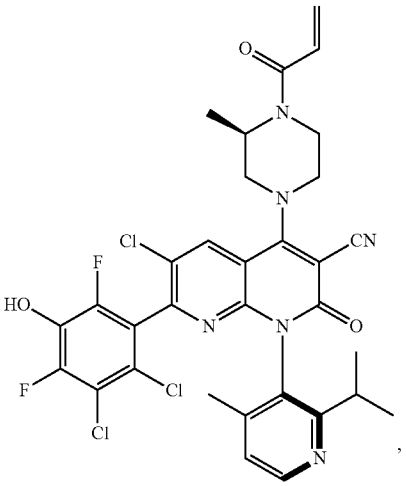

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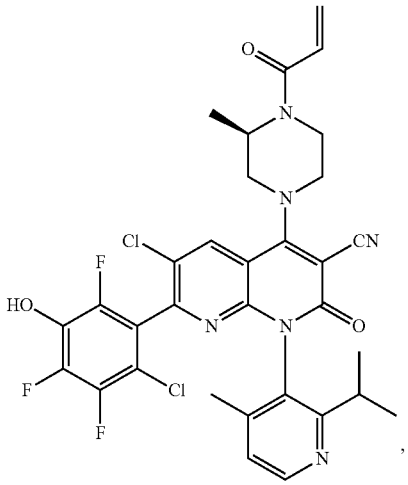

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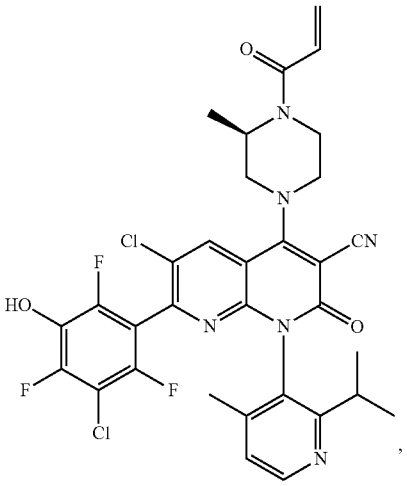

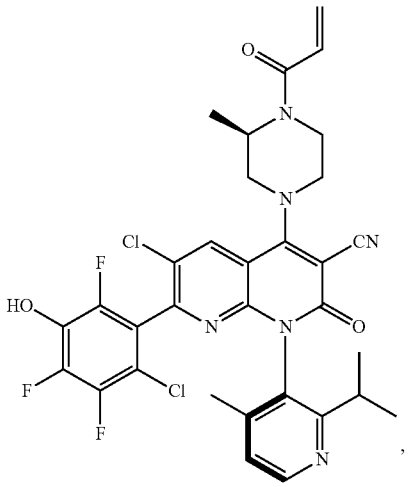

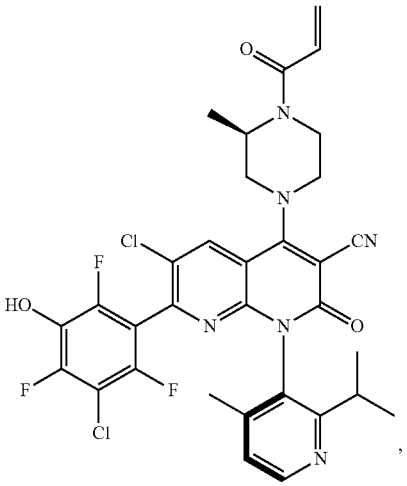

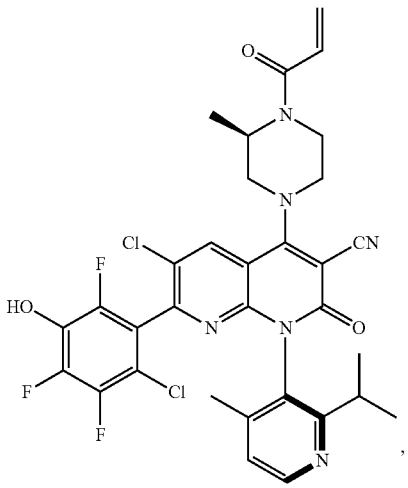

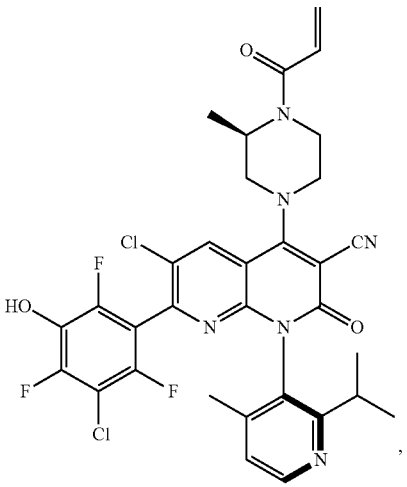

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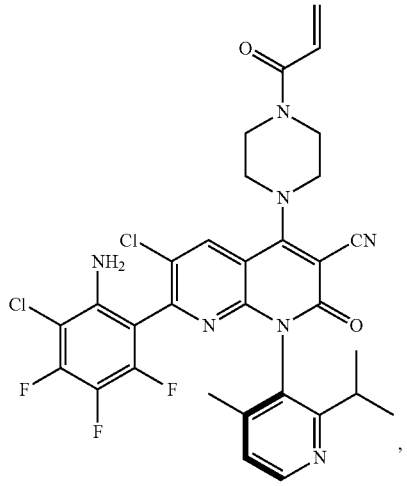

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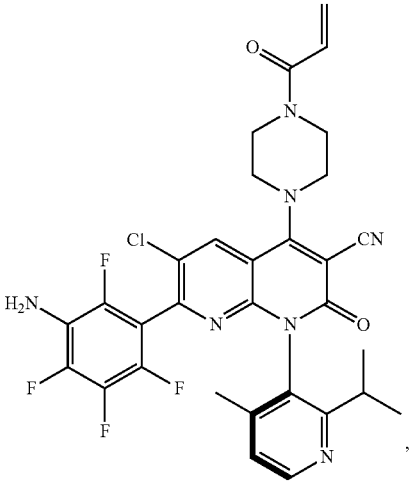

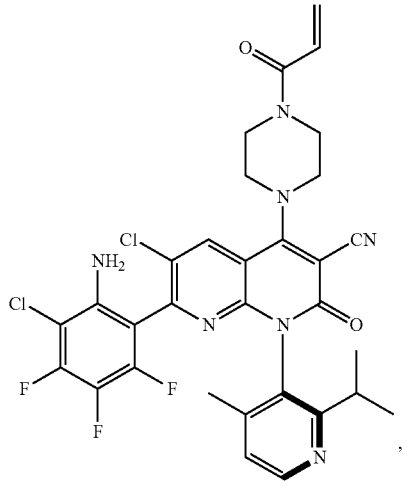

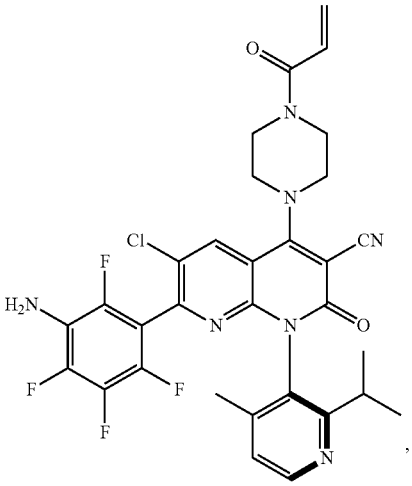

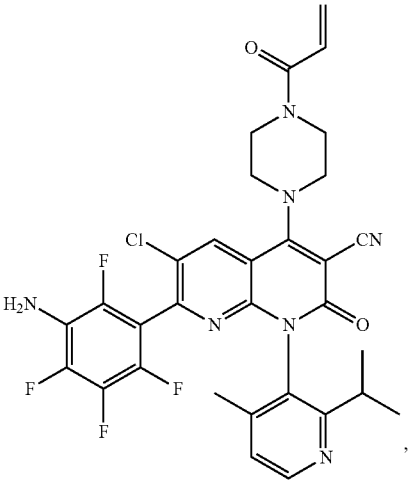

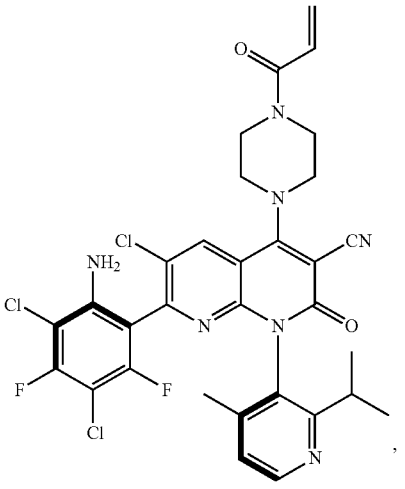

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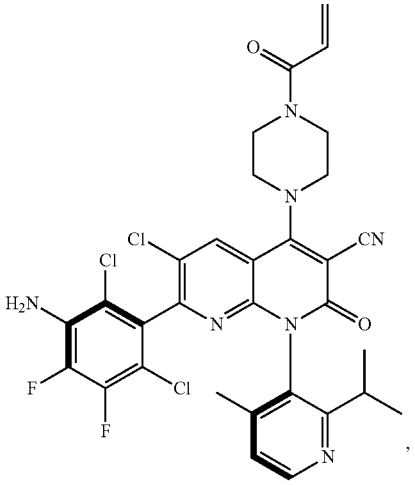

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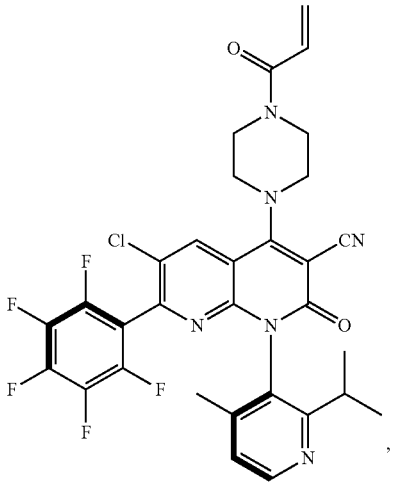

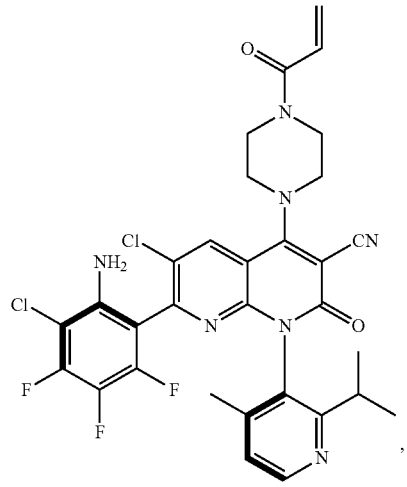

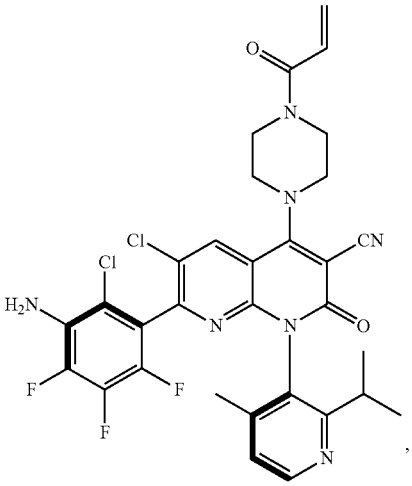

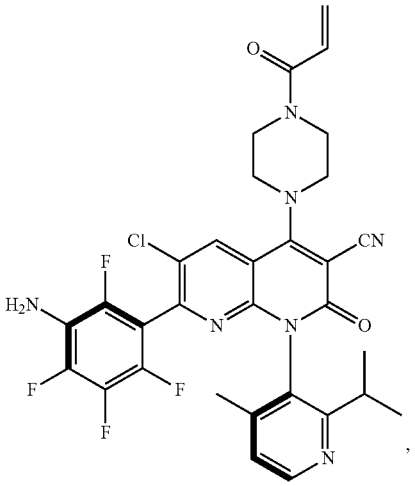

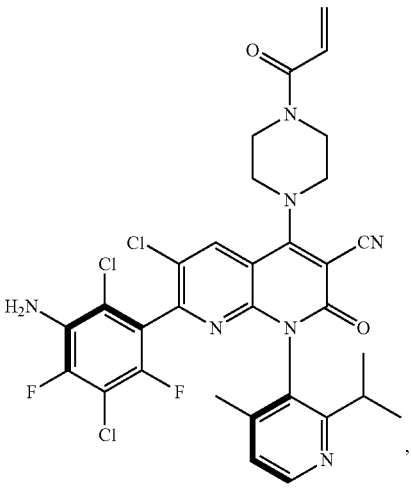

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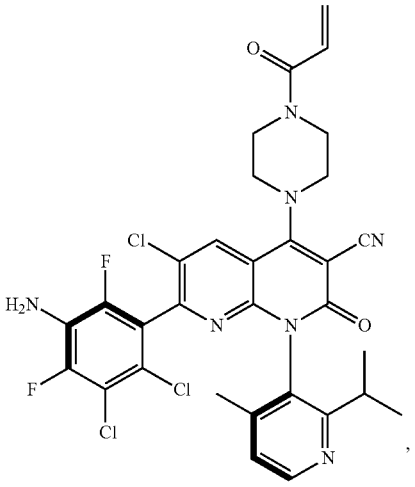

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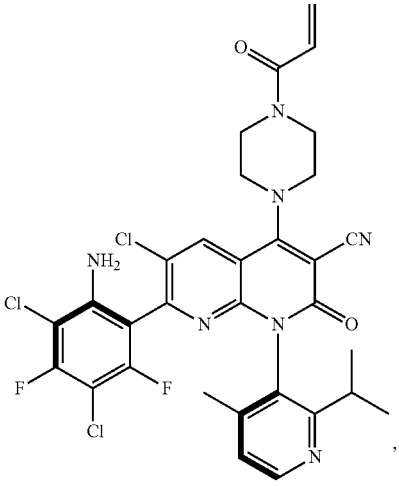

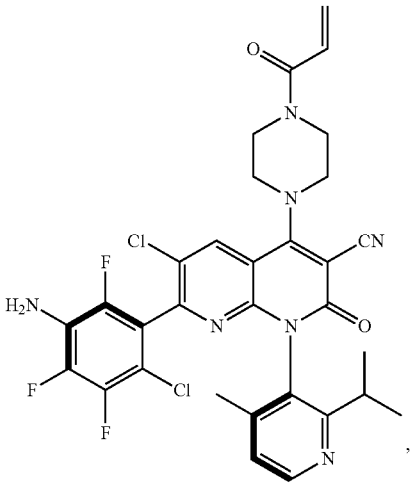

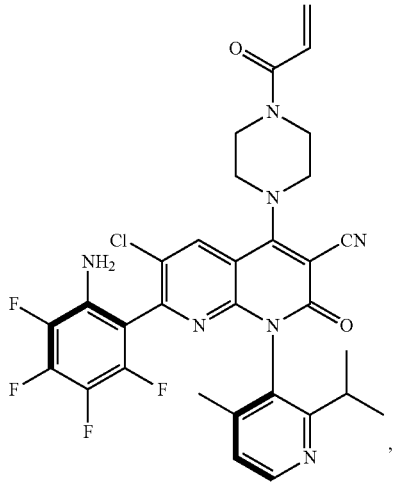

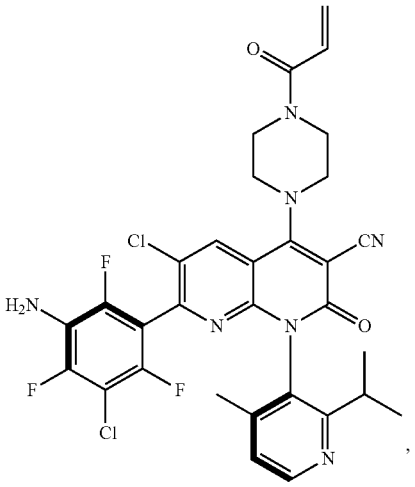

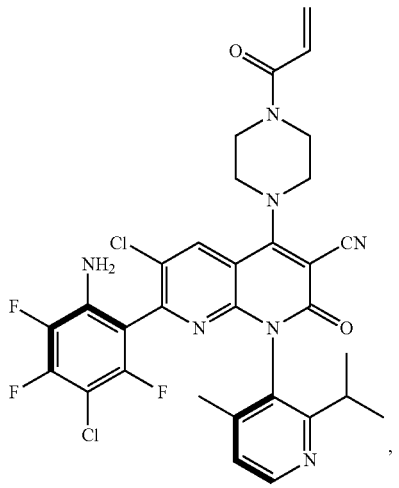

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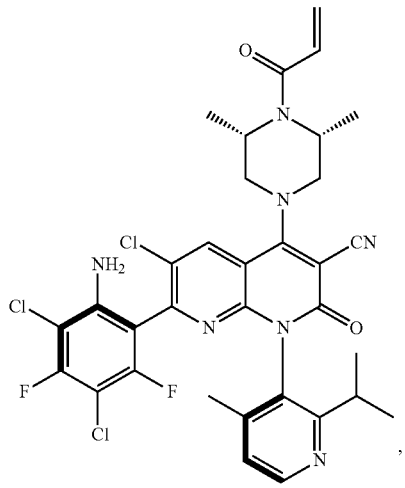

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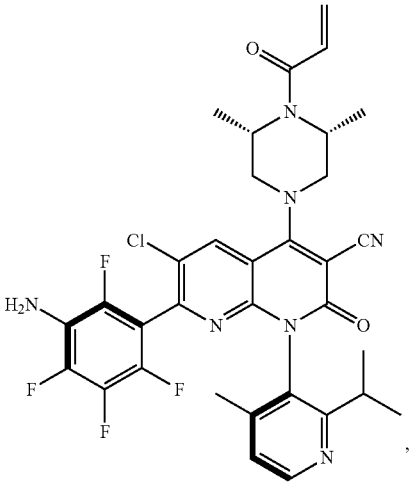

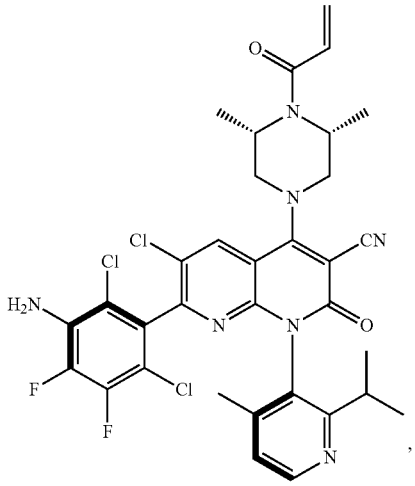

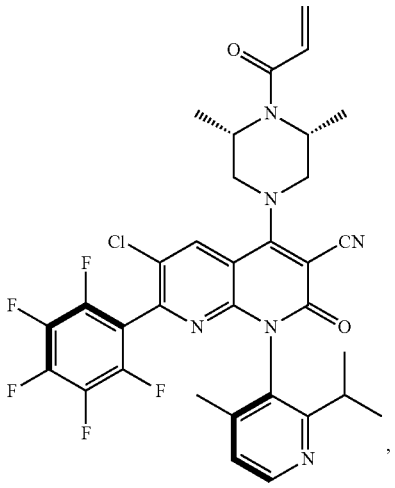

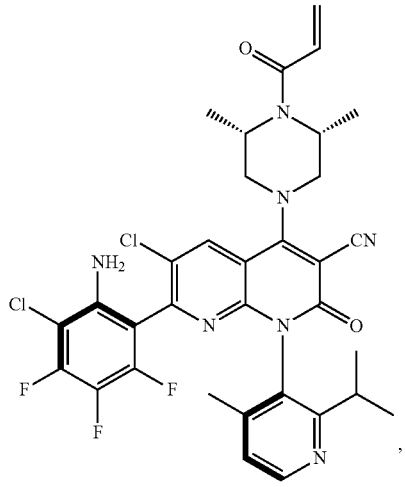

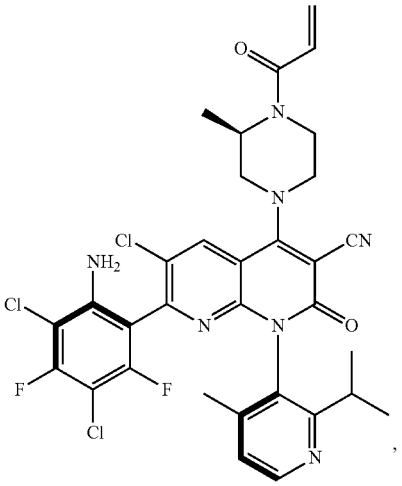

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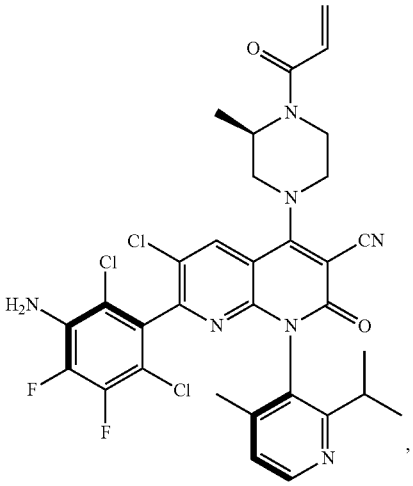

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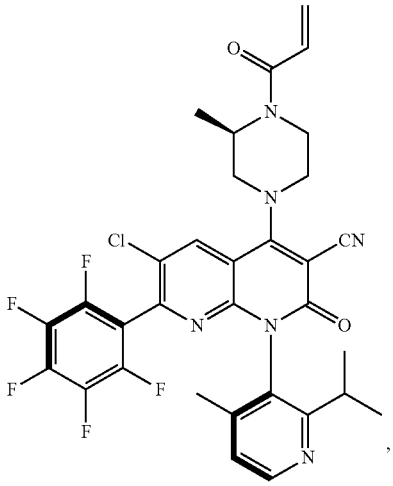

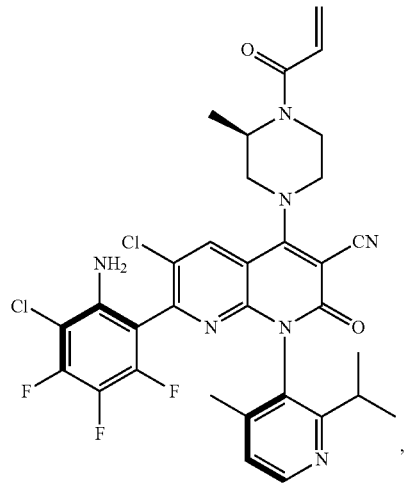

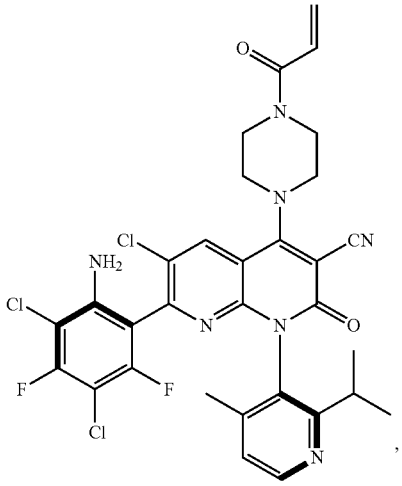

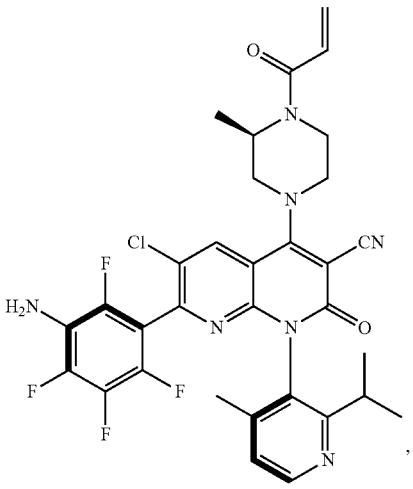

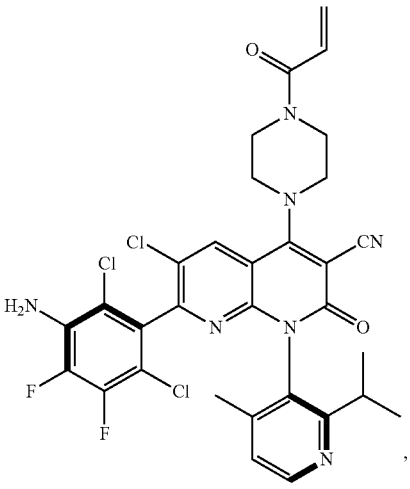

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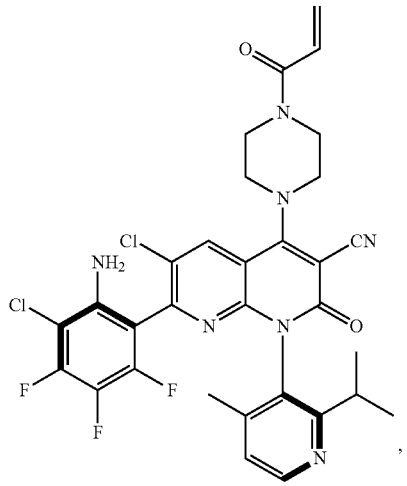

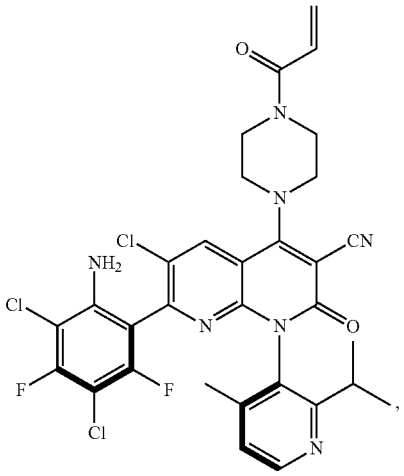

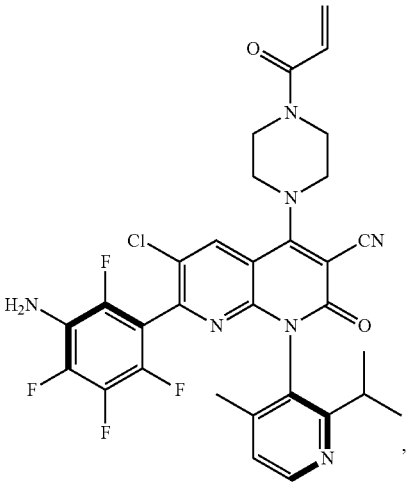

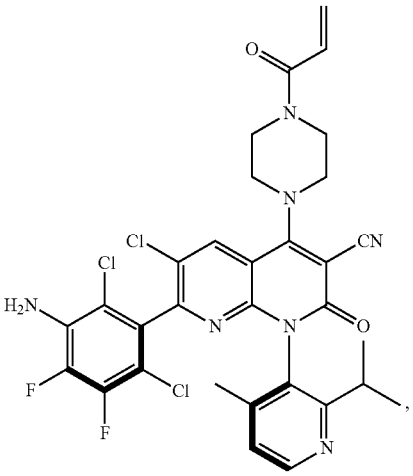

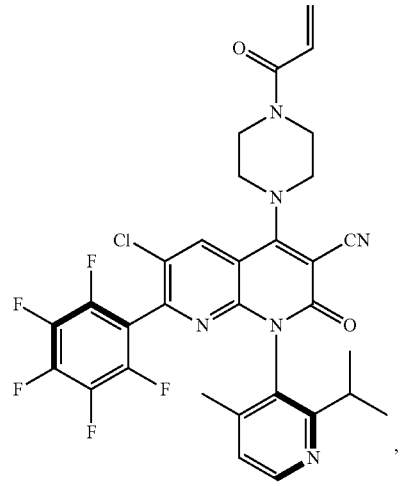

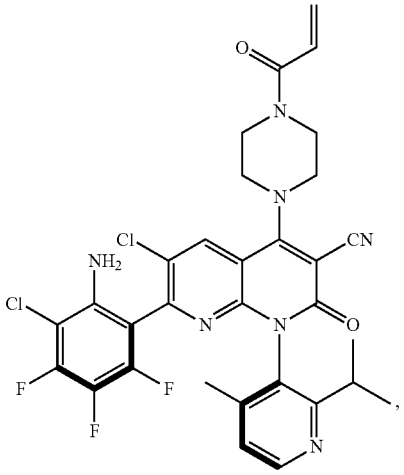

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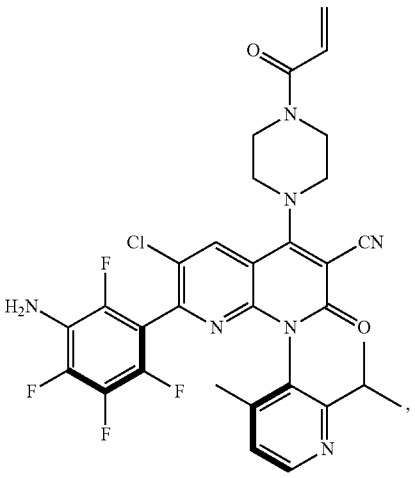

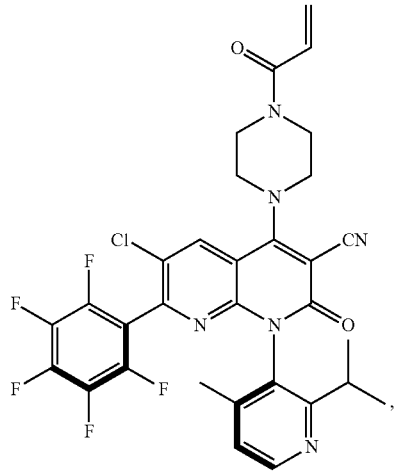

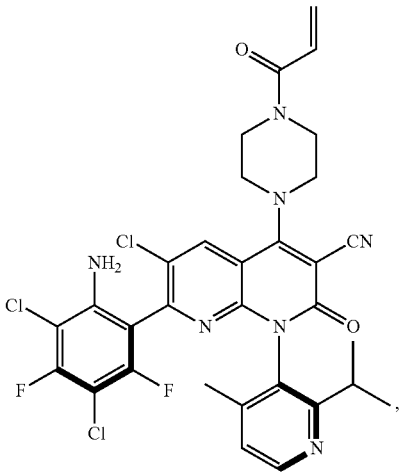

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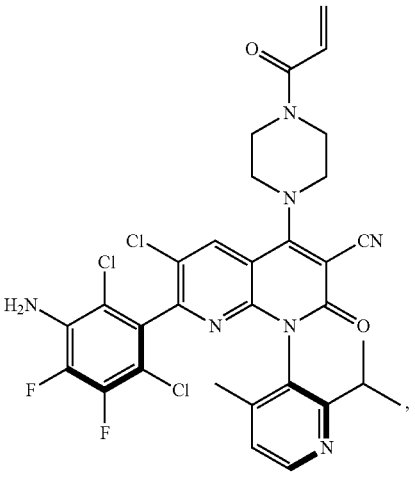

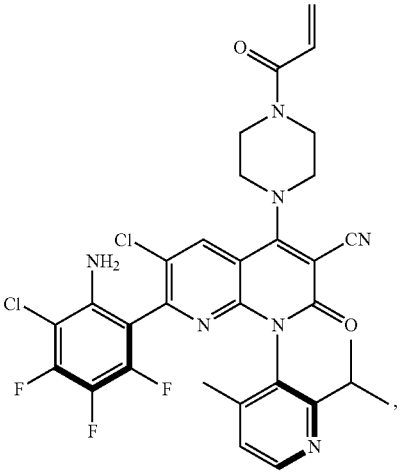

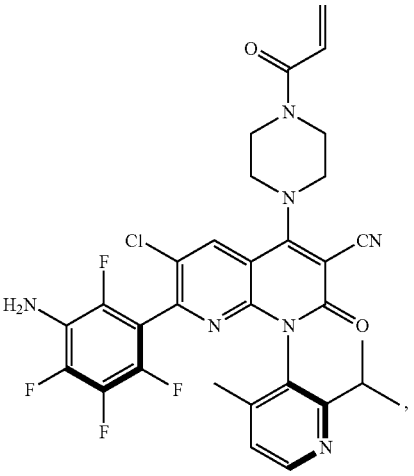

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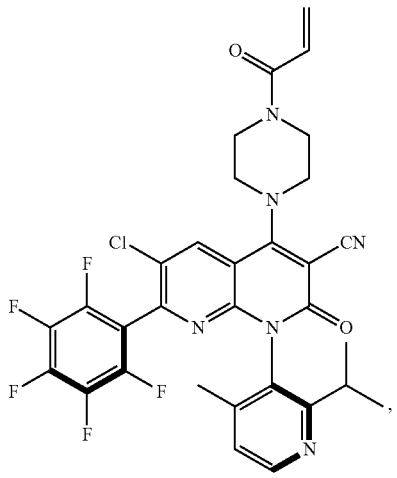

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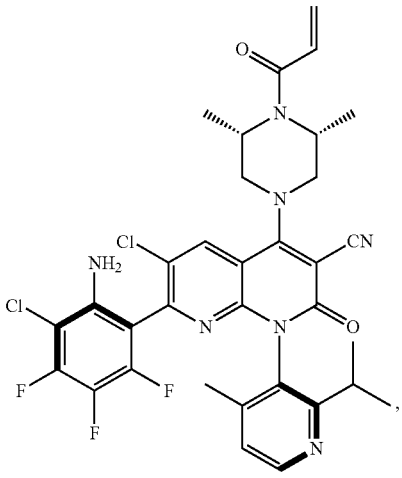

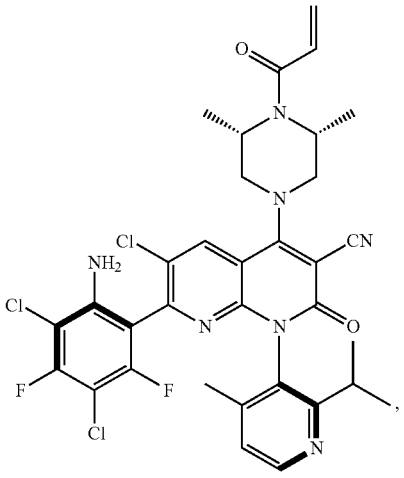

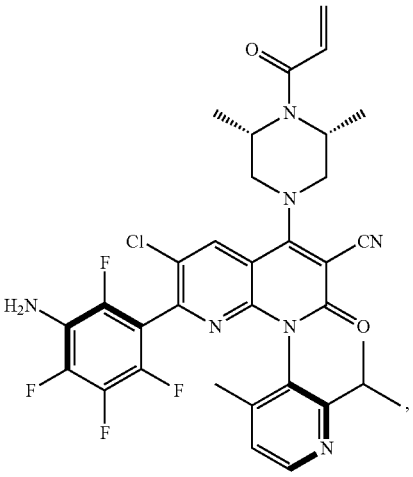

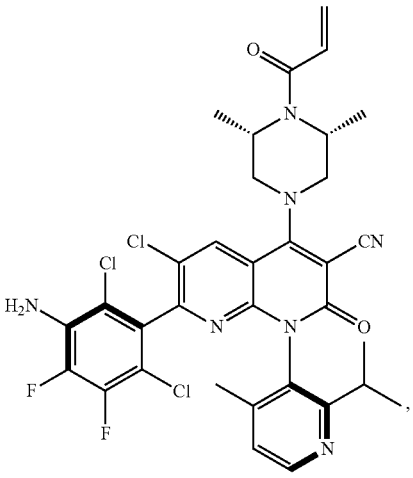

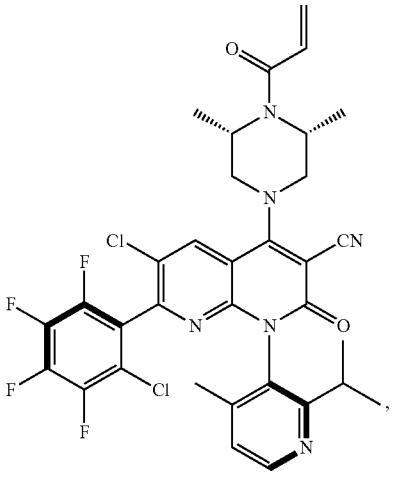

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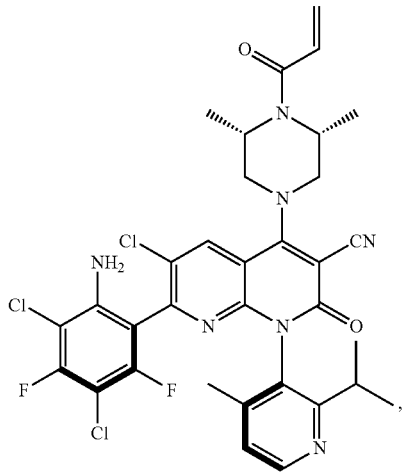

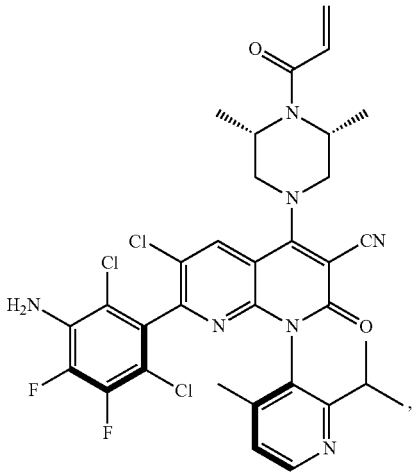

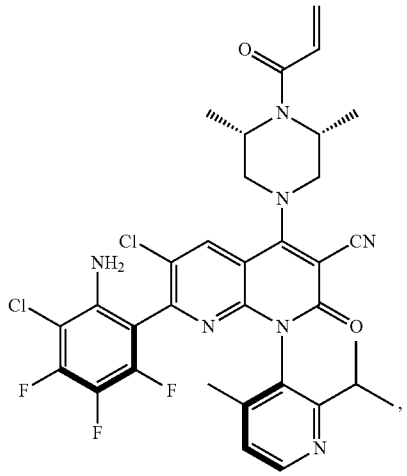

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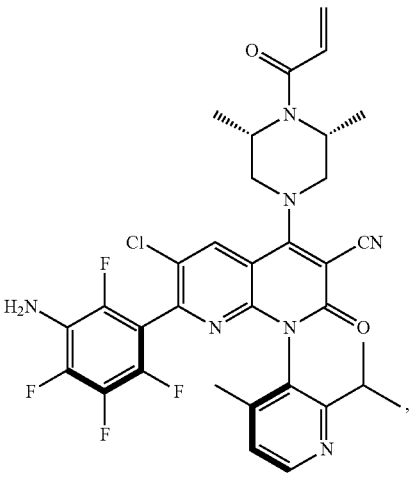

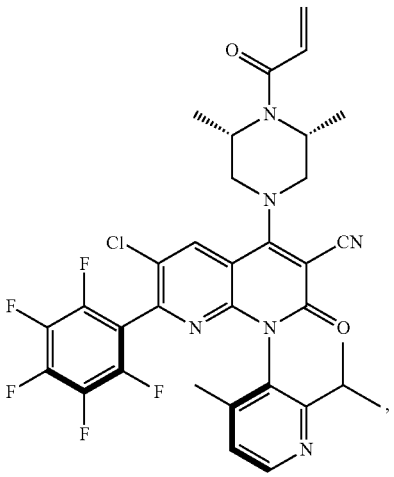

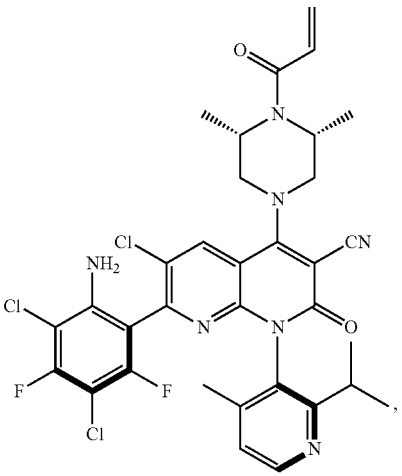

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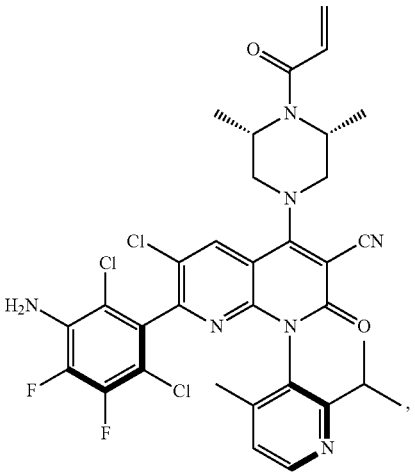

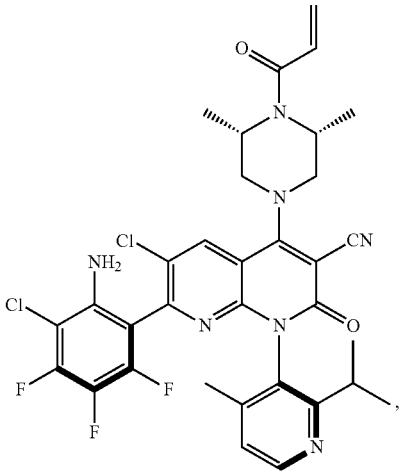

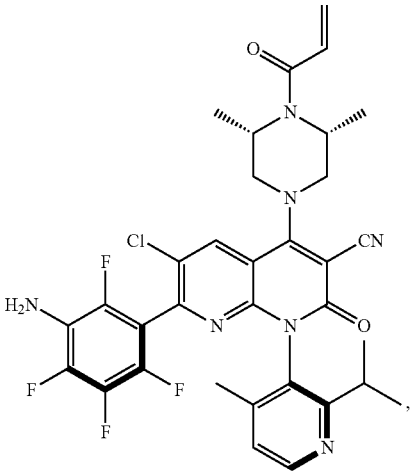

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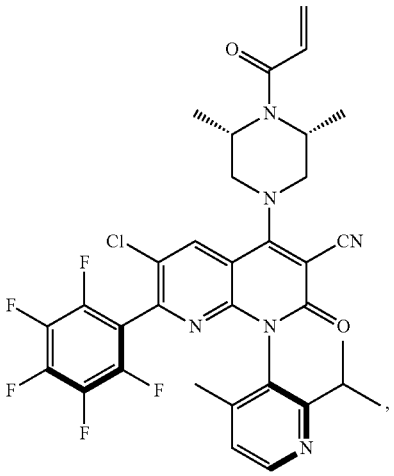

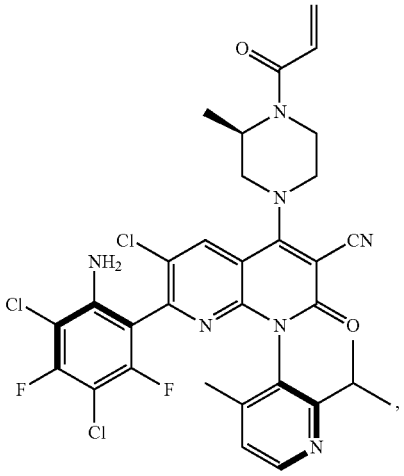

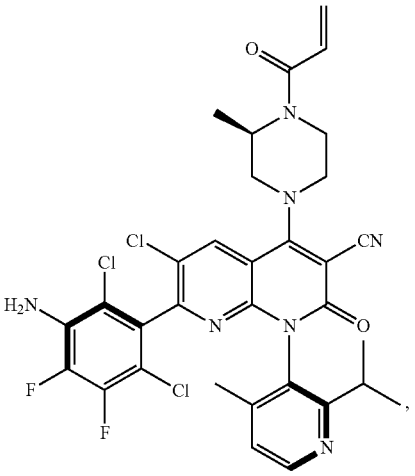

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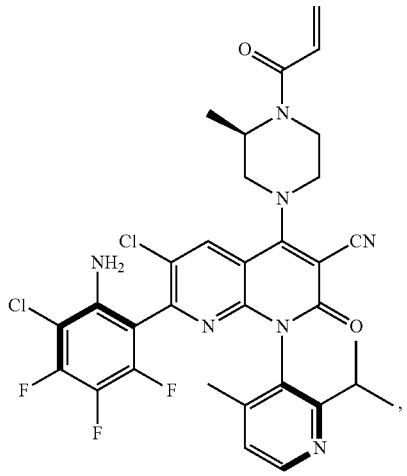

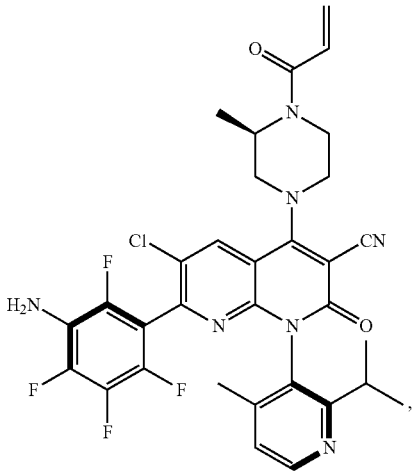

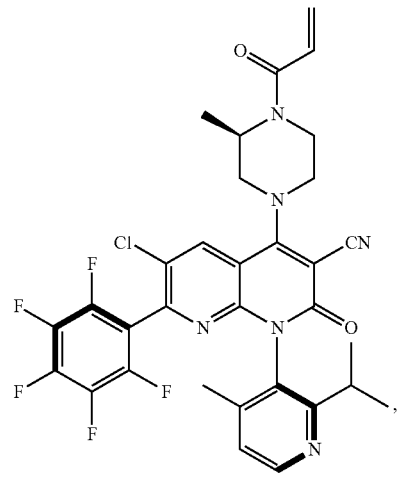

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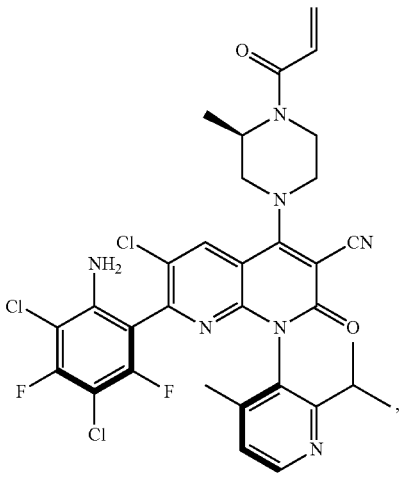

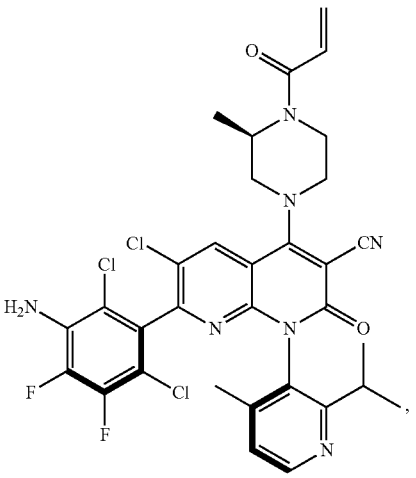

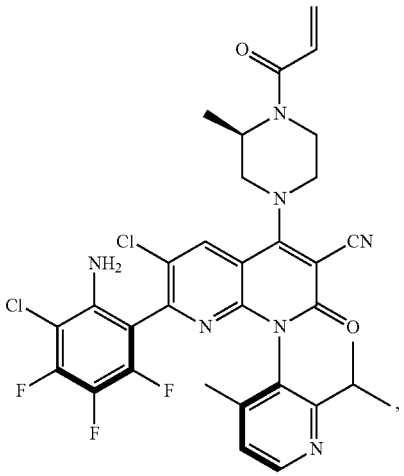

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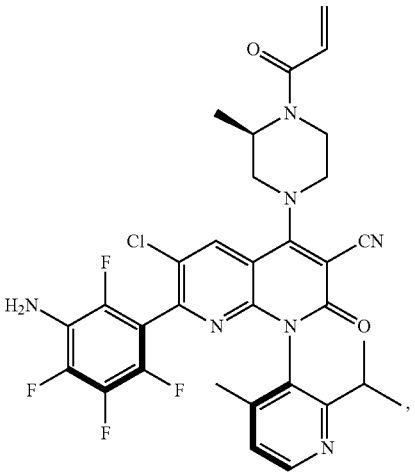

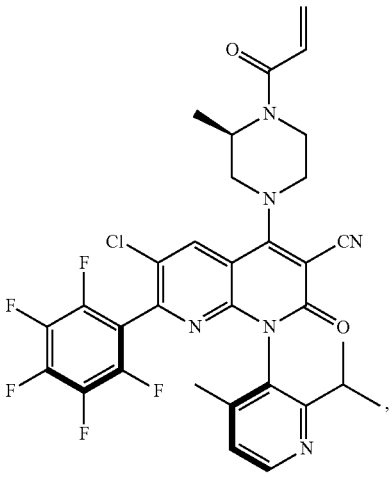

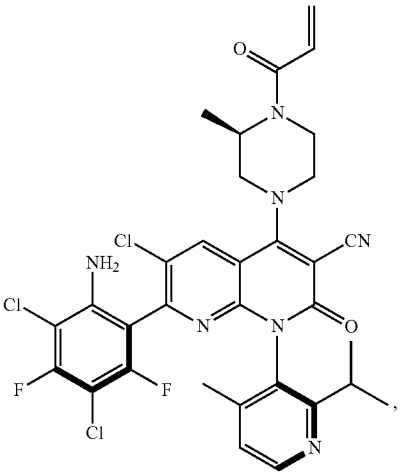

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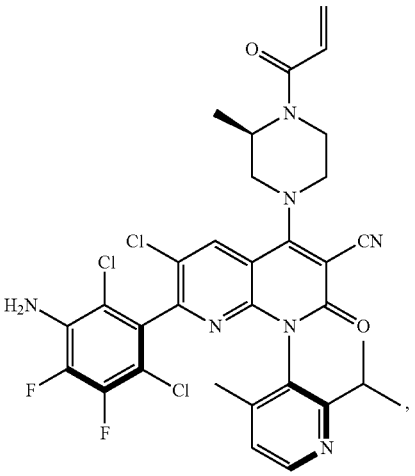

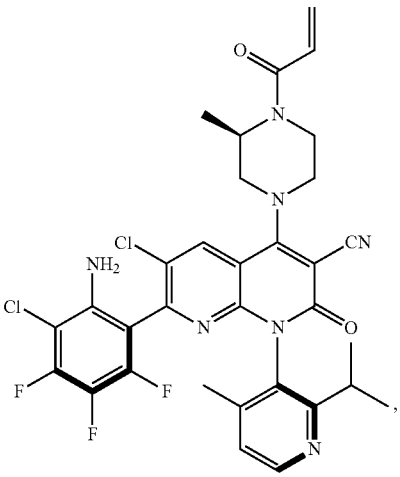

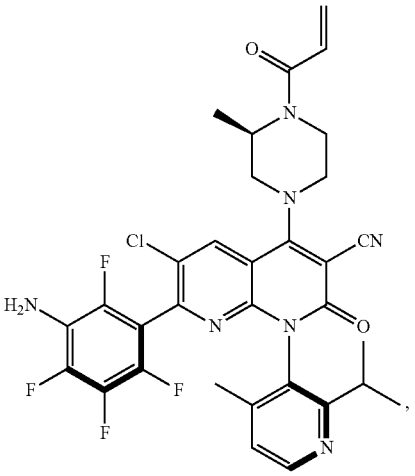

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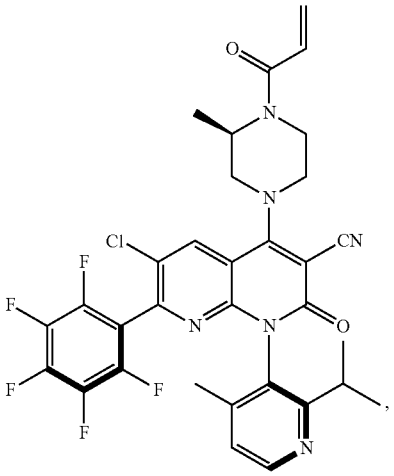

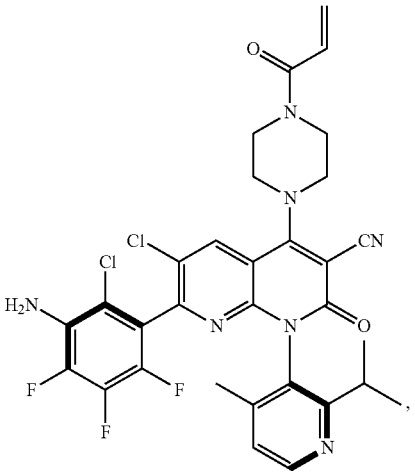

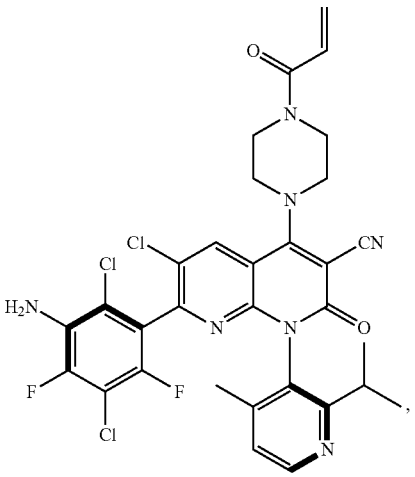

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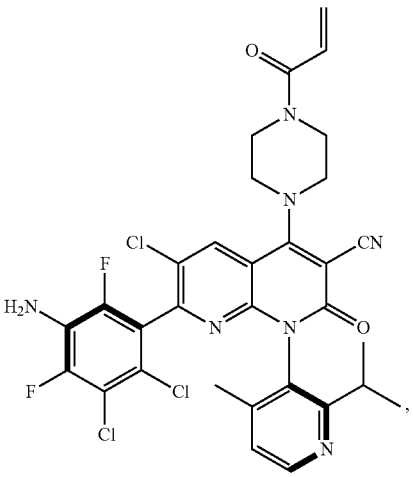

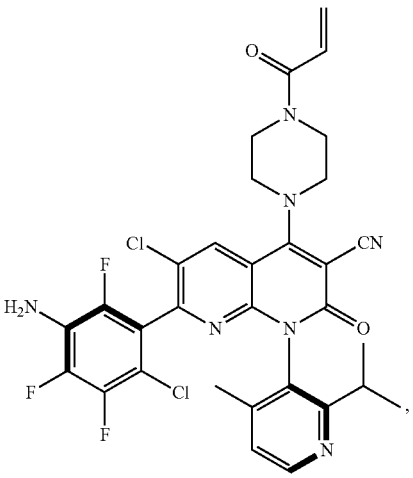

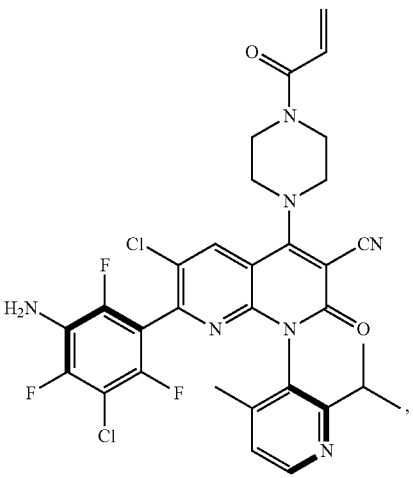

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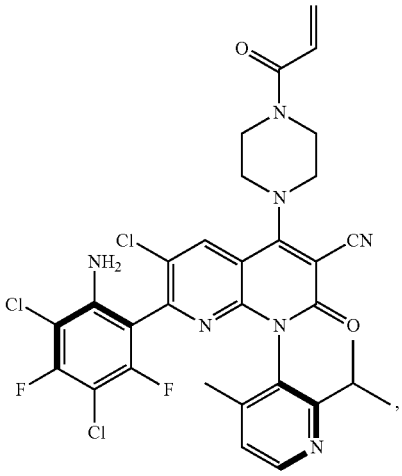

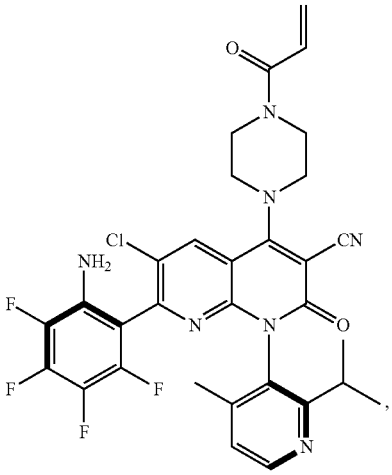

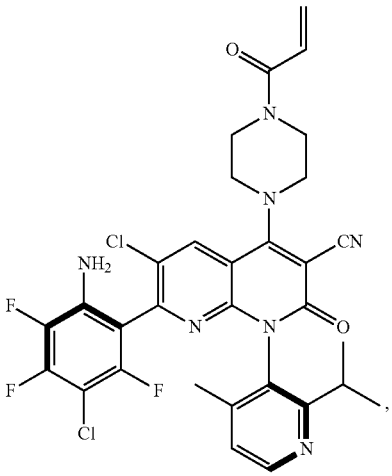

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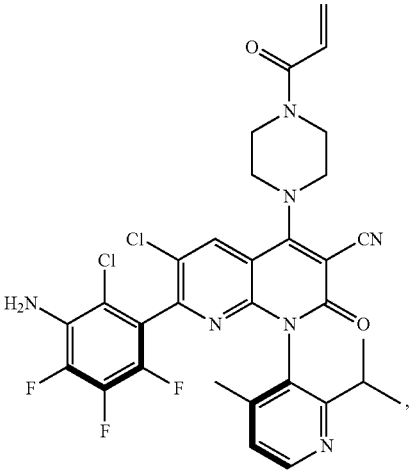

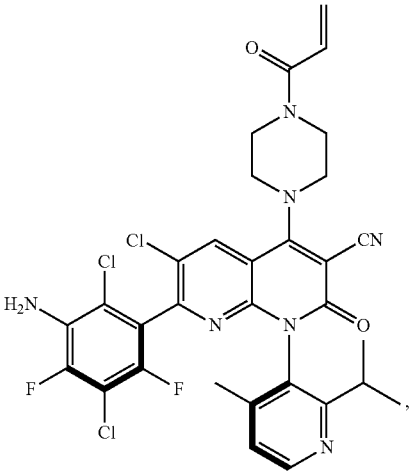

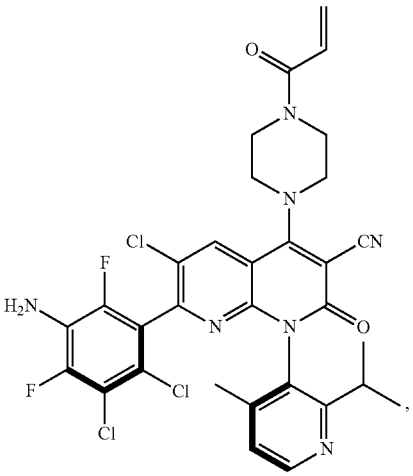

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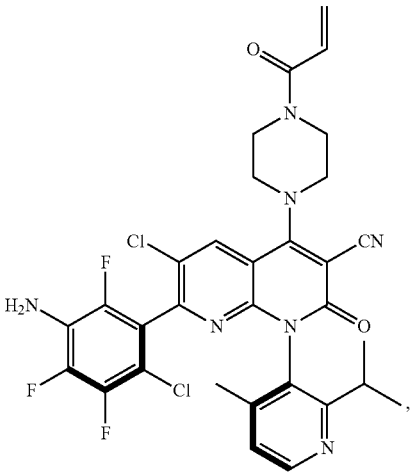

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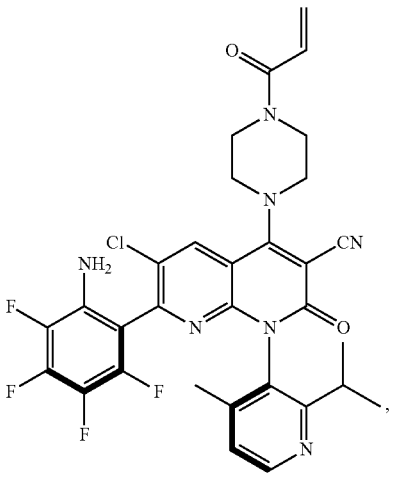

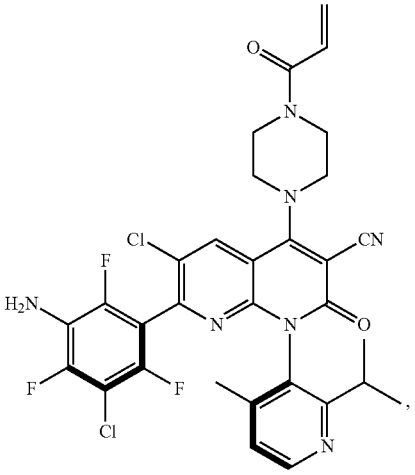

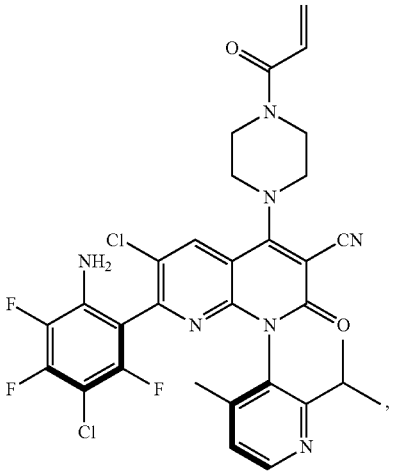

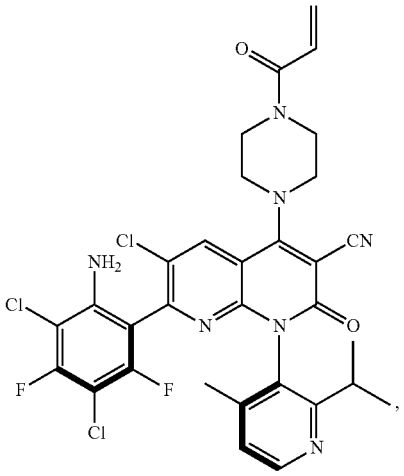

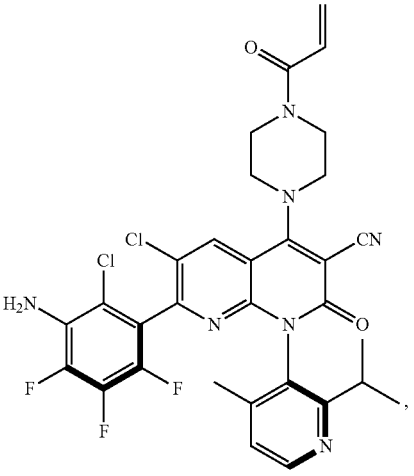

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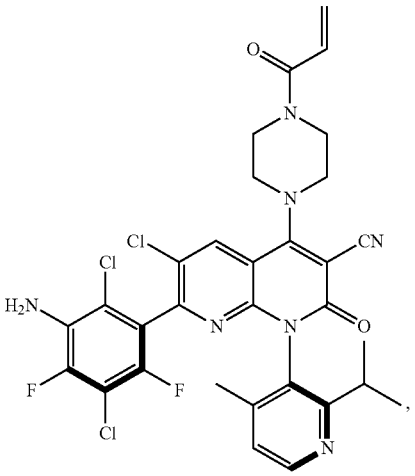

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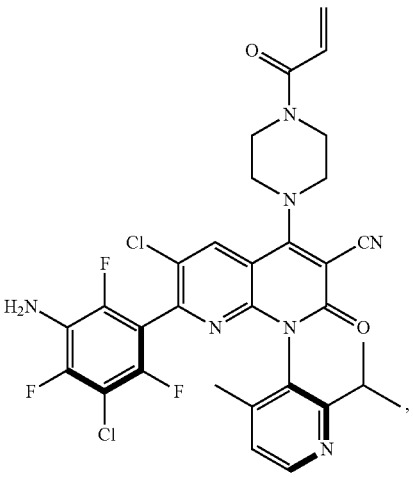

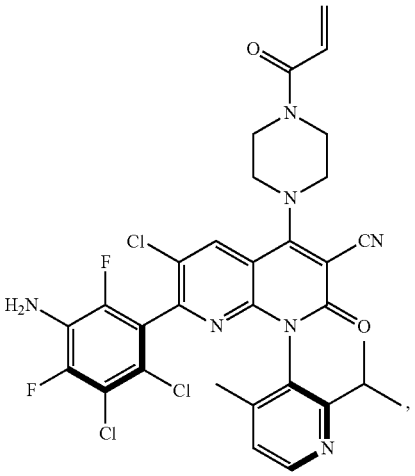

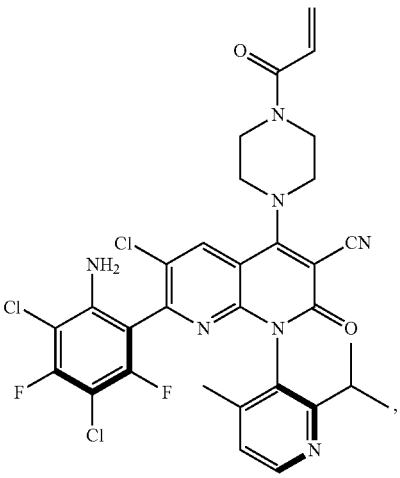

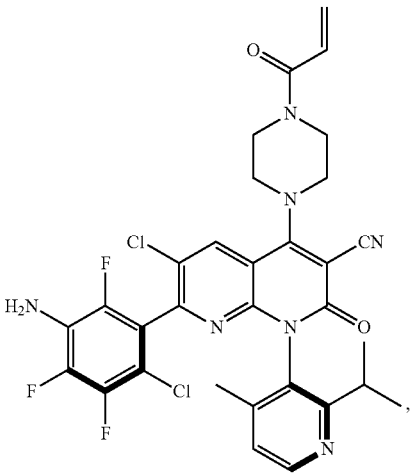

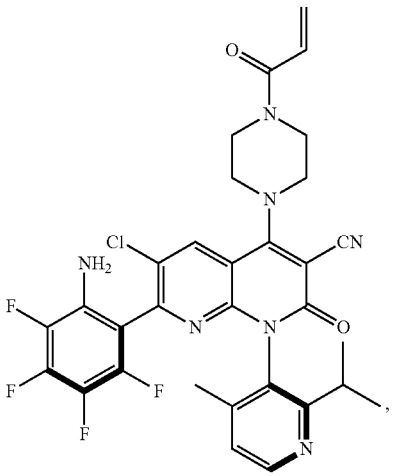

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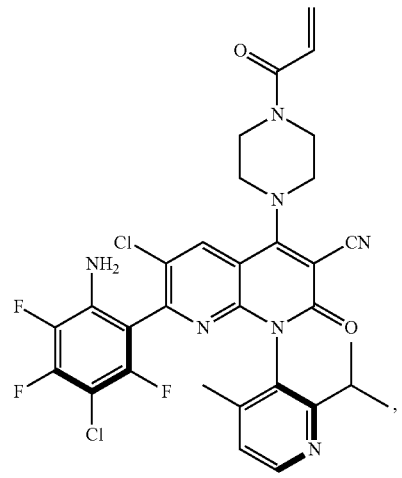

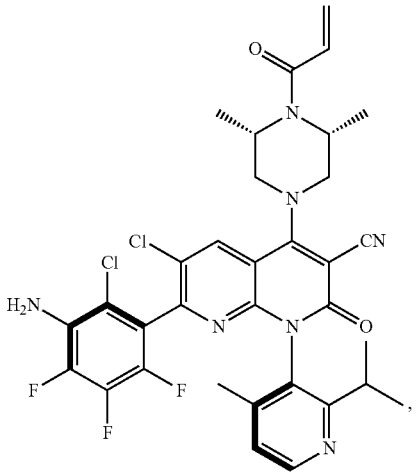

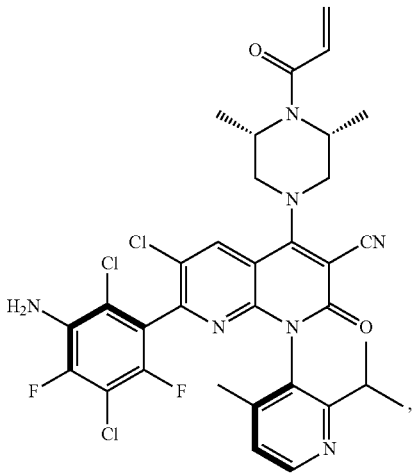

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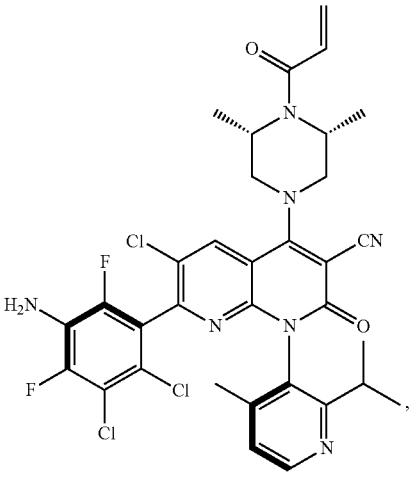

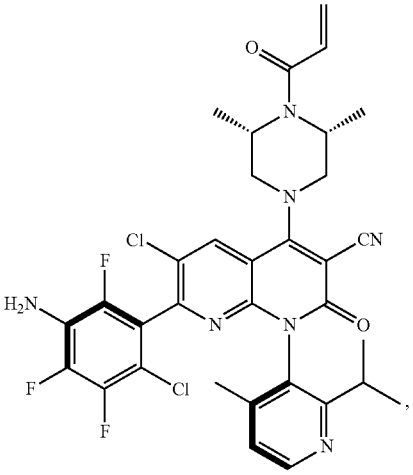

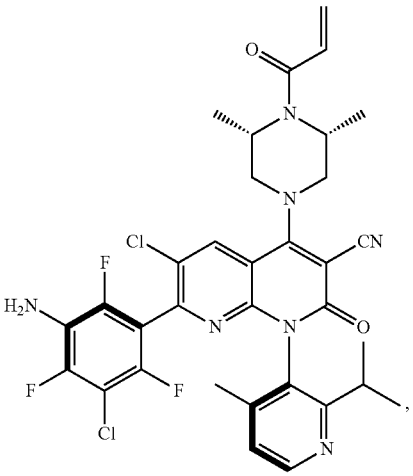

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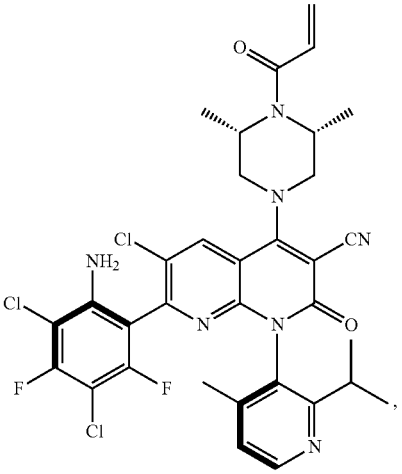

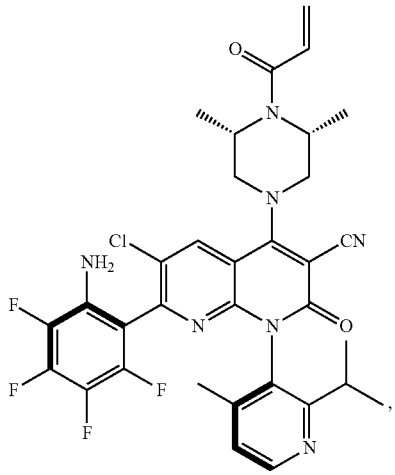

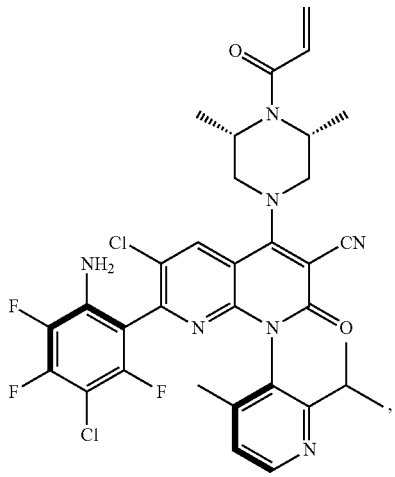

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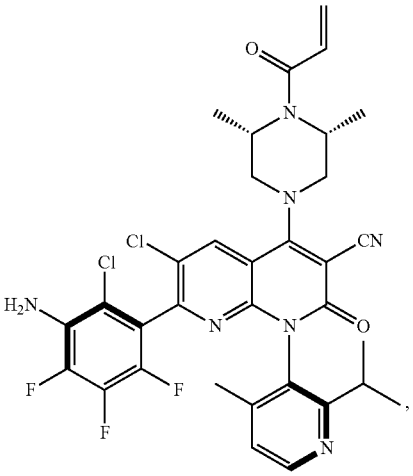

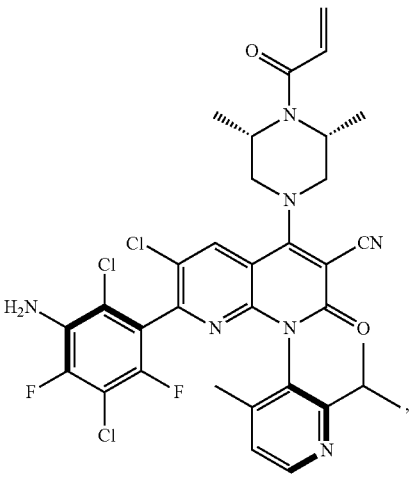

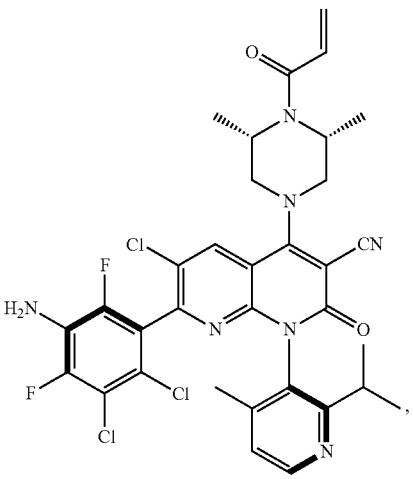

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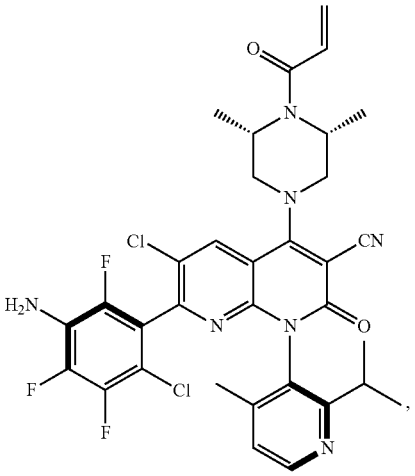

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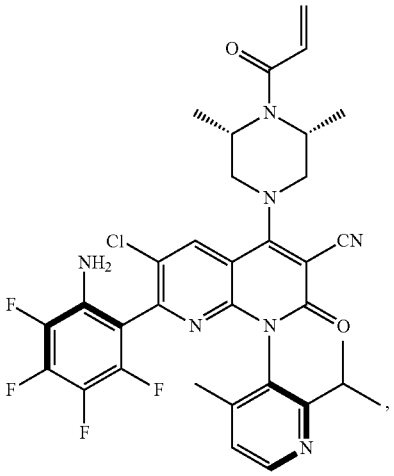

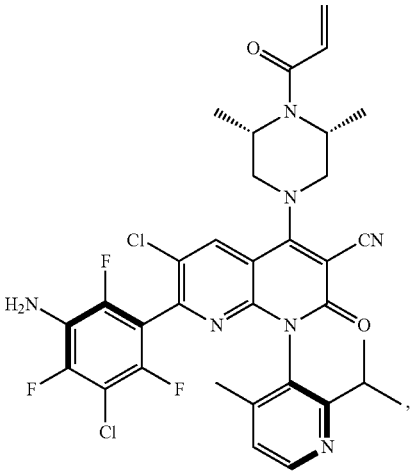

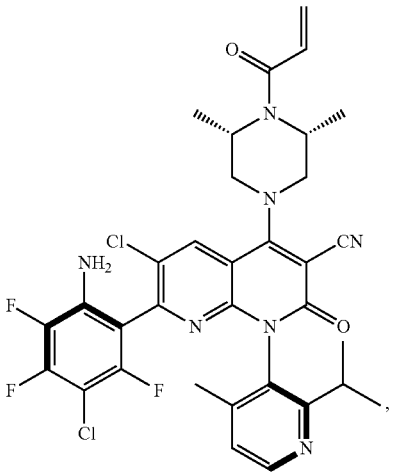

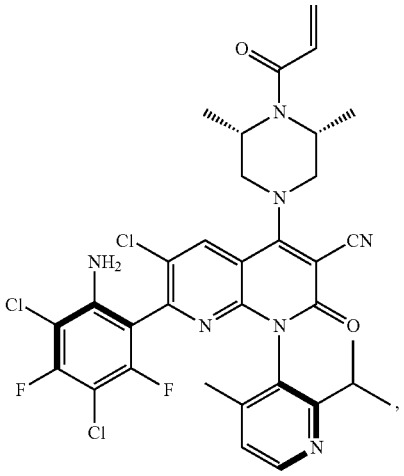

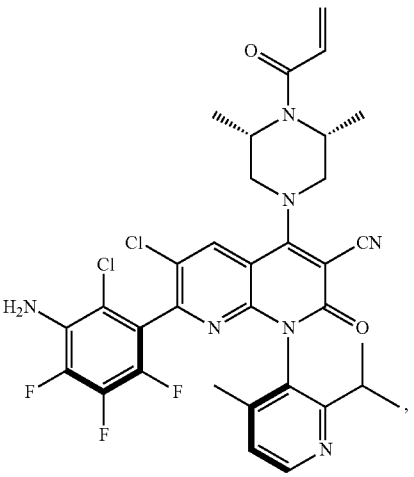

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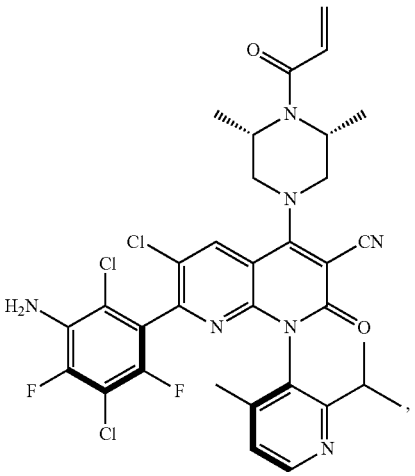

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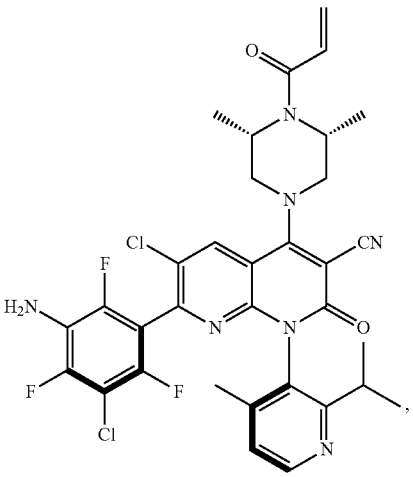

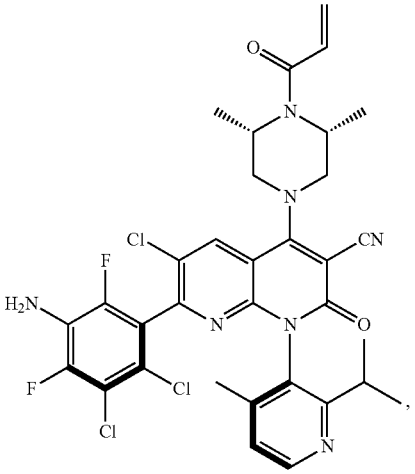

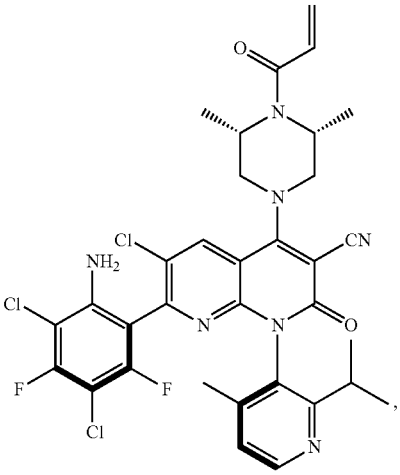

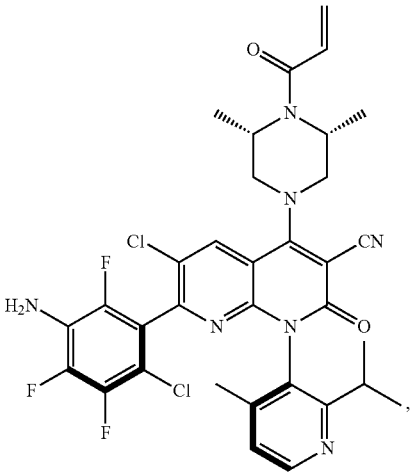

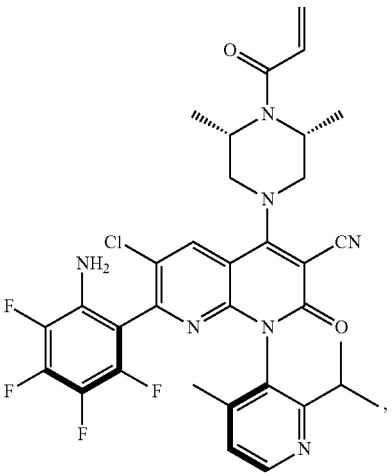

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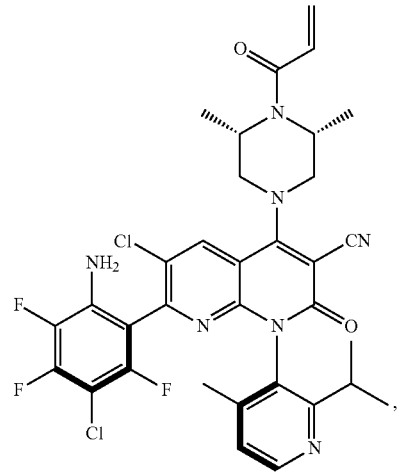

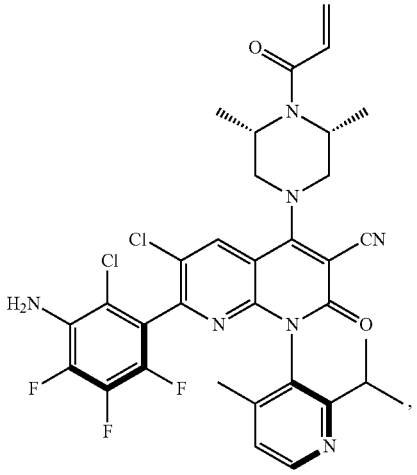

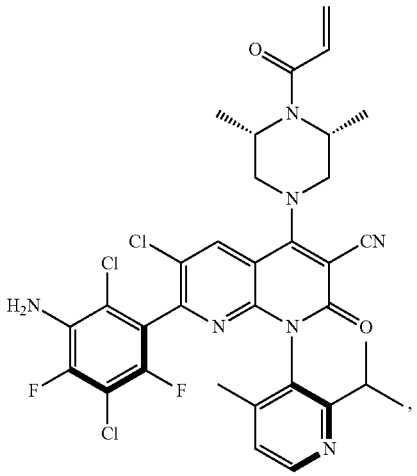

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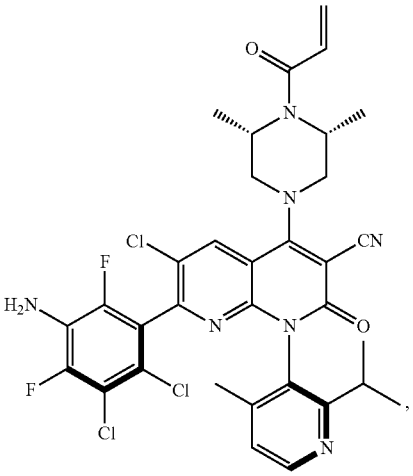

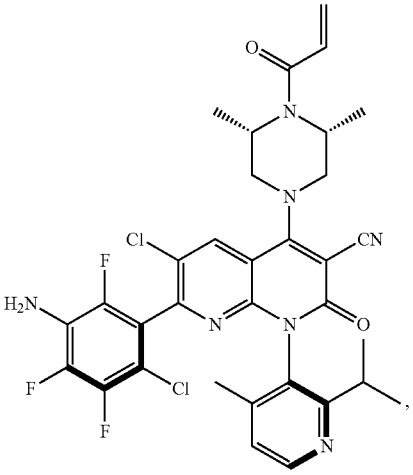

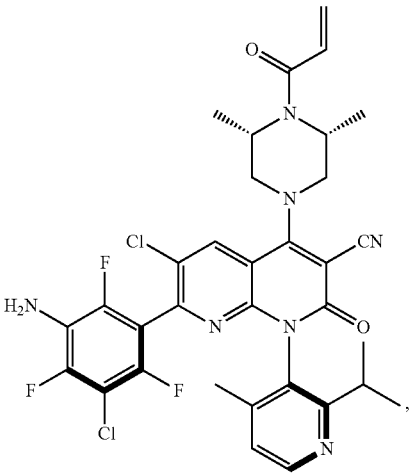

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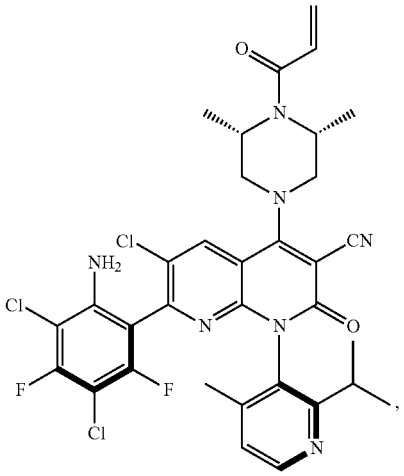

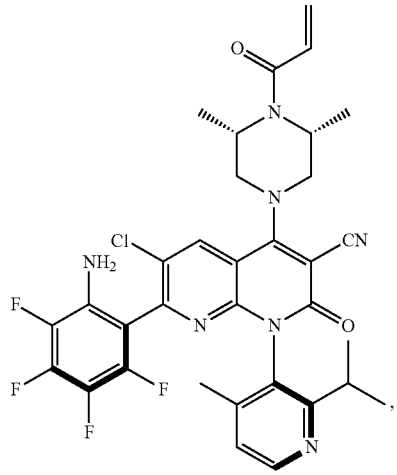

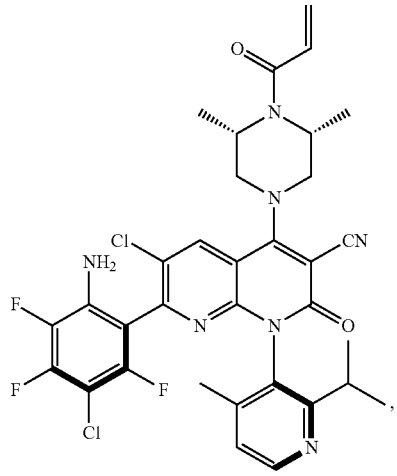

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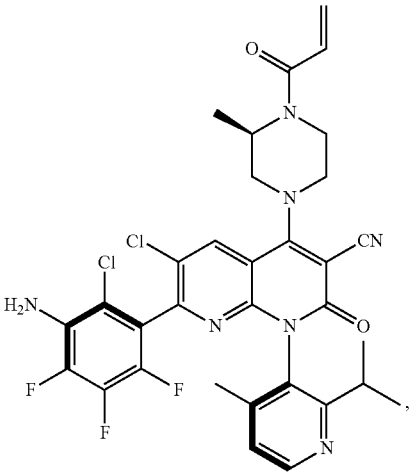

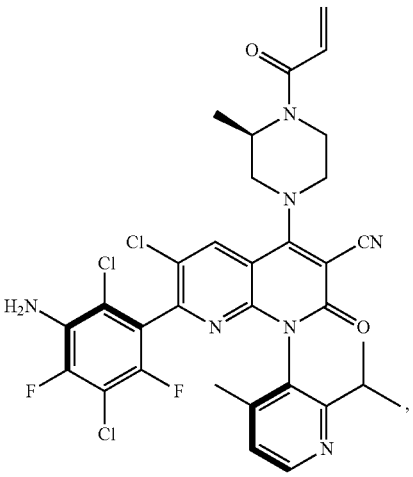

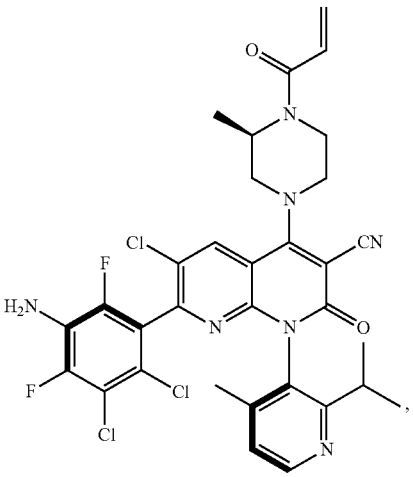

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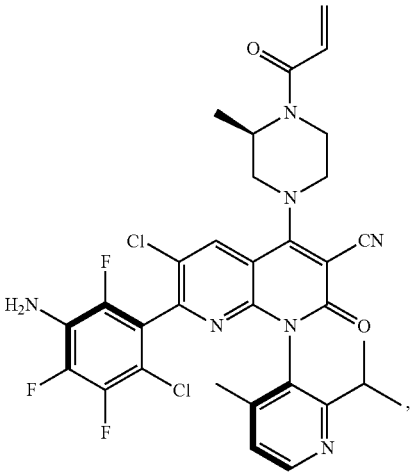

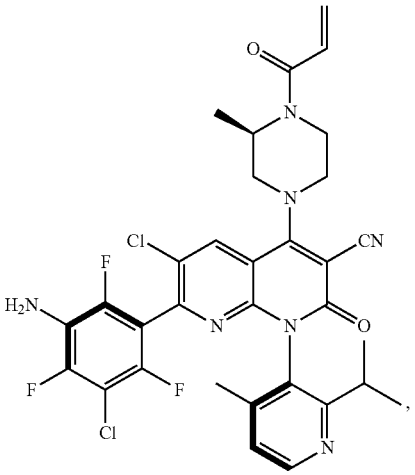

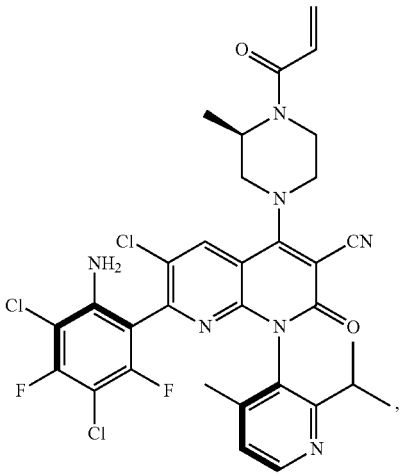

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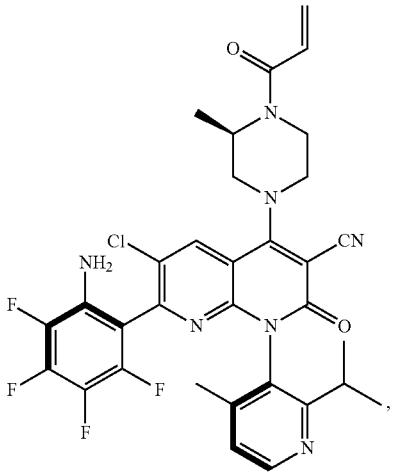

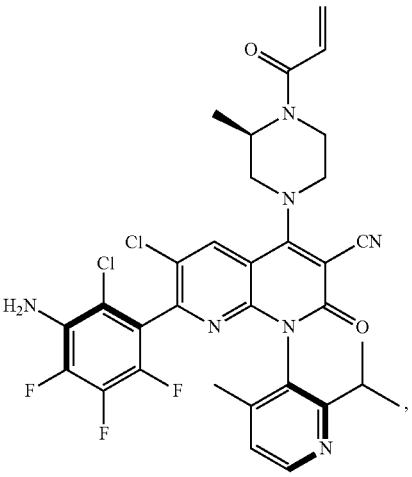

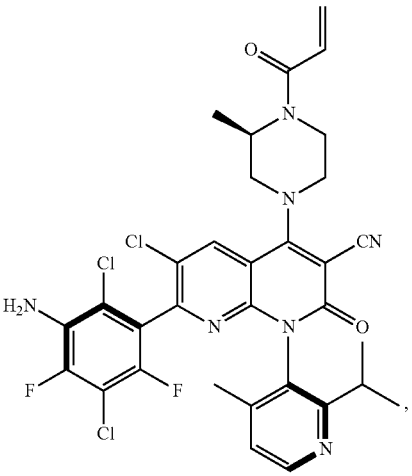

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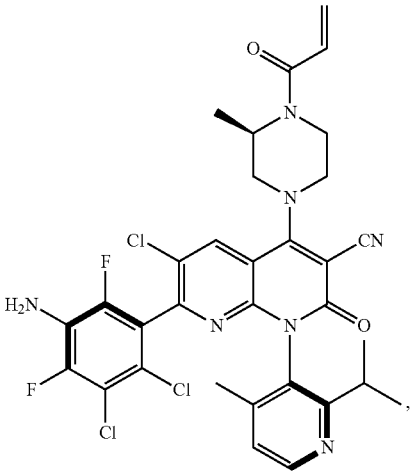

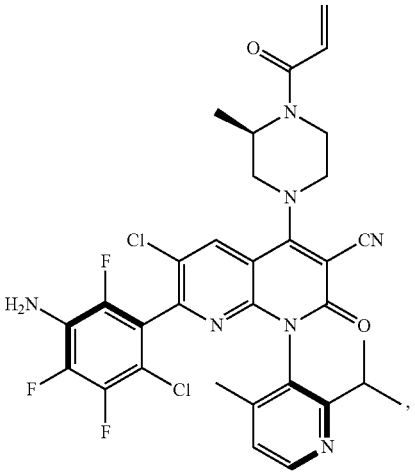

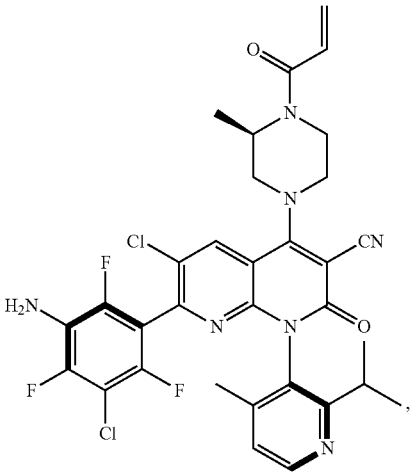

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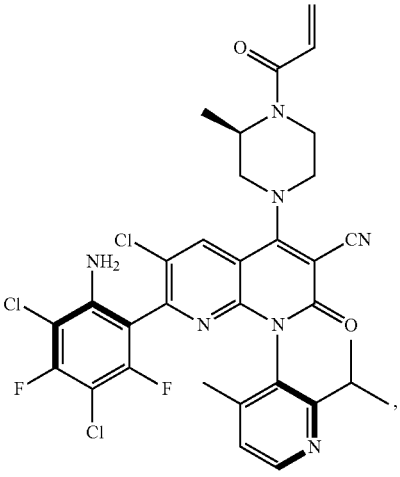

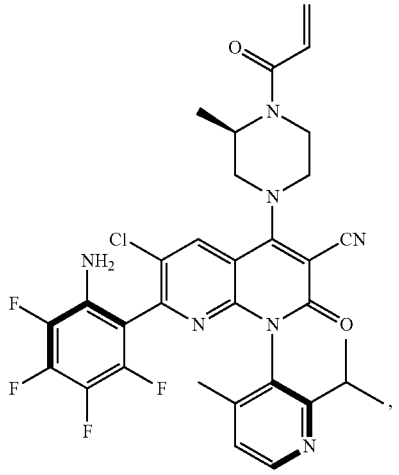

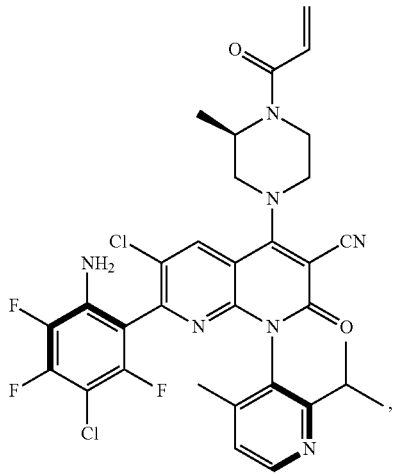

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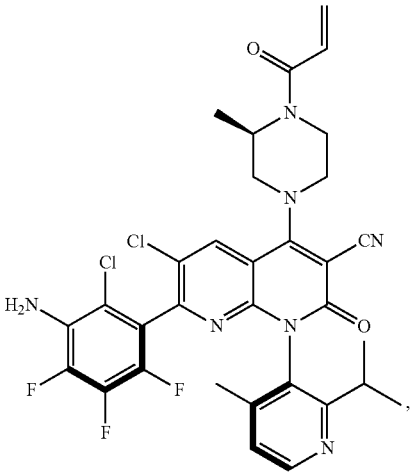

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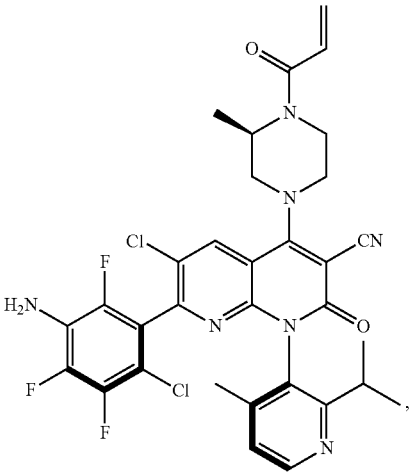

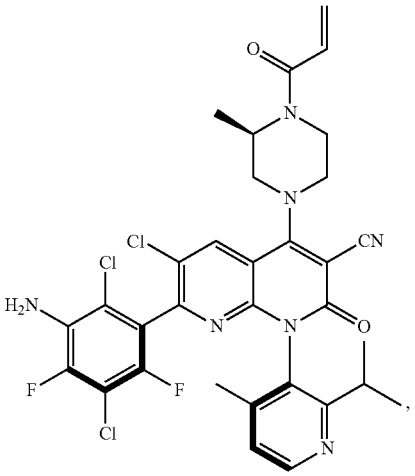

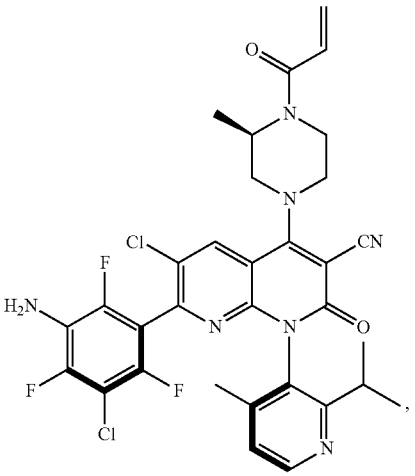

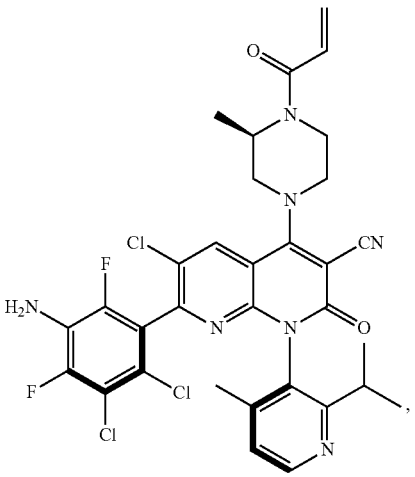

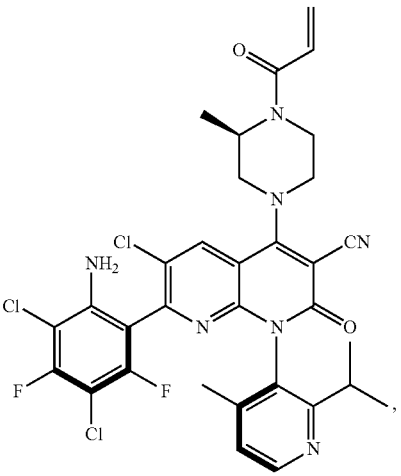

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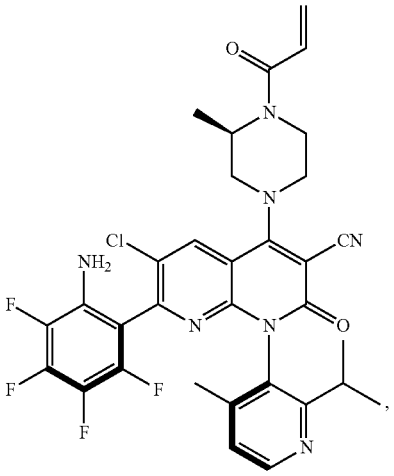

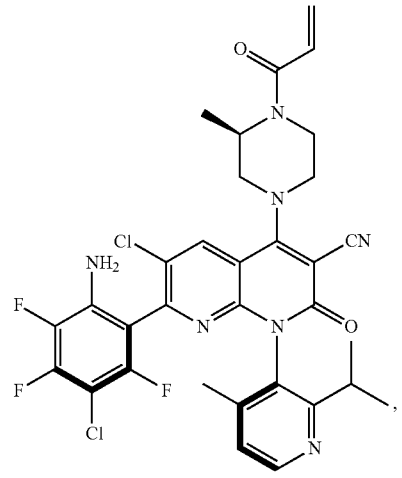

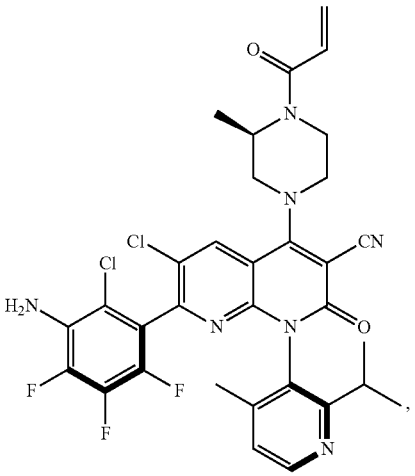

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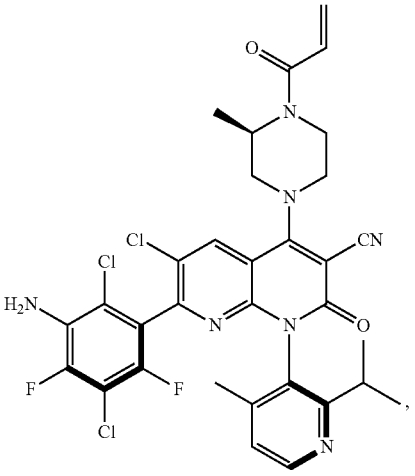

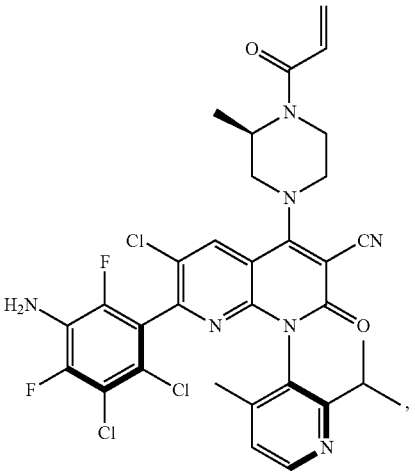

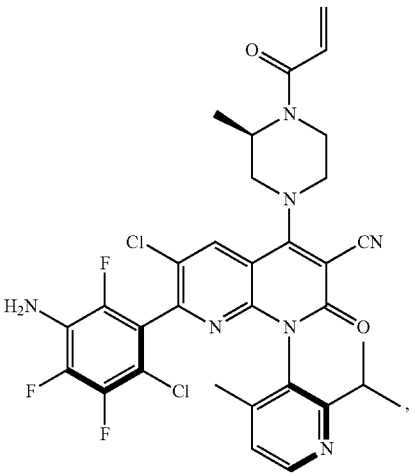

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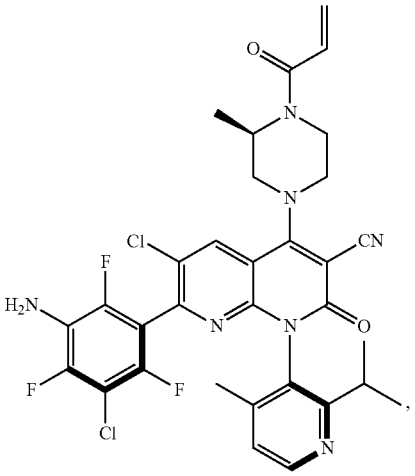

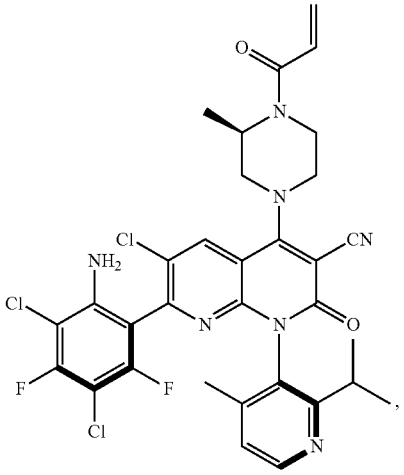

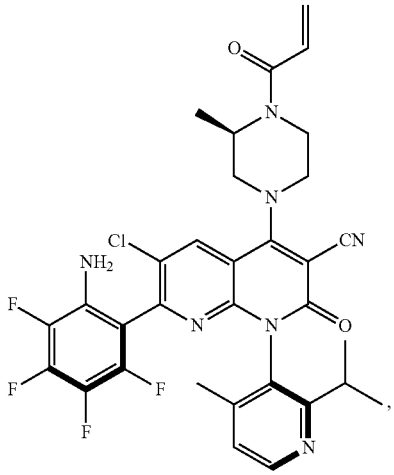

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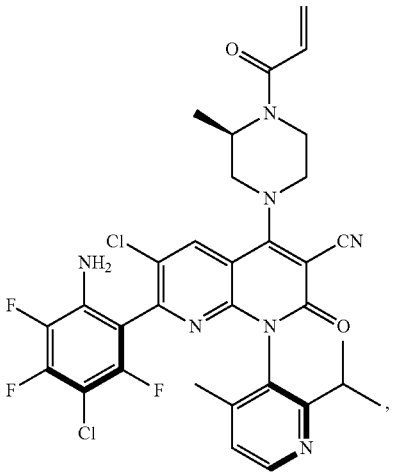

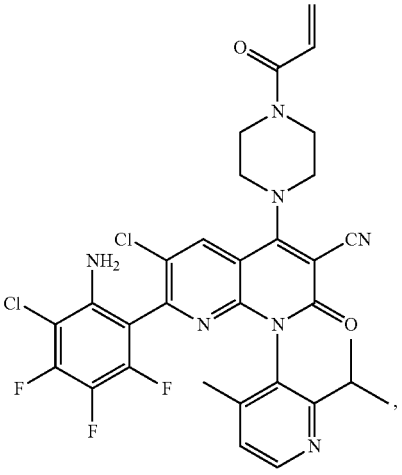

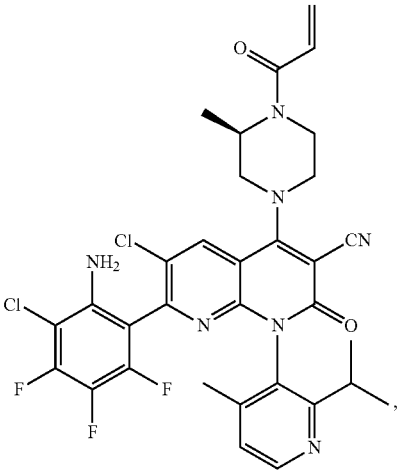

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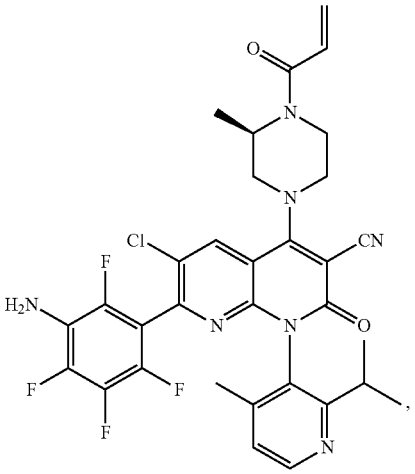

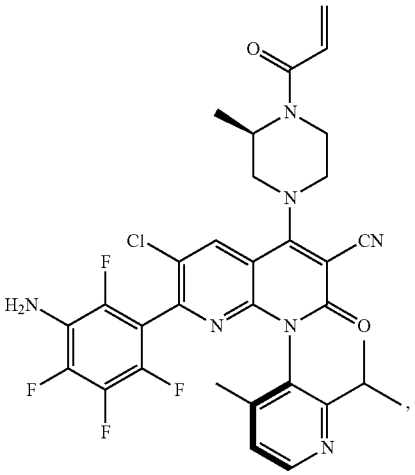

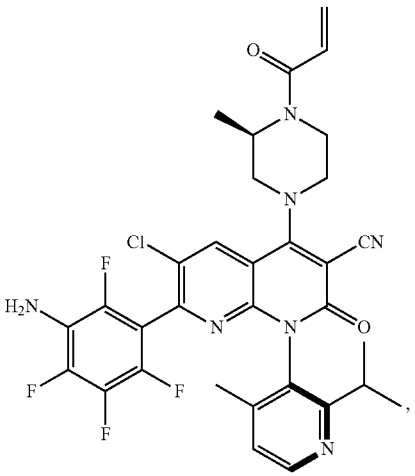

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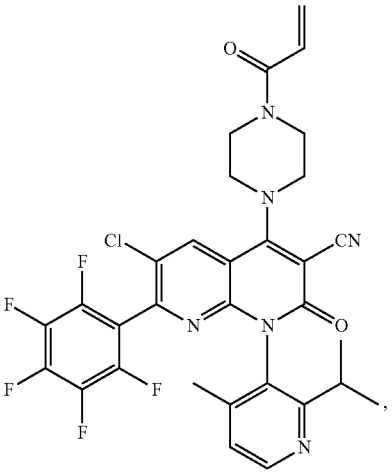

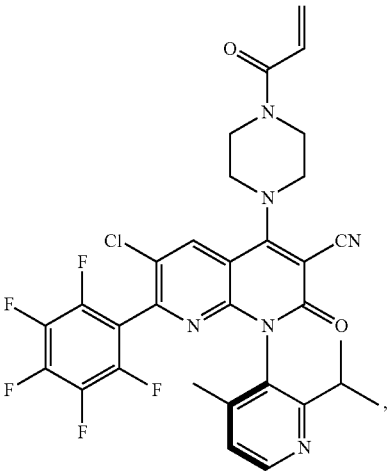

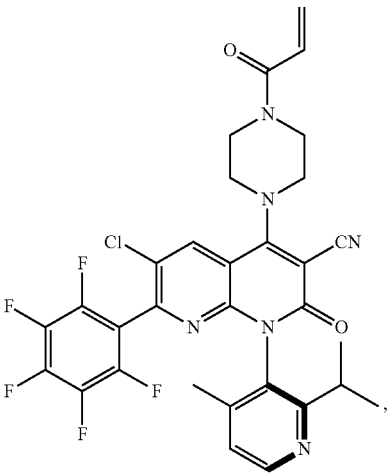

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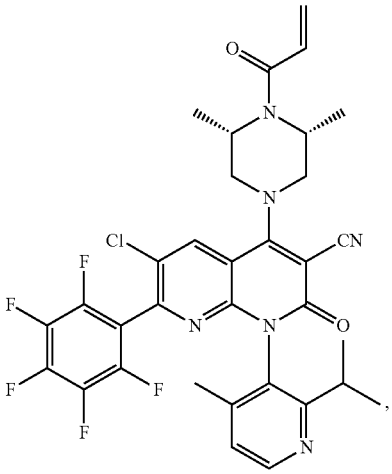

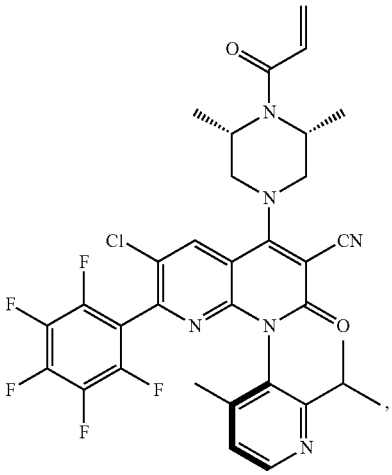

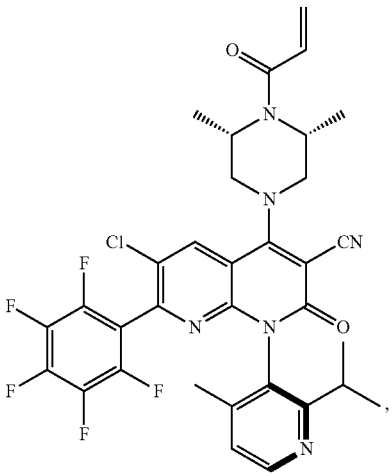

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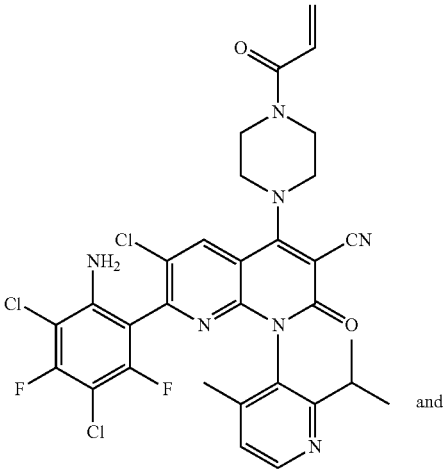

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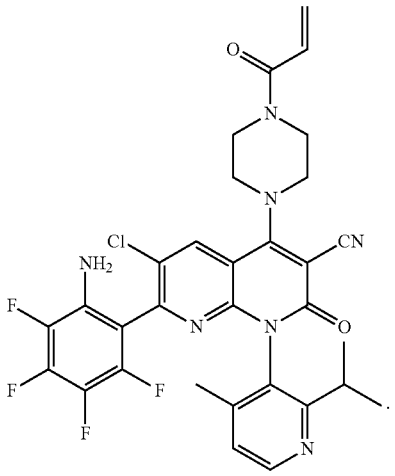
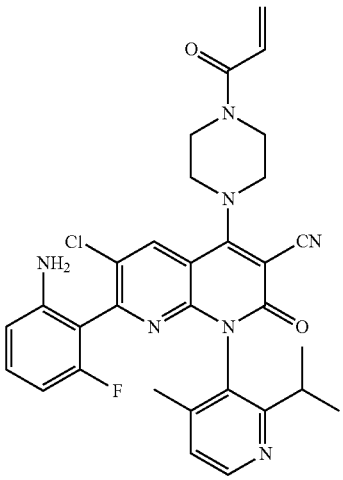


Example A

4-(4-acryloylpiperazin-1-yl)-7-(2-amino-6-fluoro-phenyl)-6-chloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound A")

[0265]

Compound A



Step 1. 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0266] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6,7-dichloro-4-hydroxy-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-hydro-1,8-naphthyridine-3-carbonitrile (980 mg, 2.51 mmol), $POCl_3$ (1150 mg, 7.50 mmol), DIEA (1.32 g, 10.21 mmol) and acetonitrile (12 mL). The mixture was stirred at 80° C. for 2 h. The reaction was cooled to room temperature and concentrated under vacuum. This resulted in 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile which was used directly in the next step.

Step 2. tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)piperazine-1-carboxylate

[0267] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,6,7-trichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (1.20 g, crude), acetonitrile (20 mL), DIEA (660 mg, 5.10 mmol) and tert-butyl piperazine-1-carboxylate (0.57 g, 3.06 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (3×50 mL), the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residues was purified by silica gel column eluted with EA/hexane (v/v=30%-70%). This resulted in 0.92 g (65% in two steps) of tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyl-yl)piperazine-1-carboxylate as yellow solid. LCMS: m/z=557 $[M+1]^+$.

Step 3. 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0268] Into a 50-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl 4-(6,7-dichloro-3-cyano-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyl-yl)piperazine-1-carboxylate (920 mg, 1.65 mmol), TFA (4 ml) and DCM (15 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum. The residue was dissolved by DCM (15 mL) in 50-mL round-bottom flask, which was followed by the added of DIEA (1.02 g, 10.08 mmol). The reaction mixture was cooled to 0° C. and acryloyl chloride (190 mg, 2.09 mmol) was added. The mixture stirred at room temperature for 2 h. The reaction was then quenched by the addition of water (30 mL). The resulting solution was extracted with ethyl acetate (3×50 mL), the organic layers were combined and washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (V/V=40%~80%). This resulted in 0.86 g (crude) of 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile as yellow solid. LCMS: m/z=511 $[M+1]^+$.

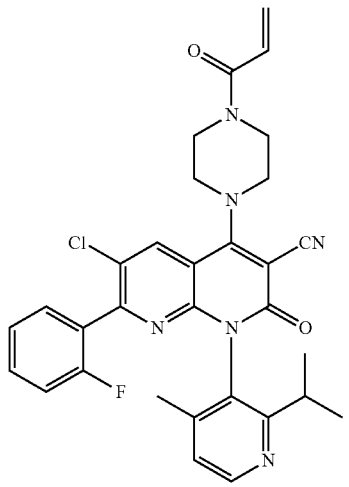
Step 4. 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-6-fluorophenyl)-6-chloro-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound A")

[0269] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (99 mg, 0.19 mmol), 3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (78 mg, 0.33 mmol), $Pd(PPh_3)_4$ (44 mg, 0.03 mmol), Na_2CO_3 (65 mg, 0.61 mmol), dioxane (4 mL) and water (1 mL). The reaction mixture was stirred at 90° C. for 2 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by Prep-HPLC CH_3CN/H_2O (v:v=1/1)). This resulted in 12 mg (10%) of 4-(4-aclyloylpiperazin-1-yl)-7-(2-amino-6-fluorophenyl)-6-chloro-1-(2-isopropyl-4-methylpyl-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Compound A") as yellow solid. LCMS: m/z=586 [M+1]+. ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.46 (d, J=5.0 Hz, 1H), 7.29 (d, J=4.7 Hz, 1H), 7.11 (d, J=6.6 Hz, 1H), 6.89 (dd, J=16.7, 10.6 Hz, 1H), 6.56-6.49 (m, 1H), 6.38-6.30 (m, 2H), 5.90-5.81 (m, 1H), 4.18-3.84 (m, 8H), 2.82-2.70 (m, 1H), 2.08-1.98 (m, 3H), 1.19 (t, J=7.1 Hz, 3H), 1.10-0.93 (m, 3H).

Amgen 6

4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 6")

[0270]



Amgen 6

Step 1. 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0271] Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-(4-acryloylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (75 mg, 0.15 mmol), (2-fluorophenyl)boronic acid (56 mg, 0.40 mmol), $Pd(dppf)Cl_2$ (25 mg, 34.17 umol), Na_2CO_3 (69 mg, 0.65 mmol), dioxane (1 mL) and water (0.2 mL). The reaction mixture was stirred at 90° C. for 2 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel column eluted with EA/hexane (v/v=7/3). The collecting fluid concentrated under vacuum. The residue was purified by Prep-

HPLC CH_3CN/H_2O (v/v=3/2). This resulted in 22 mg of 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 6") as yellow solid. LCMS: m/z=571 $[M+1]^+$.

[0272] ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.43 (d, J=5.0 Hz, 1H), 7.54-7.46 (m, 1H), 7.32-7.13 (m, 4H), 6.89 (dd, J=16.7, 10.6 Hz, 1H), 6.33 (d, J=16.7 Hz, 1H), 5.86 (d, J=10.6 Hz, 1H), 4.15-3.90 (m, 8H), 2.79-2.65 (m, 1H), 2.04 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.00 (d, J=6.7 Hz, 3H).

[0273] The mixture of 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (1.59 g) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRAL Cellulose-SB, 3 cm×25 cm, Sum; mobile phase, CO_2, IPA:ACN=1:1; Detector, UV 254 nm. This resulted in 739 mg (46%) of 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Amgen 6-1") as a yellow solid; LCMS: m/z=571 $[M+1]^+$.

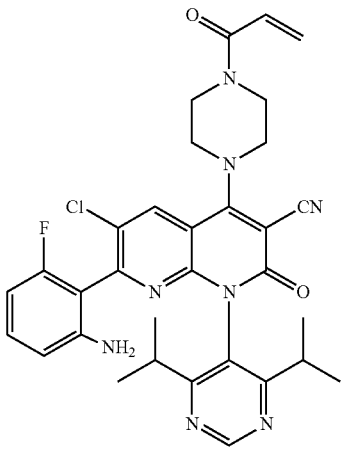
[0274] And 709 mg (45%) of 4-(4-acryloylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methyl pyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Amgen 6-2") as a yellow solid; LCMS: m/z=571 $[M+1]^+$.

[0275] ^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 (d, J=5.0 Hz, 1H), 7.52-7.37 (m, 1H), 7.30-7.08 (m, 4H), 6.87 (dd, J=16.8, 10.6 Hz, 1H), 6.38-6.24 (m, 1H), 5.83 (dd, J=10.6, 1.8 Hz, 1H), 4.09-3.82 (m, 8H), 2.78-2.63 (m, 1H), 2.02 (s, 3H), 1.16 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H).

Amgen 6.3

4-(4-acryloylpiperazin-1-yl)-7-(2-amino-6-fluorophenyl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 6.3")

[0276]



Amgen 6.3

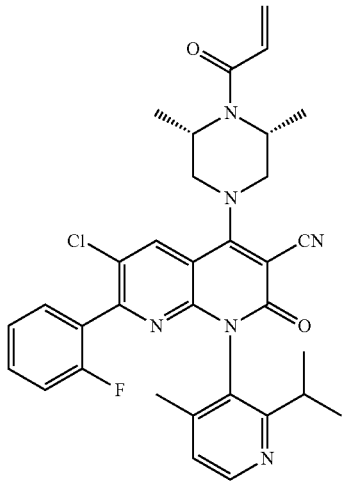
[0277] 4-(4-acryloylpiperazin-1-yl)-7-(2-amino-6-fluorophenyl)-6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 6.3") were prepared according to prior method as yellow solid. LCMS: m/z=615 $[M+1]^+$.

[0278] ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.48 (s, 1H), 7.05 (q, J=7.8 Hz, 1H), 6.93 (dd, J=16.6, 10.4 Hz, 1H), 6.44 (d, J=8.3 Hz, 1H), 6.31 (t, J=8.9 Hz, 1H), 6.21 (dd, J=16.7, 2.4 Hz, 1H), 5.77 (dd, J=10.4, 2.4 Hz, 1H), 5.08 (s, 2H), 3.90 (m, 8H), 2.90-2.74 (m, 1H), 2.70-2.55 (m, 1H), 1.07 (dd, J=12.2, 6.7 Hz, 6H), 1.00 (d, J=6.6 Hz, 3H), 0.86 (d, J=6.7 Hz, 3H).

Amgen 7.3

4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 7.3")

[0279]



Amgen 7.3

Step 1. 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile

[0280] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6,7-dichloro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (109 mg, 0.20 mmol), ((2-fluorophenyl)boronic acid (110 mg, 0.79 mmol), $Pd(PPh_3)_4$ (85 mg, 0.073 mmol), Na_2CO_3 (69 mg, 0.65 mmol), dioxane (6 mL) and water (2 mL). The reaction mixture was stirred at 80° C. for 4 h. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (3×100 mL), the organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by Prep-HPLC (CH_3CN/H_2O (v/v=1/1). This resulted in 31 mg (26% in two steps) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile ("Amgen 7.3") as yellow solid. LCMS: m/z=599 $[M+1]^+$.

[0281] ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.44 (d, J=5.0 Hz, 1H), 7.48 (dd, J=8.4, 4.6 Hz, 1H), 7.40-7.22 (m, 4H), 6.98-6.85 (m, 1H), 6.35 (d, J=16.5 Hz, 1H), 5.86 (d, J=10.6 Hz, 1H), 4.79 (s, 2H), 4.14-3.79 (m, 4H), 2.80-2.74 (m, 1H), 2.05 (s, 3H), 1.68 (d, J=7.0 Hz, 6H), 1.19 (d, J=6.8 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H).

[0282] The mixture of 4-((3 S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile atropisomers (1.48 g) was purified by Chiral-Prep-HPLC with the following conditions: Column, CHIRAL Cellulose-SB, 3 cm×25 cm, Sum; mobile phase, Hex/EtOH=(v/v=50/50); Detection wavelength, UV 254 nm. This resulted in 625 mg (42%) of 4-((3 S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the first eluting isomer, "Amgen 7.3-1") as a yellow solid; LCMS: m/z=599 $[M+1]^+$.

[0283] ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (s, 1H), 8.32 (d, J=5.0 Hz, 1H), 7.42-7.30 (m, 1H), 7.23-7.01 (m, 4H), 6.78 (dd, J=16.7, 10.6 Hz, 1H), 6.22 (dd, J=16.7, 1.9 Hz, 1H), 5.73 (dd, J=10.6, 1.9 Hz, 1H), 4.66 (s, 2H), 3.99-3.83 (m, 2H), 3.74-3.72 (m, 2H), 2.63-2.61 (m, 1H), 1.93 (s, 3H), 1.55 (d, J=7.0 Hz, 6H), 1.10-1.08 (m, 3H), 0.90-0.89 (m, 3H).

[0284] And 669 mg (45%) of 4-((3S,5R)-4-acryloyl-3,5-dimethylpiperazin-1-yl)-6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (the second eluting isomer, "Amgen 7.3-2") as a yellow solid; LCMS: m/z=599 $[M+1]^+$.

[0285] ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.43 (d, J=5.0 Hz, 1H), 7.57-7.41 (m, 1H), 7.37-7.07 (m, 4H), 6.90 (dd, J=16.7, 10.6 Hz, 1H), 6.34 (dd, J=16.7, 1.9 Hz, 1H), 5.85 (dd, J=10.6, 1.9 Hz, 1H), 4.78 (s, 2H), 4.07-3.98 (m, 2H), 3.86-3.84 (m, 2H), 2.76-2.74 (m, 1H), 2.05 (s, 3H), 1.68-1.66 (m, 6H), 1.12-1.10 (m, 3H), 0.91-0.89 (m, 3H).

Pharmacological Testing

1. SOS1 Catalyzed Nucleotide Exchange Assay

[0286] HIS-KRAS (G12C, aa 2-185, Sino biological) was diluted to 5 μM in EDTA buffer (20 mM HEPES, pH 7.4, 50 mM NaCl, 10 mM EDTA, 0.01% (v/v) Tween-20) and incubated for 30 min at 25° C. The EDTA pretreated HIS-KRAS (G12C) was diluted to 12 nM in assay buffer (25 mM HEPES, pH 7.4, 120 mM NaCl, 5 mM $MgCl_2$, 1 mM DTT, 0.01% (v/v) Tween 20, 0.1% (w/v) BSA) containing 120 nM GDP (Sigma) and MAb Anti 6HIS-Tb cryptate Gold (Cisbio) and incubated for 1 hour at 25° C. to prepare GDP-loaded HIS-KRAS (G12C). The GDP-loaded HIS-KRAS (G12C) was pre-incubation with diluted compounds in a 384-well plate (Greiner) for 1 hour, then purified SOS1 ExD (Flag tag, aa 564-1049) and BODIPY™ FL GTP (Invitrogen) were added to the assay wells (Final concentration: 3 nM HIS-KRAS (G12C), 2 μM SOS1 ExD, 80 nM BODIPY™ FL GTP, 21 ng/mL MAb Anti 6HIS-Tb cryptate Gold) and incubated for 4 hours at 25° C. TR-FRET signals were then read on Tecan Spark multimode microplate reader. The parameters were F486: Excitation 340 nm, Emission 486 nm, Lag time 100 μs, Integration time 200 μs; F515: Excitation 340 nm, Emission 515 nm, Lag time 100 μs, Integration time 200 μs. TR-FRET ratios for each individual wells were calculated by equation: TR-FRET ratio=(Signal F515/Signal F486)*10000. Then the data were analyzed using a 4-parameter logistic model to calculate IC_{50} values. The results of the SOS1 catalyzed nucleotide exchange assay are in the following Table 8:

TABLE 8

Compound	SOS1 catalyzed nucleotide exchange IC_{50}(nM)
Compound 1	3.06
Compound 1-1	14.1
Compound 1-2	1.41
Compound 2	6.66
Compound 3	3.67
Compound 4	3.48
Compound 5	5.97
Compound 6	1.51
Compound 7	14.9
Compound 8	6.68
Compound 9	2.30
Compound 10-1	43.9
Compound 10-2	4.16
Compound 11-1	29.6
Compound 11-2	2.11
Compound 12	3.85
Compound 12-1	16.0
Compound 12-2	2.01
Compound 13	6.63
Compound 13-1	2.73
Compound 13-2	11.5
Compound 14	3.56
Compound 15-1	6.87
Compound 15-2	83.9
Compound A	1.69
Amgen 6	4.40
Amgen 6.3	2.77
Amgen 7.3	10.5

[0287] From the Table 8, it can be seen that the representative compounds in the present invention have better activity to inhibit the SOS1 catalyzed nucleotide exchange.

2. Phospho-ERIC1/2(THR202/TYR204) HTRF Assay

[0288] NCI-H358 cells expressing KRAS G12C were cultured in RPMI 1640 medium (Gibco) containing 10% fetal bovine serum (Gibco). The NCI-H358 cells in culture medium were seeded in 96-well plates at a concentration of 40,000 cells/well and then put in a 37° C./5% CO_2 cell incubator to incubate overnight. The next day, culture medium was removed and the compound diluted in assay medium (RPMI 1640, 0.1% FBS) was added in each well. After 2 hours incubation in a 37° C./5% CO_2 cell incubator, the assay medium in 96-well plates was removed, then 50 μL of 1× blocking reagent-supplemented lysis buffer (Cisbio) was added and the plates were incubated at 25° C. for 45 min with shaking. 10 μL of cell lysates from the 96-well plates were transferred to a 384-well plate (Greiner) containing 2.5

μL/well HTRF® pre-mixed antibodies (Cisbio 64AERPEH). Incubate 4 hours at 25° C. and then read HTRF signals on Tecan Spark multimode microplate reader. The data were analyzed using a 4-parameter logistic model to calculate IC_{50} values. The results of the Phospho-ERK1/2 (THR202/TYR204) HTRF assay are in the following Table 9:

TABLE 9

Compound	p-ERK IC_{50}(nM)
Compound 1	16.4
Compound 1-1	176
Compound 1-2	10.2
Compound 2	33.6
Compound 3	21.4
Compound 4	40.1
Compound 5	141
Compound 6	25.1
Compound 8	48.0
Compound 9	26.3
Compound 10-1	217
Compound 10-2	22.0
Compound 11-1	258
Compound 11-2	23.6
Compound 12	39.7
Compound 12-1	117
Compound 12-2	12.3
Compound 13	87.0
Compound 13-1	21.8
Compound 13-2	138
Compound 14	37.6
Compound 15-1	44.0
Compound 15-2	327
Compound A	14.2
Amgen 6	29.9
Amgen 6.3	20.1
Amgen 7.3	44.5

[0289] From Table 9, it can be seen that representative compounds in the present invention have better activity to inhibit the phosphorylation of ERK1/2 the NCI-H358 cells.

3. Mouse Pharmacokinetic Study

[0290] The purpose of this study was to evaluate the pharmacokinetic properties of compounds in Balb/c mouse (♀) following single dose administration. The day before administration, mice were fasted overnight and free access to water. Six mice were needed for each compound and the six mice were divided into two groups (n=3/group), group A and group B. Mice in group A were treated with a single 3 mg/kg dose of compound (iv). Mice in group B were treated with a single 10 mg/kg dose of compound (po). For each mouse in group A, blood samples were collected at pre-dose, and at the time point of 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post-dose. For each mouse in group B, blood samples were collected at pre-dose, and at the time point of 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-dose. Blood samples were placed on ice until centrifugation to obtain plasma samples. The plasma samples were stored at −80° C. until analysis. The concentration of compound in plasma samples were determined using a LC-MS/MS method. The results are in the following Table 10:

TABLE 10

	3 mg/kg, iv		10 mg/kg, po		
			$AUC_{0\text{-}24\ h}$		
Compound	CL (mL/min/kg)	Vss (L/kg)	C_{max} (ng/mL)	(ng · h/mL)	Oral BA (F %)
Compound 1	21.4	1.87	1397	4025	51.3
Compound 11	7.2	1.0	3340	9587	38
Compound 13	9.8	1.4	3013	12763	74
Compound 14	10	0.9	4023	10498	63
Compound A	65.2	1.13	241	207	8.05
Amgen 6	72	2.6	901	1032	44
Amgen 6.3	32	1.4	1587	1658	32

[0291] From Table 10, it can be seen that Compound 1, Compound 11, Compound 13 and Compound 14 have excellent pharmacokinetic properties (such as the higher C_{max} and AUC) in mouse model comparative with the Compound A, Amgen 6 and Amgen 6.3, which make them more suitable for treating cancers with KRAS G12C mutation as an orally therapeutic active ingredient in clinic.

4. Doe Pharmacokinetic Study

[0292] The purpose of this study was to evaluate the pharmacokinetic properties of compounds in beagle dog following single dose administration. The day before administration, dogs were fasted overnight and free access to water. Four beagle dogs were needed for each compound and the four dogs were divided into two groups (one male (♂) and one female (♀) in each group). Dogs in group A were treated with a single 1 mg/kg dose of compound (iv). Dogs in group B were treated with a single 10 mg/kg dose of compound (po). For dogs in group A, blood samples were collected at pre-dose, and at the time point of 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h. For dogs in group B, blood samples were collected at pre-dose, and at the time point of 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post-dose. Blood samples were placed on ice until centrifugation to obtain plasma samples. The plasma samples were stored at −80° C. until analysis. The concentration of compound in plasma samples were determined using a LC-MS/MS method. The results are in following Table 11:

TABLE 11

Compound	Sex	1 mg/kg, iv CL (mL/min/kg)	Vss (L/kg)	10 mg/kg, po C_{max} (ng/mL)	$AUC_{0-24\ h}$ (ng · h/mL)	Oral BA (F %)
Compound 1-2	♂	15.9	0.9	3420	6724	64.3
	♀	18.1	1.1	2980	5953	65.1
Compound 9	♂	17.7	1.37	2490	7788	83.2
	♀	20.5	1.72	2260	6323	78.5
Amgen 6	♂	11.8	0.412	3690	2944	20.9
	♀	15.5	0.543	2580	1326	12.4
Amgen 6.3	♂	239	2.3	8.0	5.1	0.7
	♀	329	3.1	—	—	—

[0293] From Table 11, it can be seen that Compound 1-2 and Compound 9 have excellent pharmacokinetic properties (such as the higher C_{max} and AUC) in beagle dog model comparative with the Amgen 6 and 6.3, which make them more suitable for treating cancers with KRAS G12C mutation as an orally therapeutic active ingredient in clinic.

5. Cynomolgus Monkey Pharmacokinetic Study

[0294] The purpose of this study was to evaluate the pharmacokinetic properties of compounds in Cynomolgus monkey following single dose administration. The day before administration, monkeys were fasted overnight and free access to water. Four monkeys are needed for each compound and the four monkeys were divided into two groups (one male (♂) and one female (♀) in each group), group A and group B. Monkeys in group A were treated with a single 1 mg/kg dose of compound (iv). Monkeys in group B were treated with a single 3 mg/kg dose of compound (po). For monkeys in group A, blood samples were collected at pre-dose, and at the time point of 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h. For monkeys in group B, blood samples were collected at pre-dose, and at the time point of 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post-dose. Blood samples were placed on ice until centrifugation to obtain plasma samples. The plasma samples were stored at −80° C. until analysis. The concentration of compound in plasma samples were determined using a LC-MS/MS method. The results are in following Table 12:

TABLE 12

Compound	Sex	1 mg/kg, iv CL (mL/min/kg)	Vss (L/kg)	3 mg/kg, po C_{max} (ng/mL)	$AUC_{0-24\ h}$ (ng · h/mL)	Oral BA (F %)
Compound 1-2	♂	5.25	0.61	2030	7938	83.5
	♀	7.19	0.86	2680	6854	98.9
Compound 9	♂	6.06	0.66	2130	9697	120
	♀	5.73	0.77	1060	3741	44.4

[0295] From Table 12, it can be seen that Compound 1-2 and Compound 9 have excellent pharmacokinetic properties (such as the higher C_{max} and AUC) in monkey model, which make them more suitable for treating cancers with KRAS G12C mutation as an orally therapeutic active ingredient in clinic.

6. The Efficacy in NCI-H1373 Xenograft Model

[0296] NCI-H1373 cells (5.0E+06 cells) were injected subcutaneously into the right flank of female BALB/c nude mice (6-8 weeks) in a mixture with PBS and Matrigel (Corning) (PBS/Matrigel=1:1 (v/v)). Mice were monitored daily and caliper measurements began when tumors became visible. Tumor volume was calculated by measuring two perpendicular diameters using the formula: $(L*W^2)/2$ in which L and W refer to the length and width tumor diameter, respectively. When the average tumor volume reached 150-200 mm^3, mice were grouped randomly (n=6/group) and treated with compounds. Tumor volume and mice weight was measured twice a week during treatment (~3 weeks). Tumor growth inhibition rates were calculated by TGI %=$(1-(Vt-Vt_0)/(Vc-Vc_0))*100\%$, wherein Vc and Vt are the mean tumor volume of control and treated groups at the end of the study respectively, and Vc_0 and Vt_0 are the mean tumor volume of control and treated groups at the start respectively. The results are in the following Table 13 and FIG. **8**:

TABLE 13

Groups	Tumor volume at the start, mm^3	Tumor volume at the end (Day 21), mm^3	TGI %
Vehicle	193	1879	—
Compound 1-2, 10 mg/kg, QD	193	144	103
Compound 12-2, 10 mg/kg, QD	193	63	108

[0297] From Table 13 and FIG. **8**, it can be seen that Compound 1-2 and Compound 12-2 have excellent efficacy in vivo.

7. Safety Exploration in MIA PaCa-2 Xenograft Model

[0298] MIA PaCa-2 cells (1.0E+07 cells) were injected subcutaneously into the right flank of female BALB/c nude mice (6-8 weeks) in a mixture with PBS and Matrigel (Corning) (PBS/Matrigel=1:1 (v/v)). Mice were monitored

daily and caliper measurements began when tumors became visible. Tumor volume was calculated by measuring two perpendicular diameters using the following formula: $(L*W^2)/2$ in which L and W refer to the length and width tumor diameter, respectively. After mice were grouped to study the efficacy, the remaining mice (n=6) were used to explore the safety. The mice were treated with 400 mg/kg compound 1-2 (po, QD) for 22 days, and mice body weight was measured twice a week during treatment. The weight of mice varies with the number of days after cell inoculation is shown in FIG. **9**. From FIG. **9**, it can be seen that the Compound 1-2 have good safety.

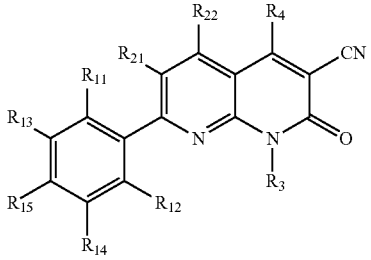
[0299] It is to be understood that, if any prior art publication is referred to herein; such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and Examples should not be construed as limiting the scope of the invention.

What is claimed is:

1-49. (canceled)

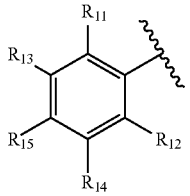
50. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof:

(I)

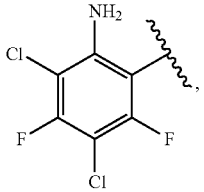


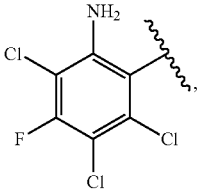
Wherein:

the



in the formula (I) is selected from:





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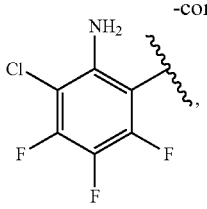

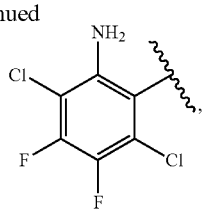

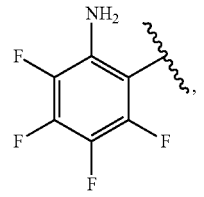

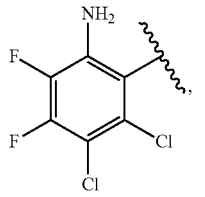

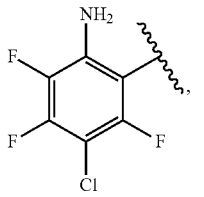

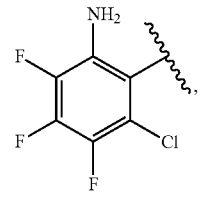

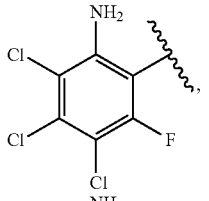

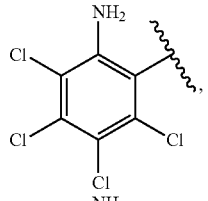

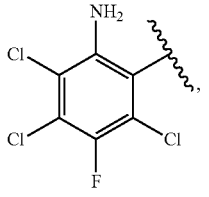

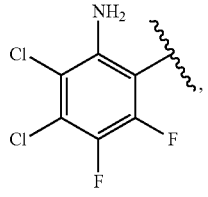

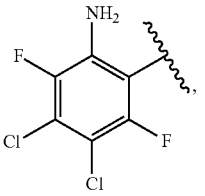

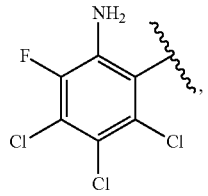

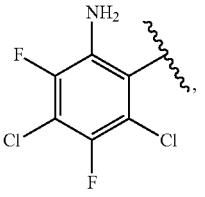

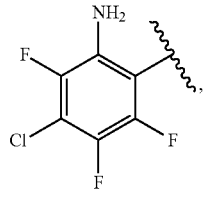

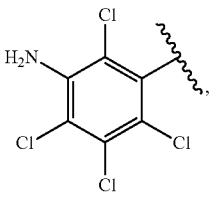

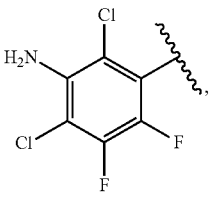

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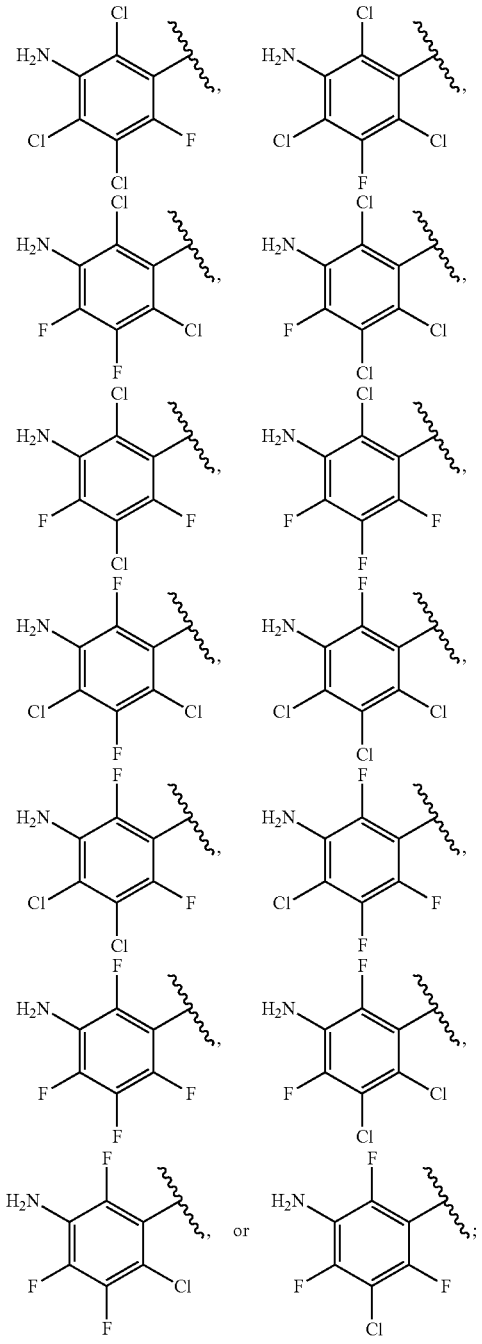
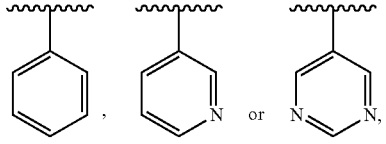


R_{21} is selected from halogen;

R_{22} is selected from hydrogen;

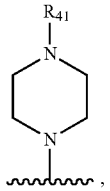
R_3 is selected from



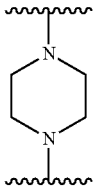
each hydrogen in the R_3 at each occurrence is independently optionally substituted by 1 R_{31} or 2 R_{31};

Each R_{31} at each occurrence is independently selected from —C_{1-6} alkyl;

R_4 is selected from

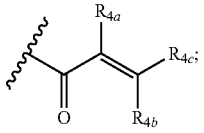


each hydrogen in the



is independently optionally substituted with 1 R_{42} or 2 R_{42};

R_{41} is selected from



R_{4a}, R_{4b} or R_{4c} is independently selected from hydrogen or halogen;

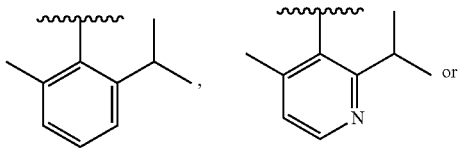
Each R_{42} at each occurrence is independently selected from —C_{1-6}alkyl or —C_{1-6}alkylene-CN.

51. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, wherein:

R_{21} is selected from —Cl.

52. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, wherein:

R_3 is selected from



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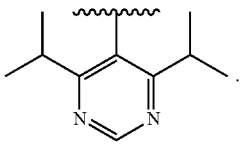
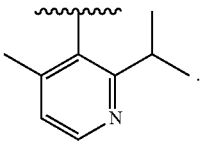


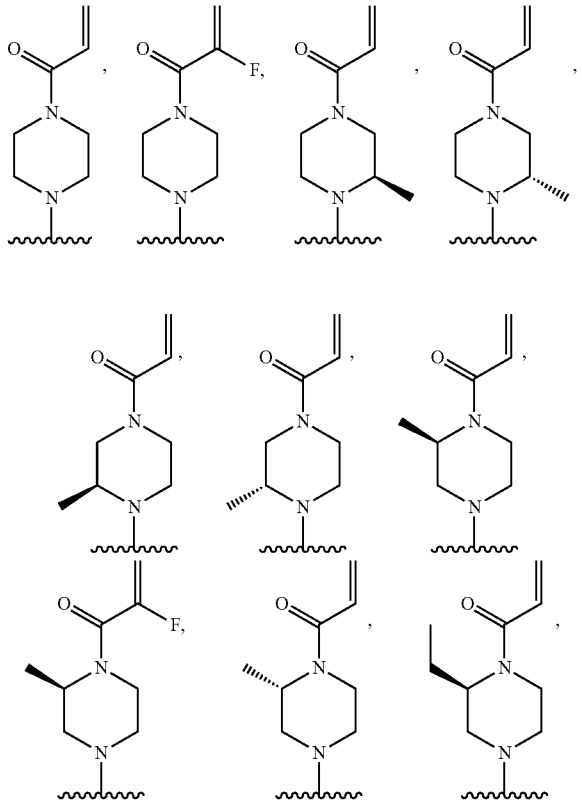
53. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **52**, wherein:

R_3 is selected from



54. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, wherein:

R_4 is selected from:



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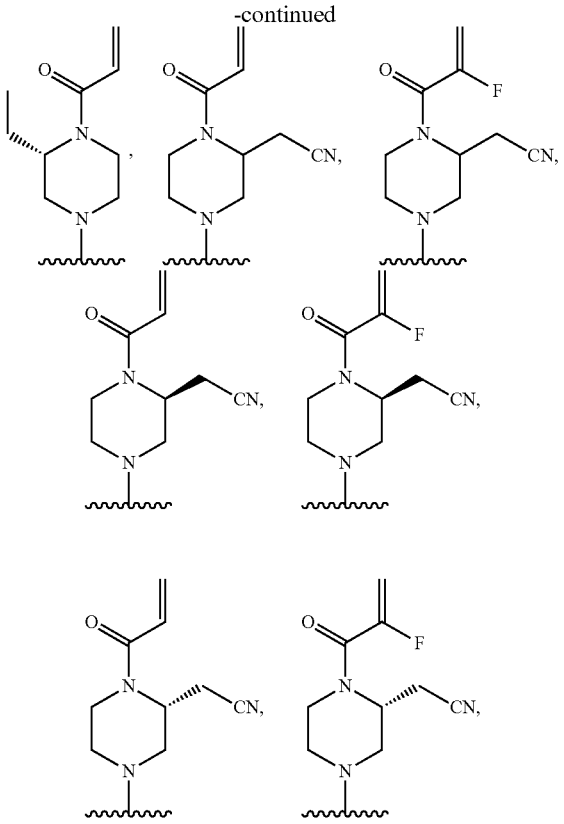
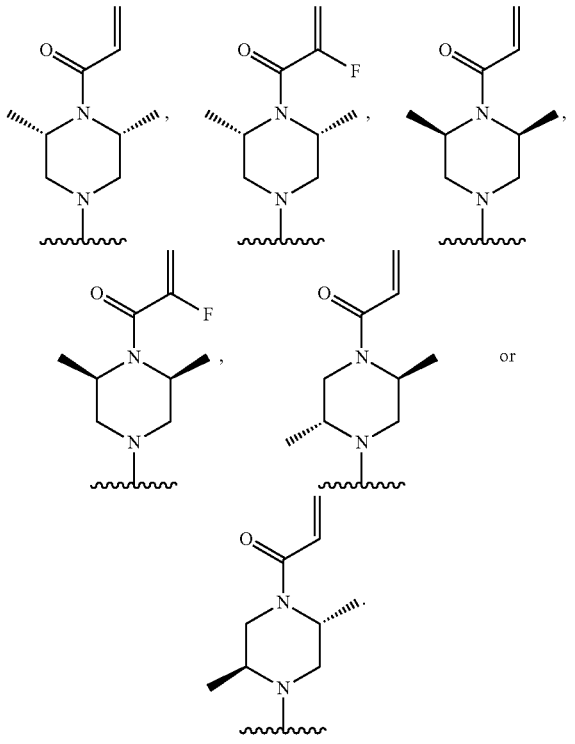
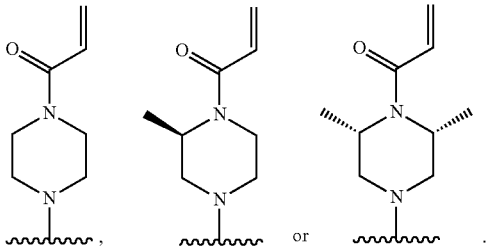




55. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt

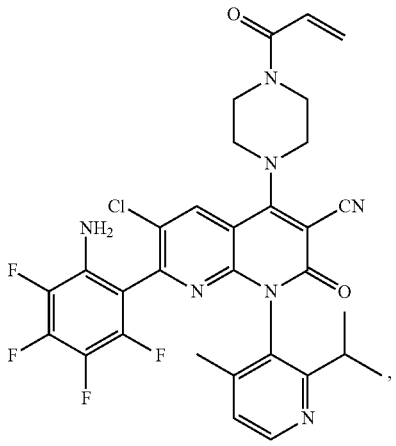
thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **54**, wherein:

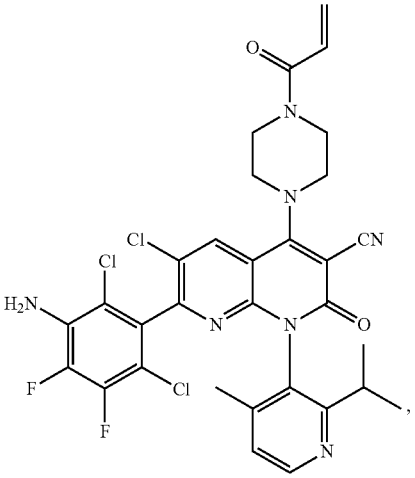
R_4 is selected from:



56. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, wherein:

the compound is selected from:





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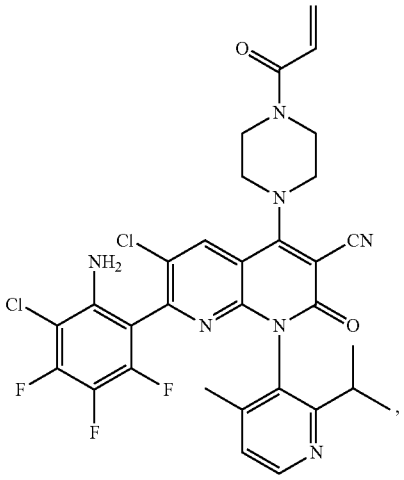

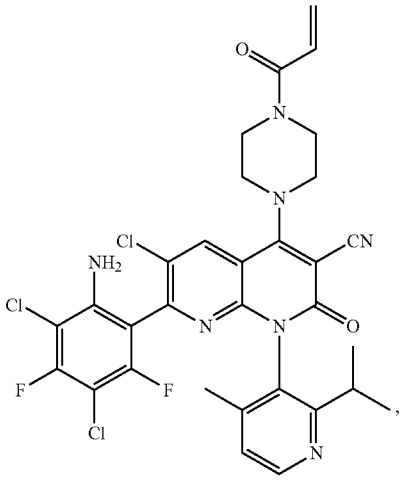

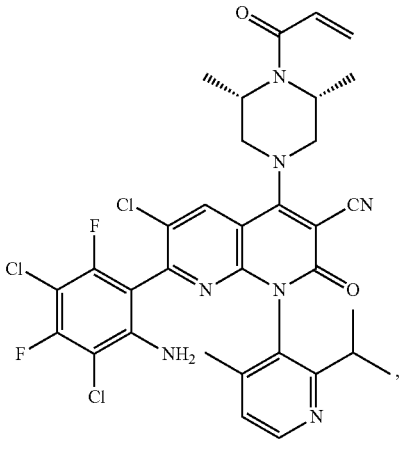

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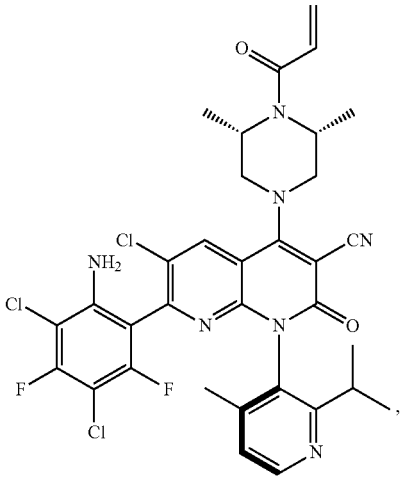

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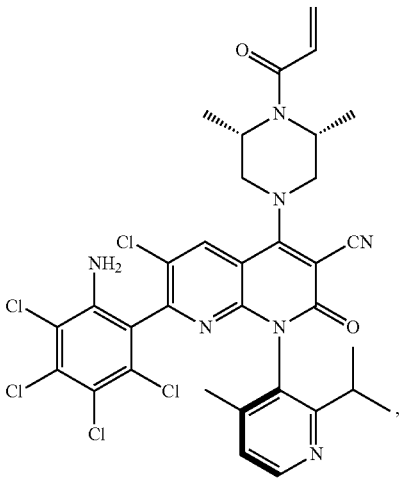

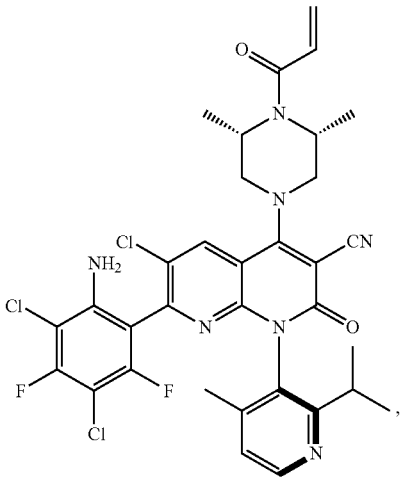

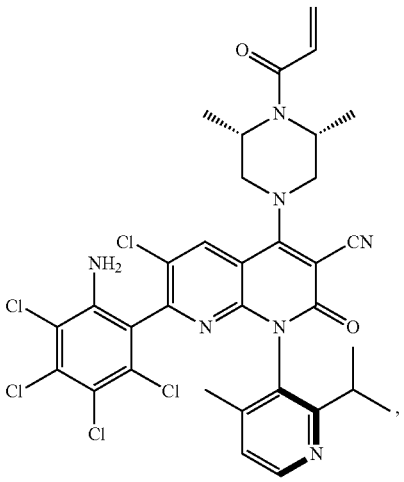

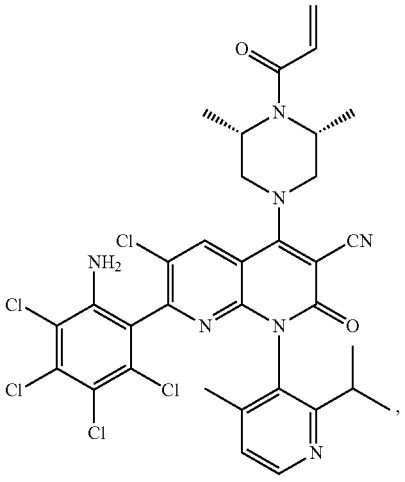

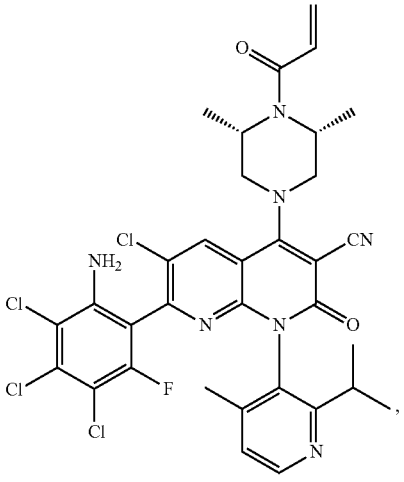

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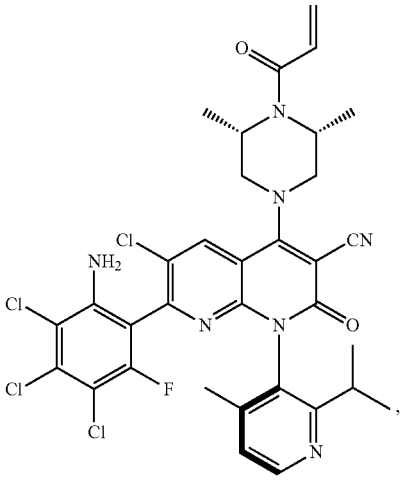

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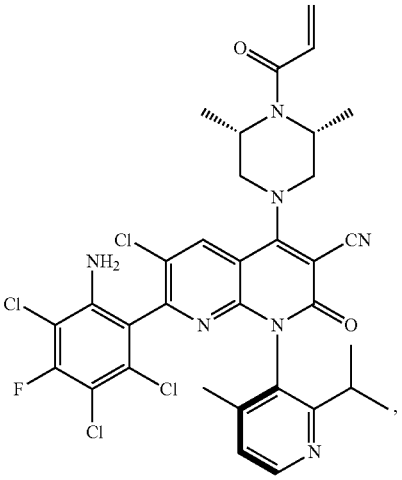

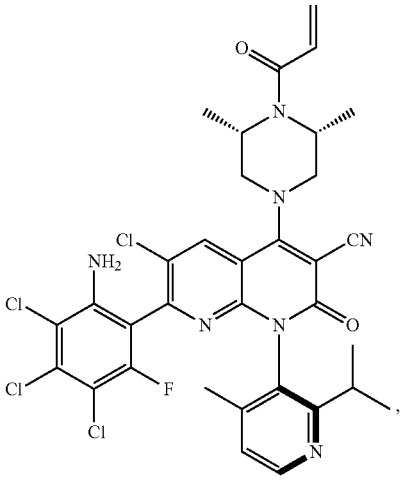

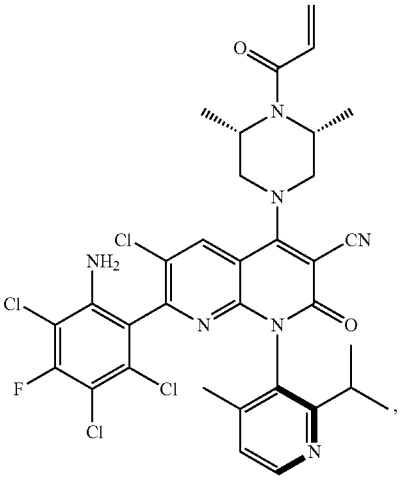

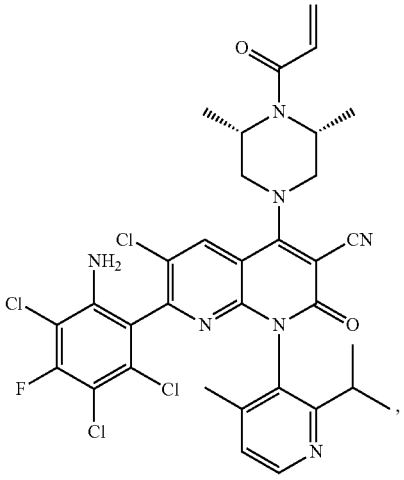

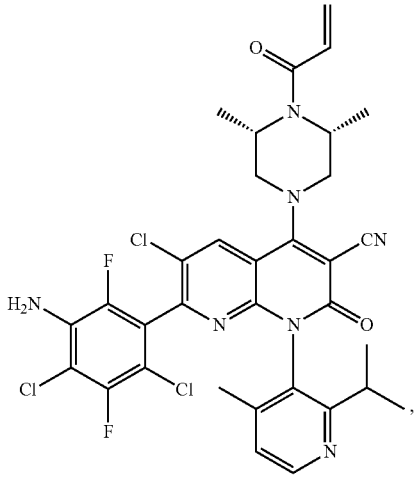

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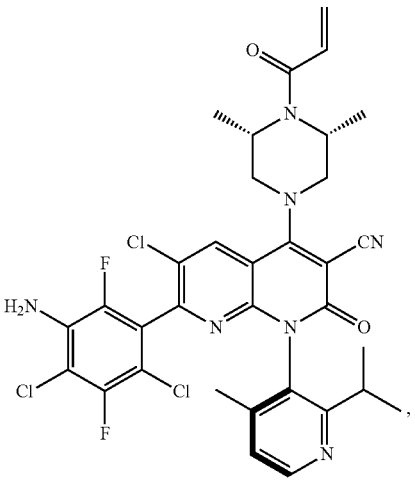

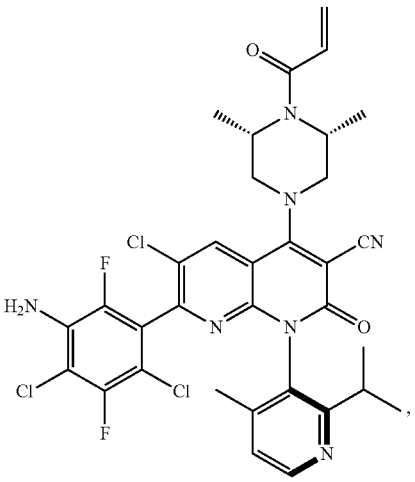

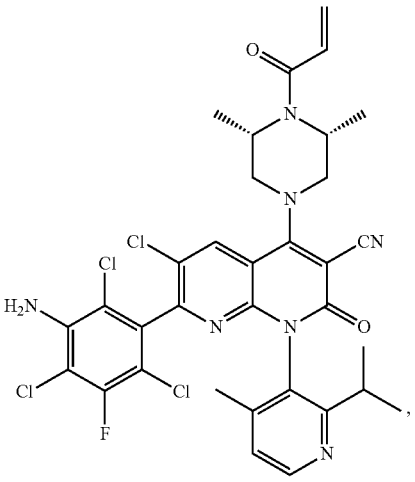

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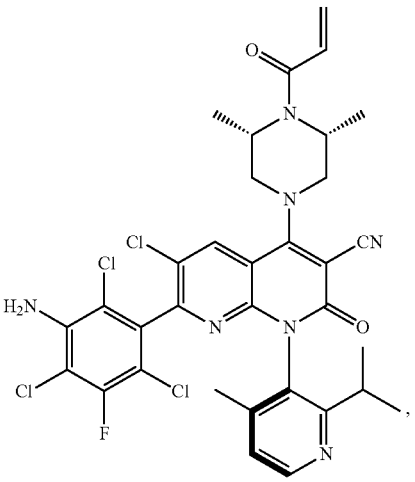

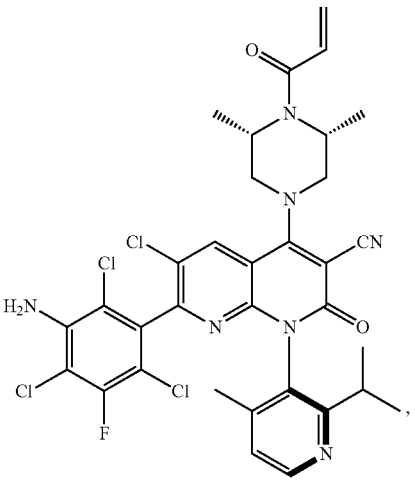

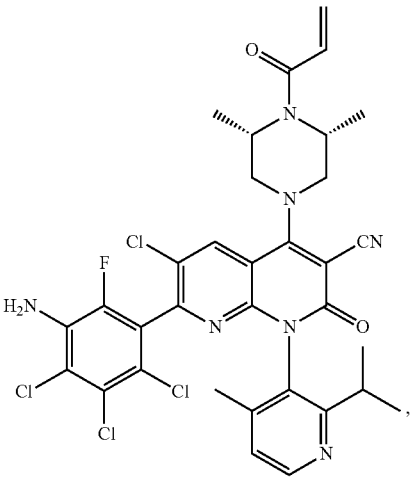

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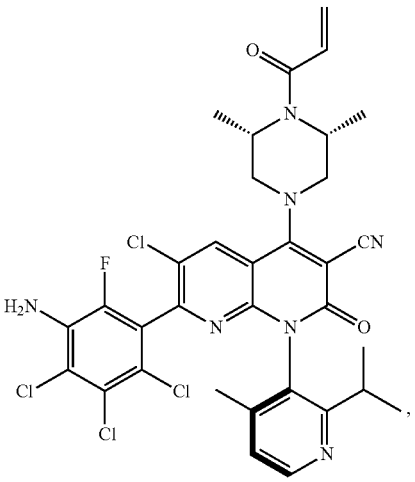

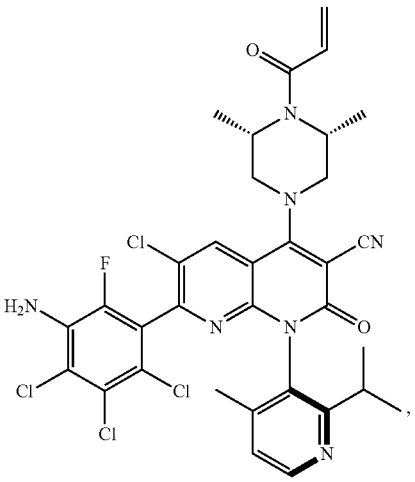

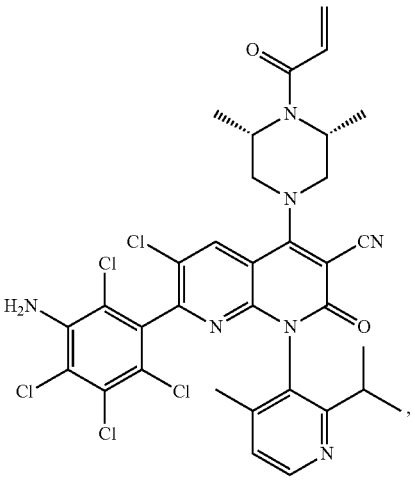

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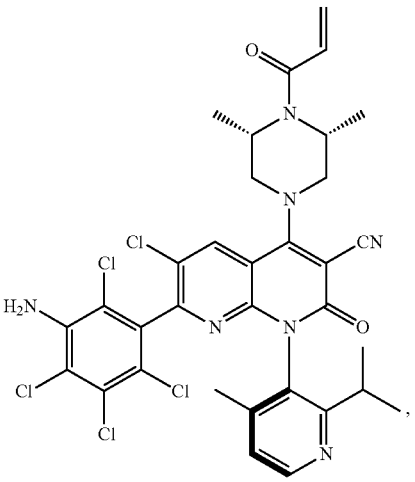

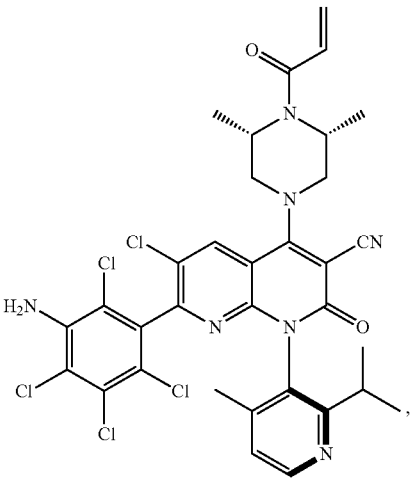

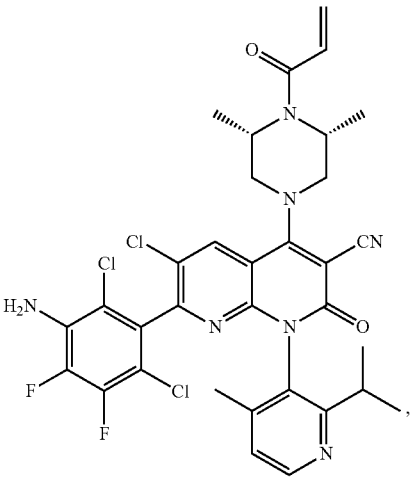

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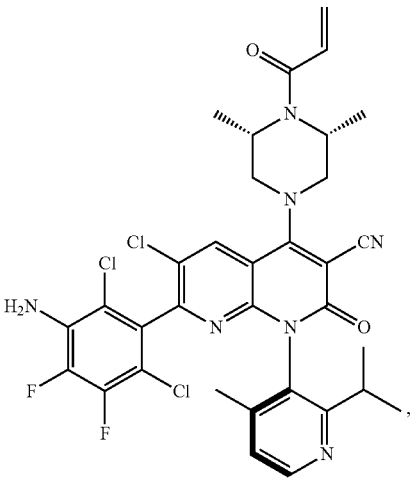

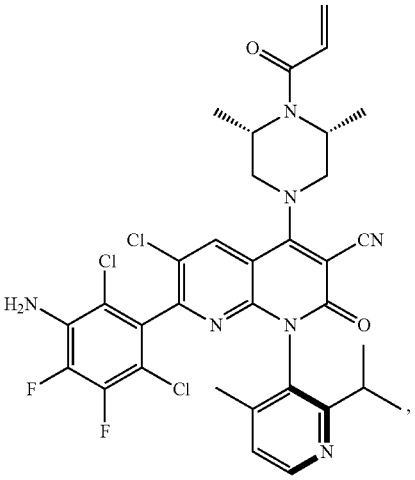

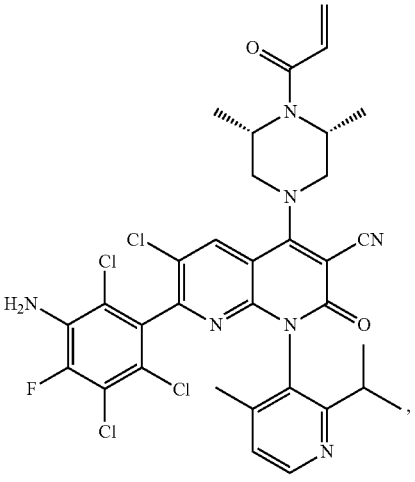

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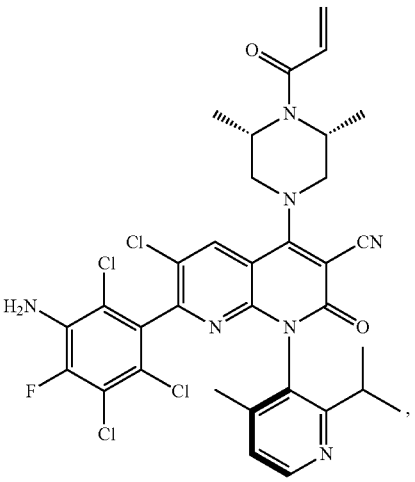

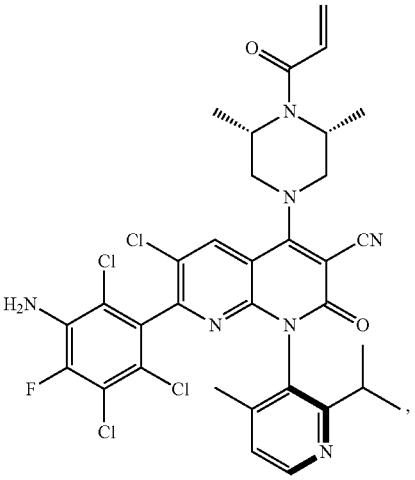

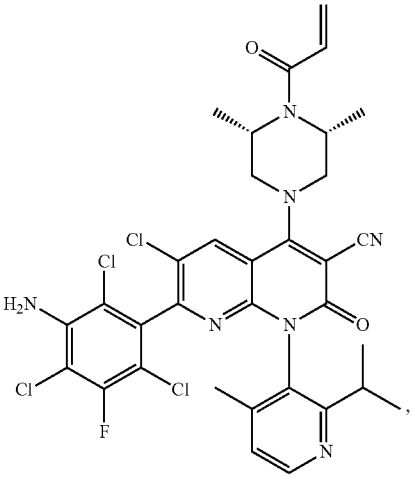

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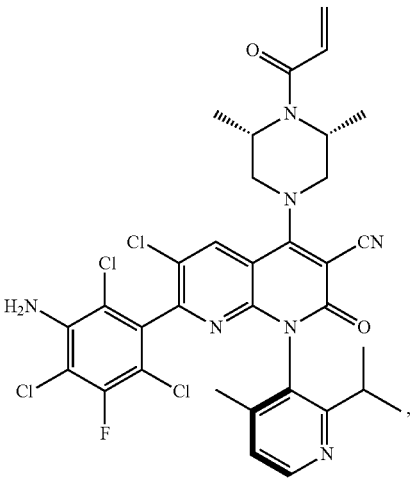

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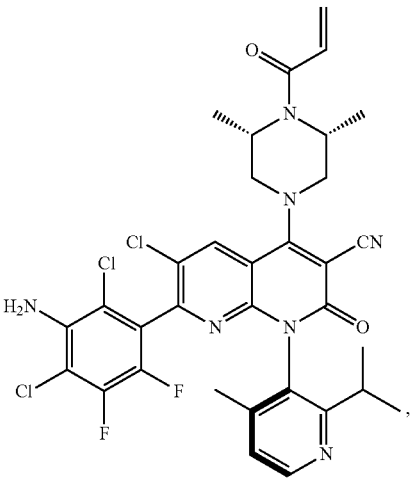

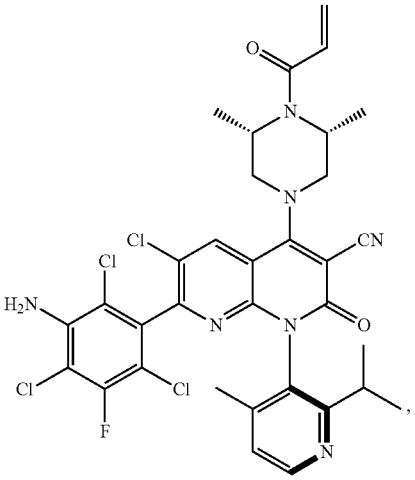

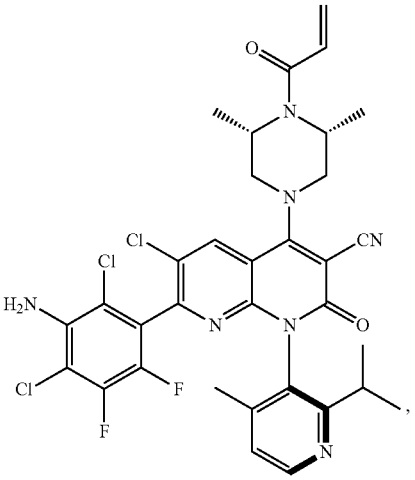

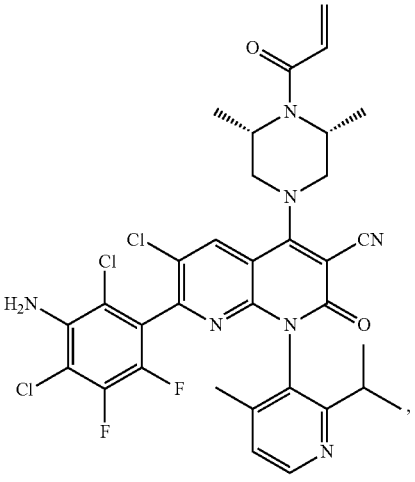

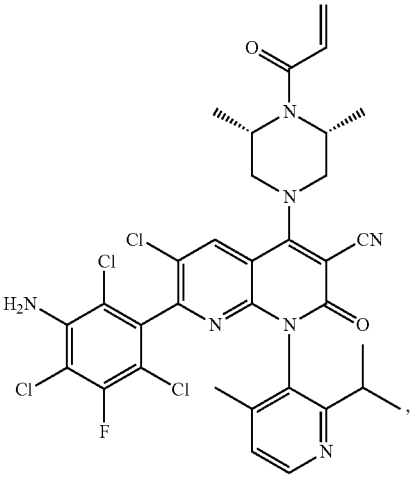

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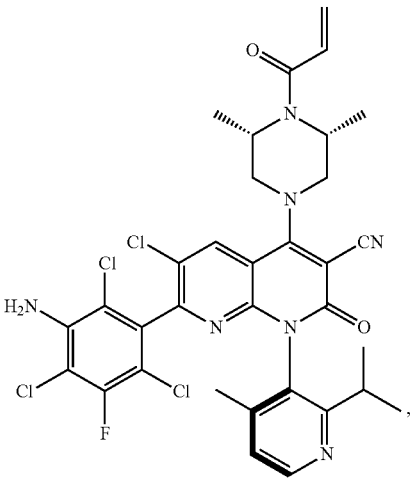

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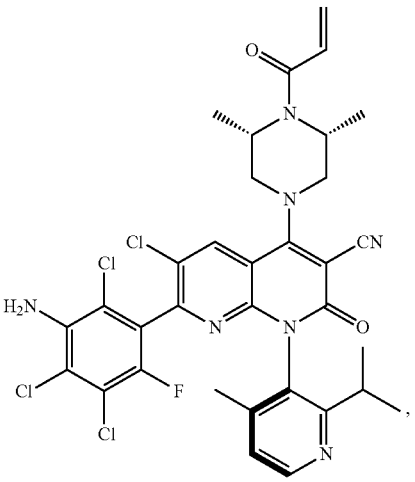

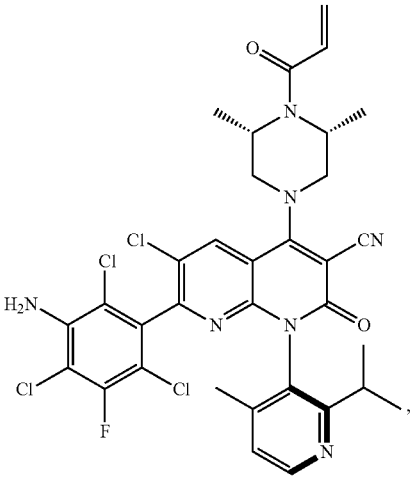

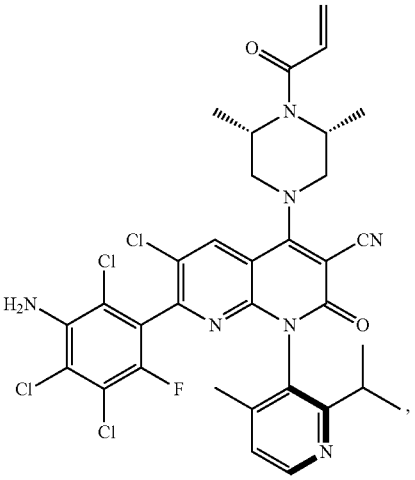

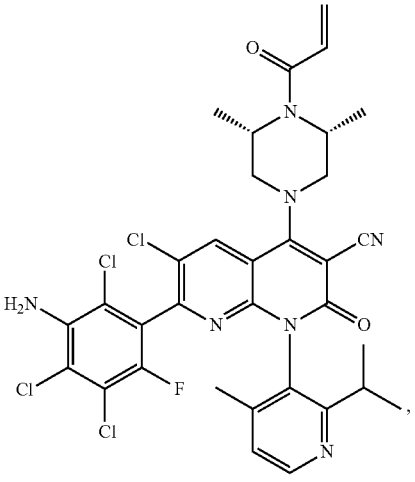

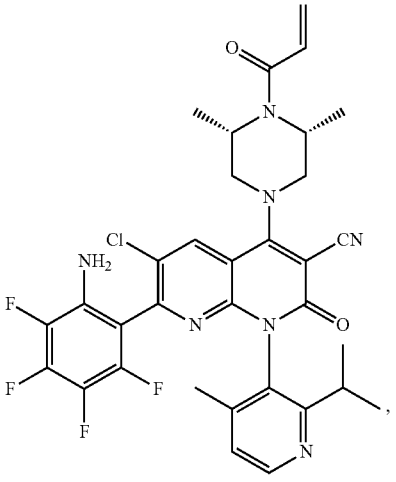

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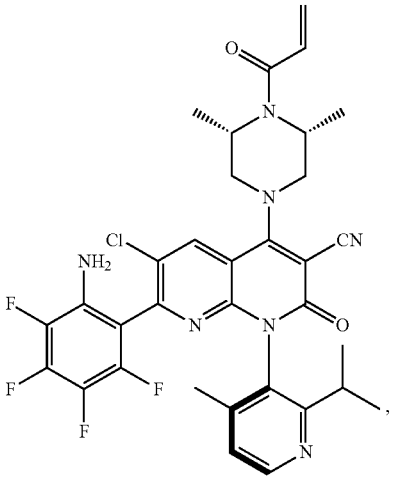

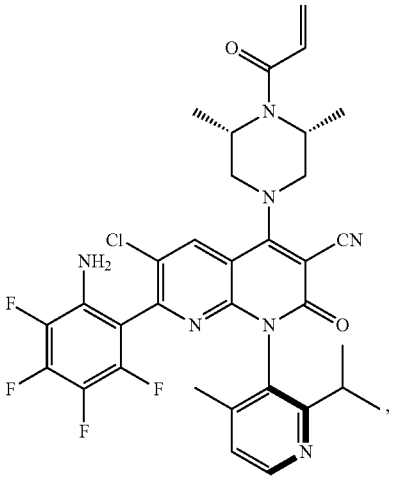

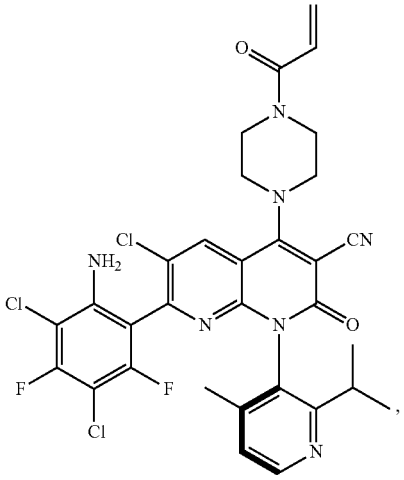

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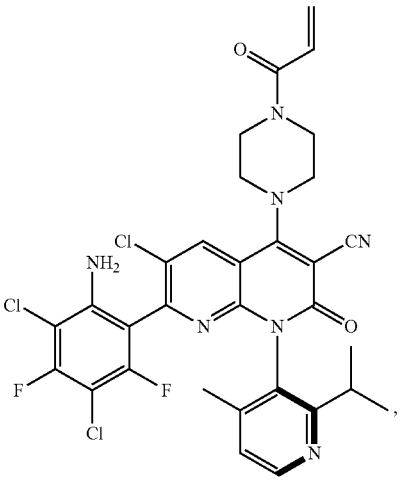

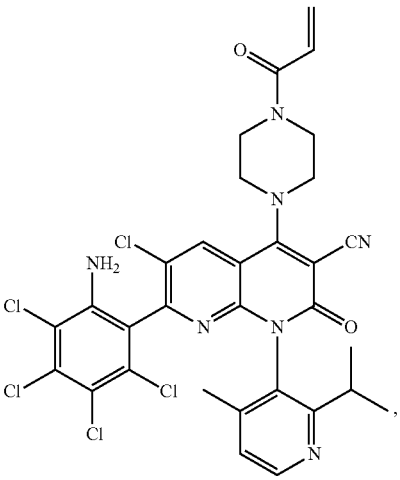

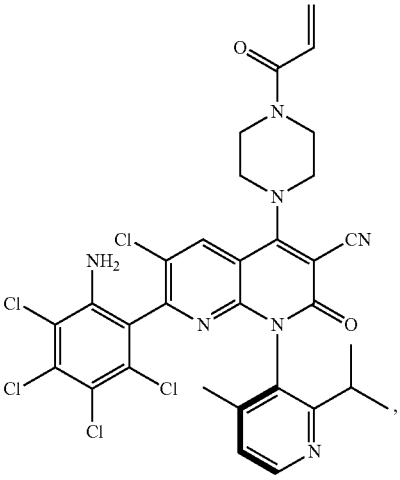

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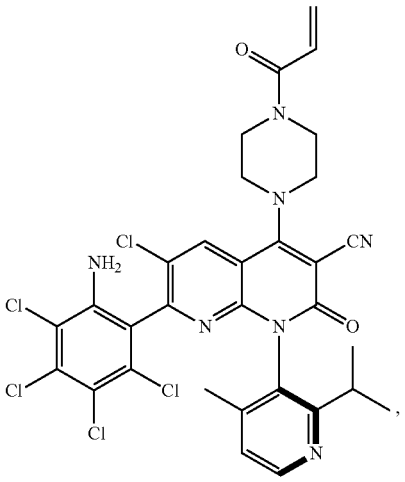

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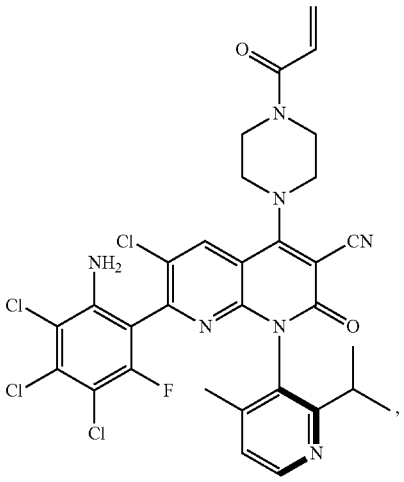

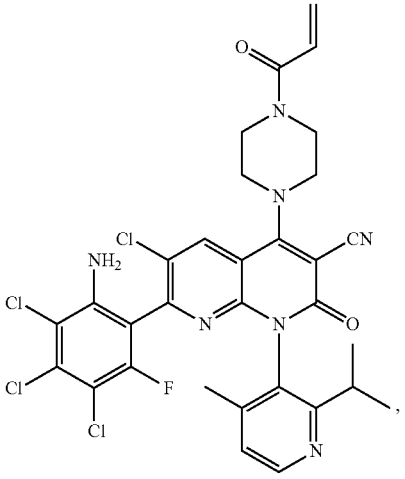

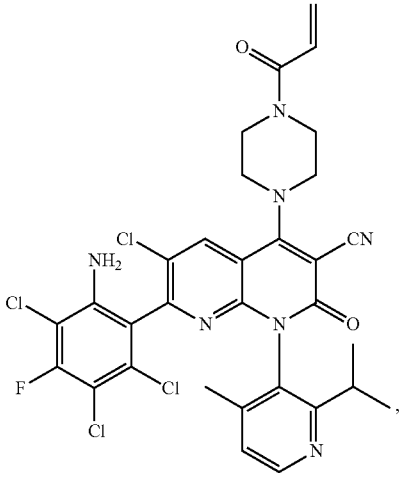

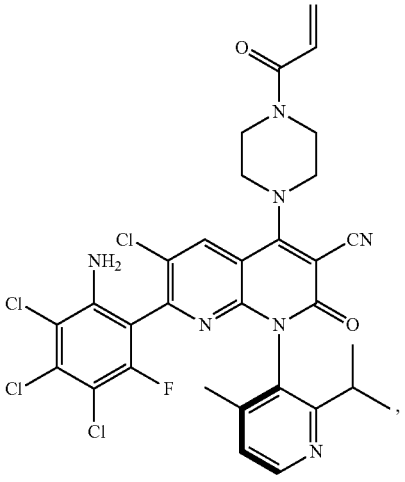

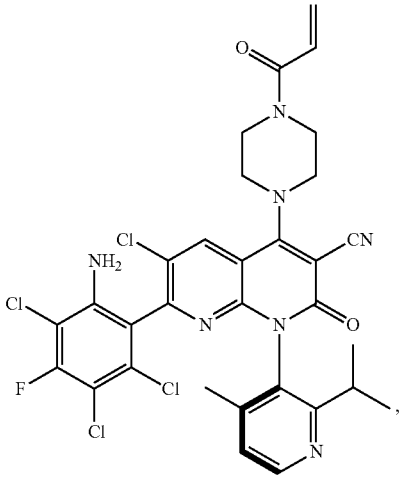

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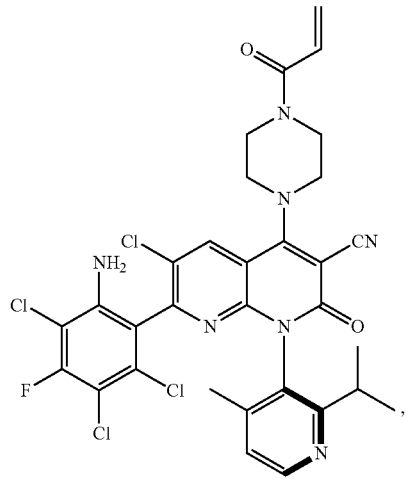

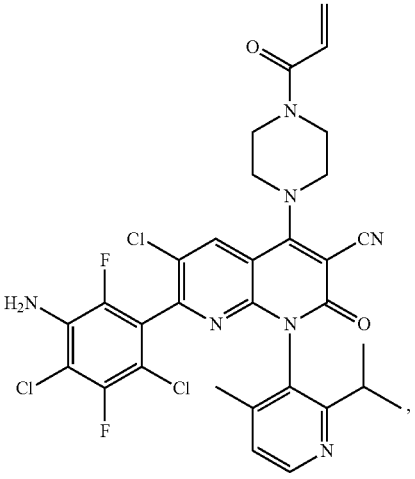

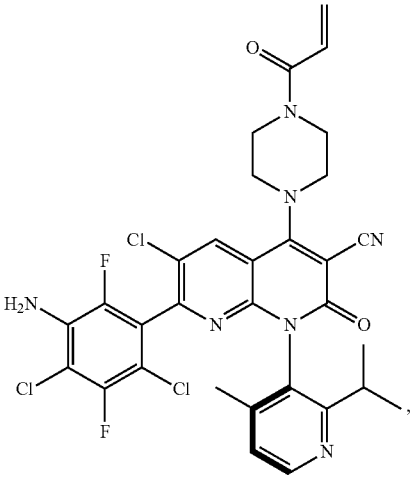

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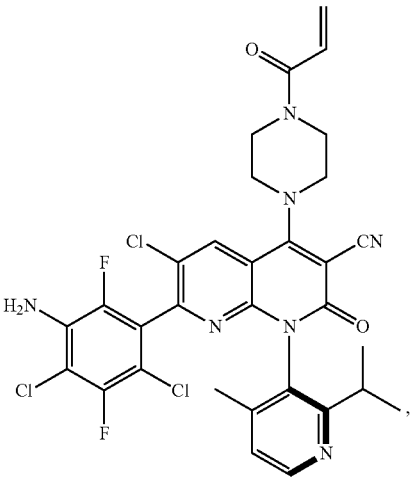

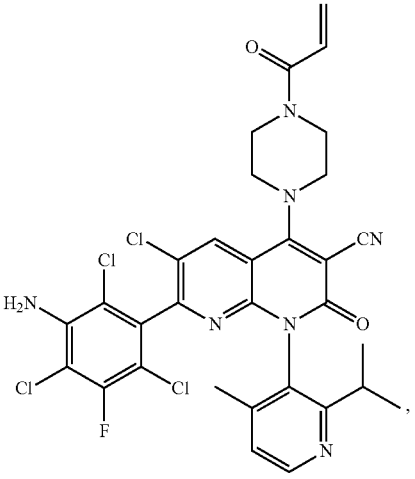

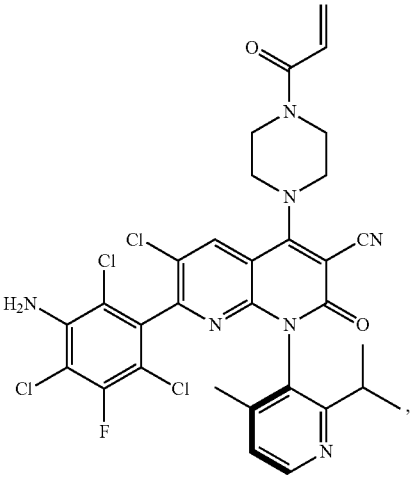

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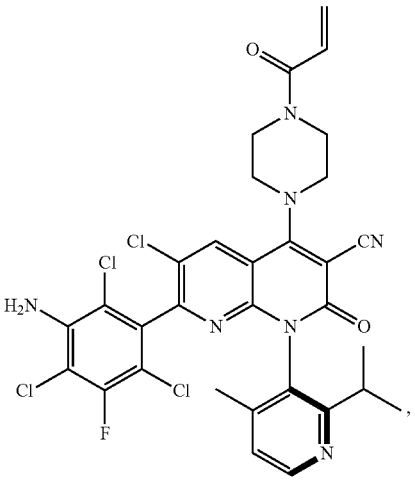

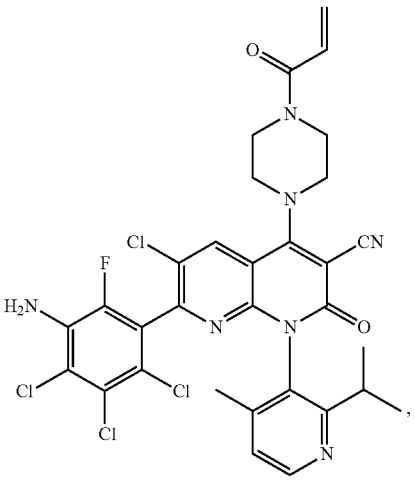

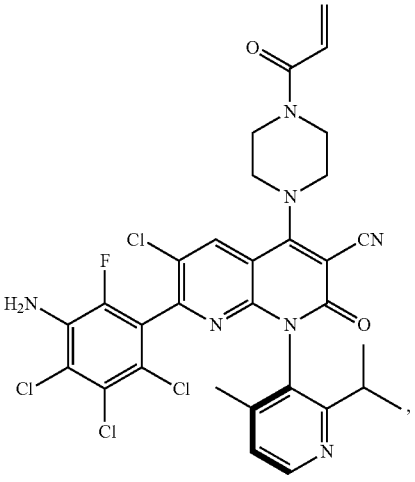

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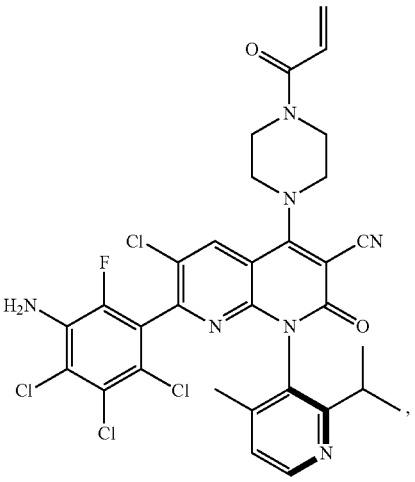

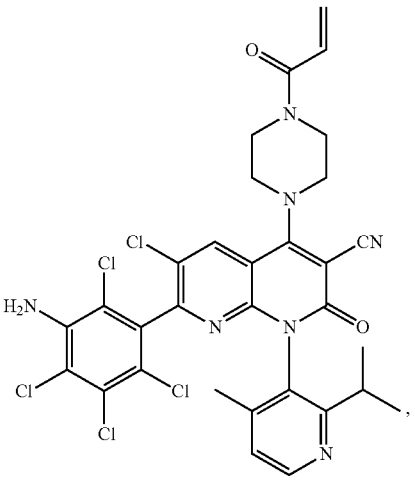

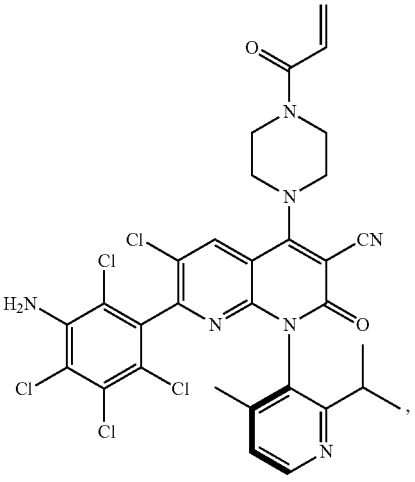

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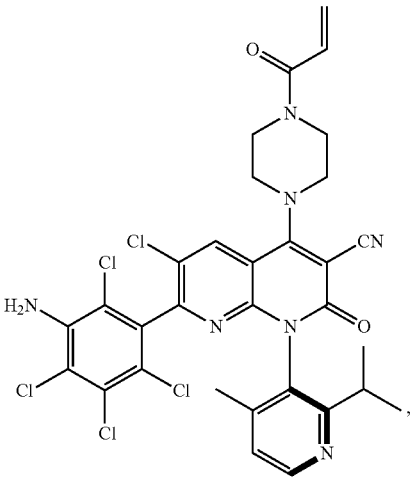

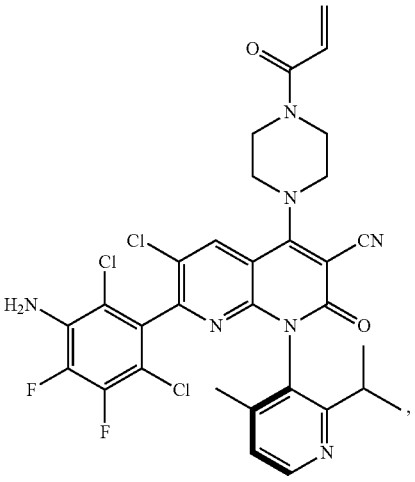

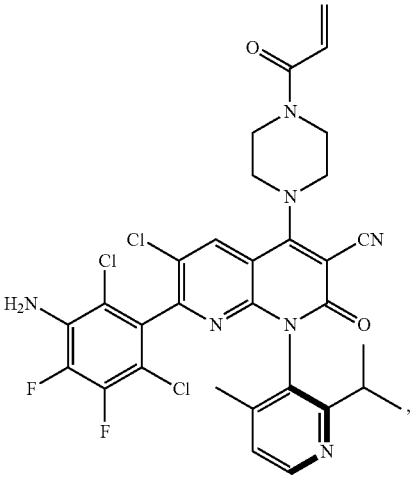

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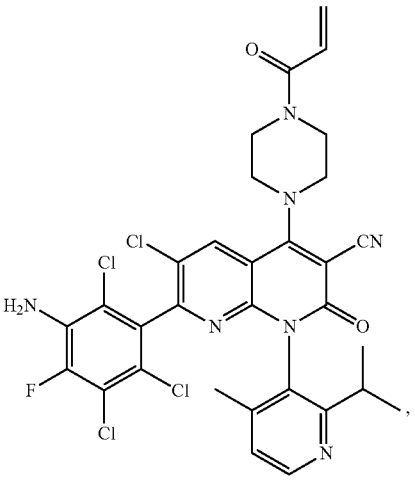

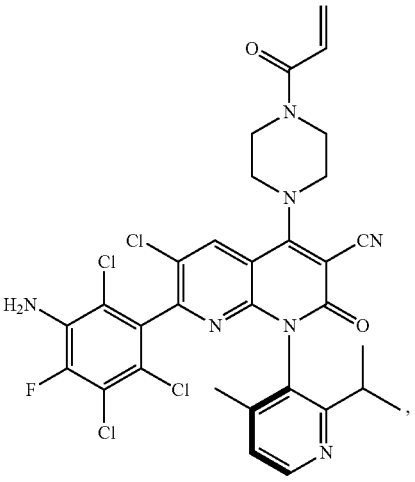

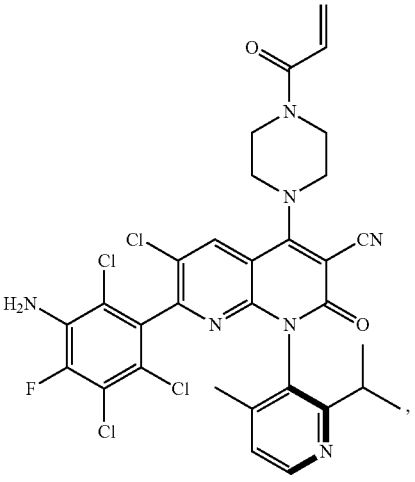

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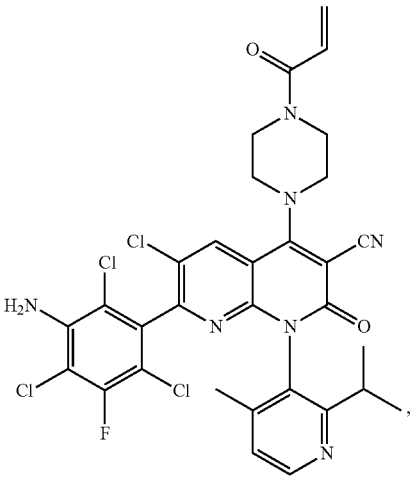

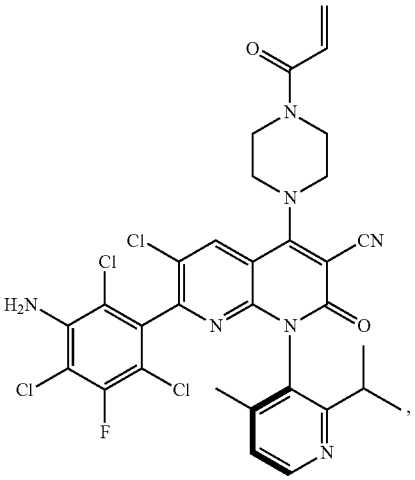

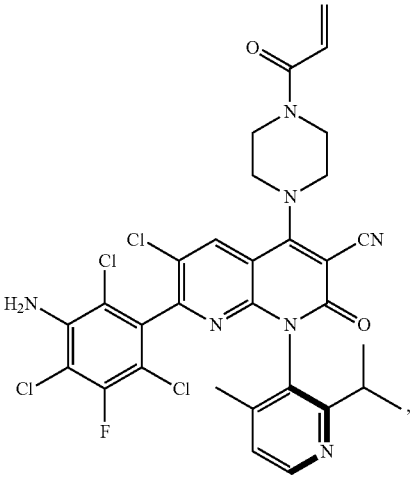

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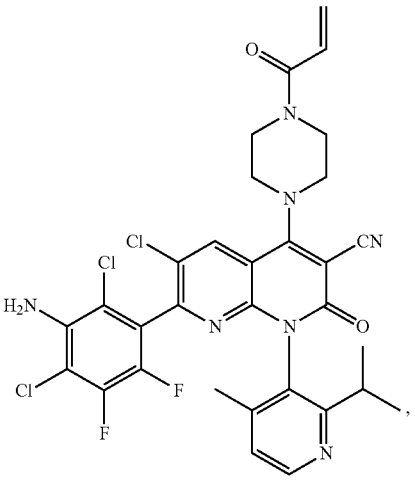

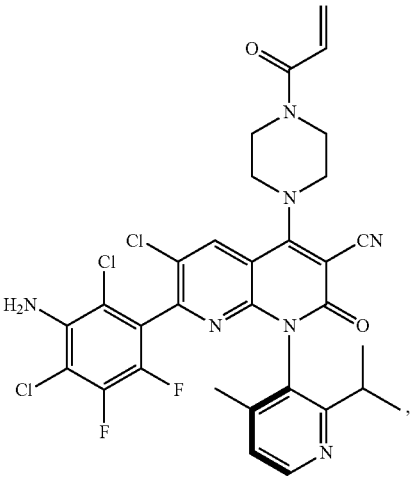

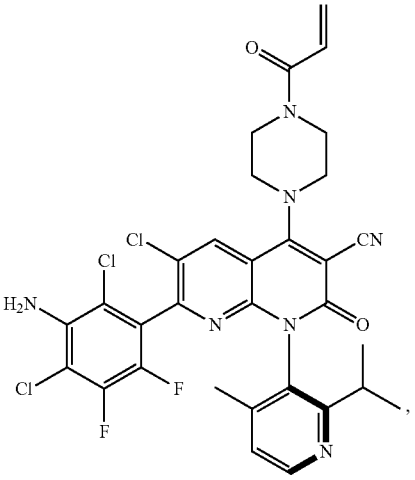

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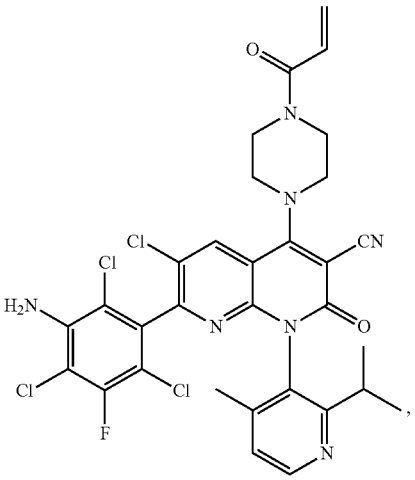

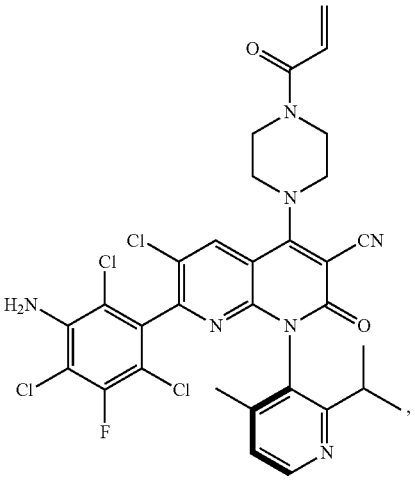

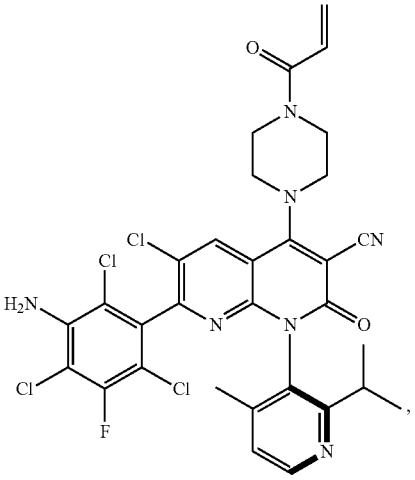

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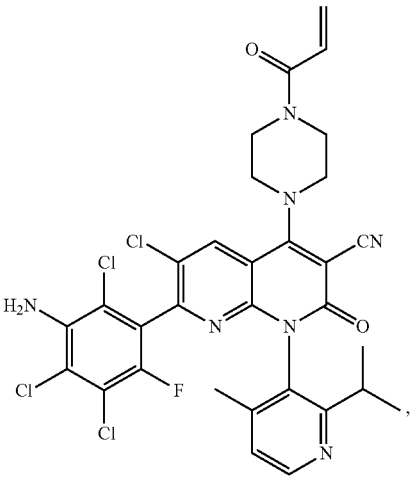

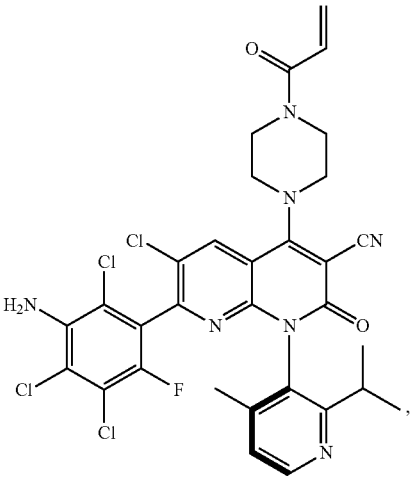

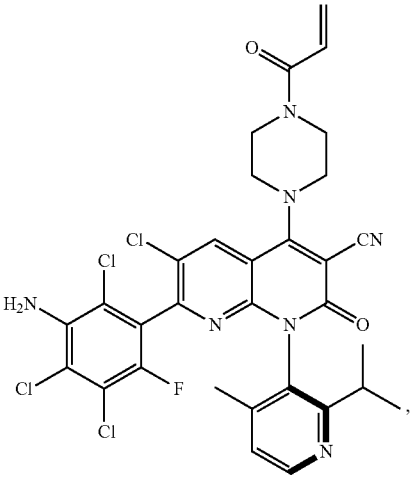

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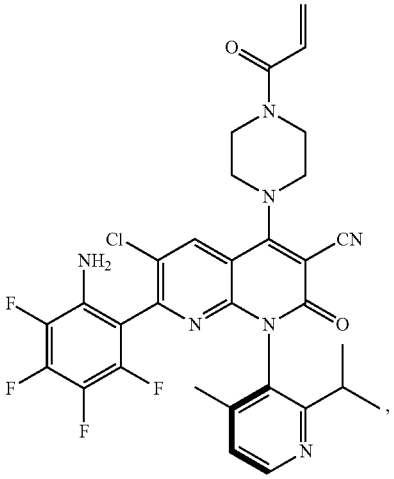

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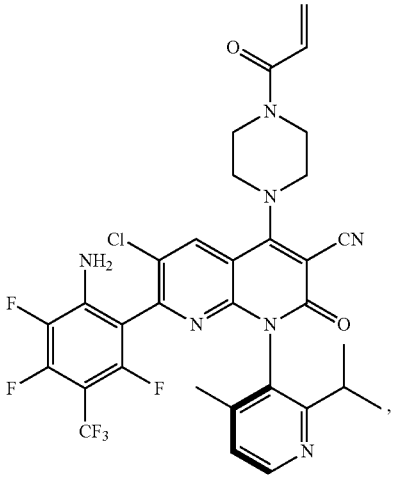

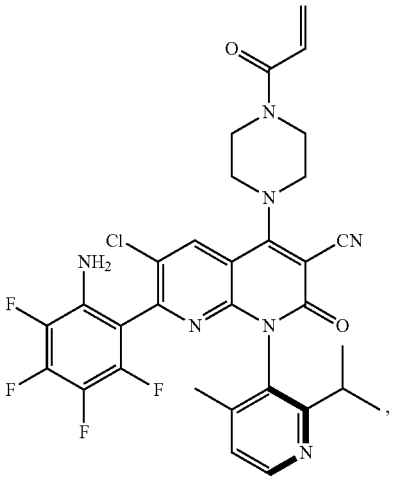

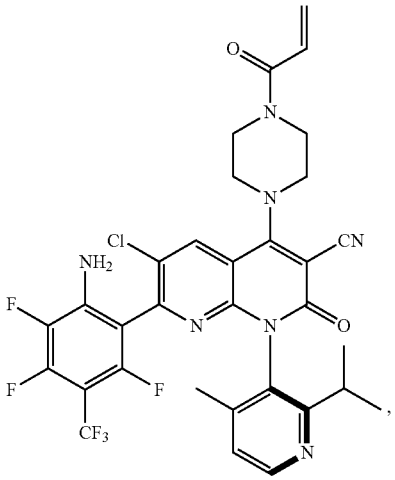

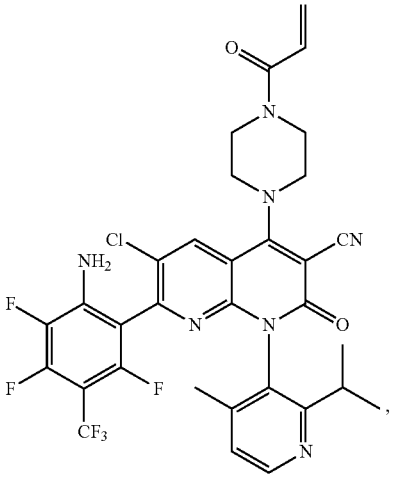

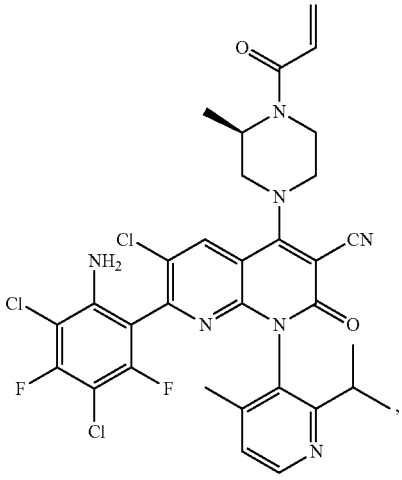

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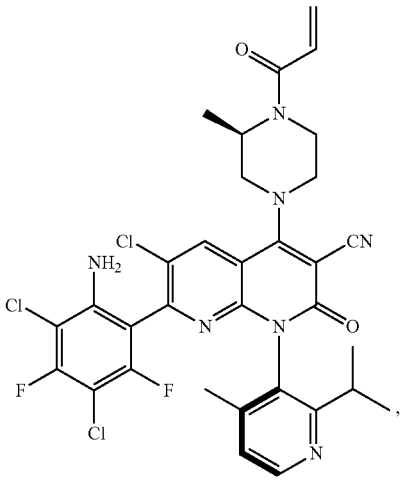

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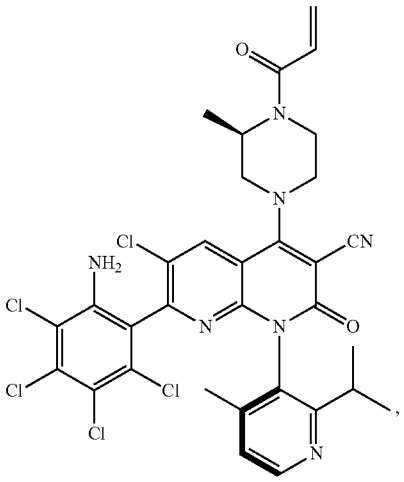

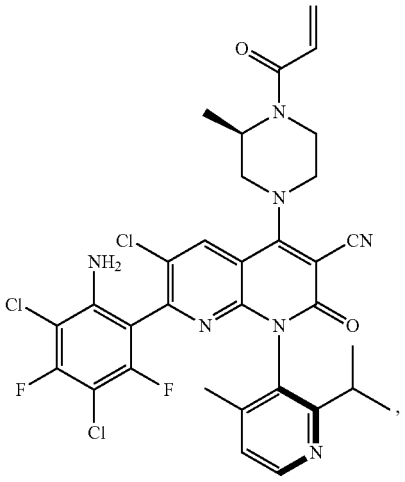

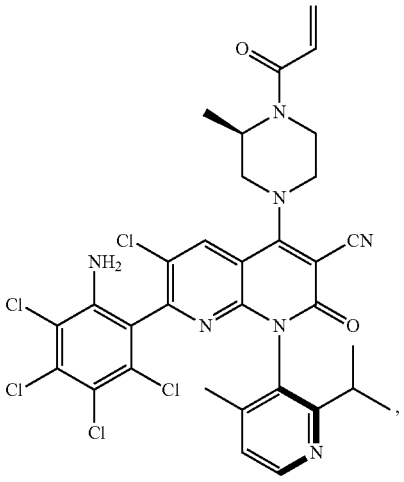

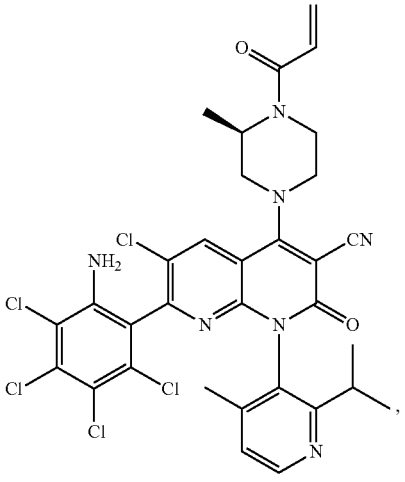

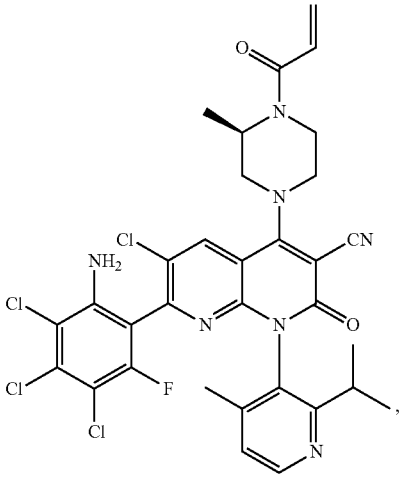

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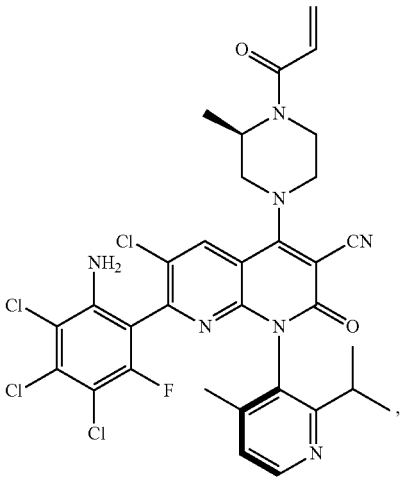

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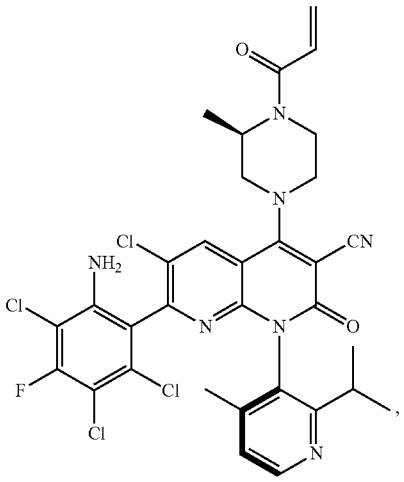

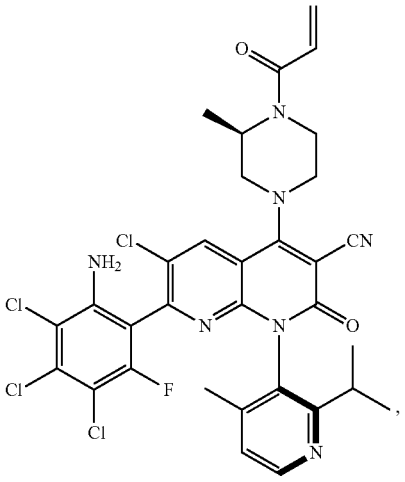

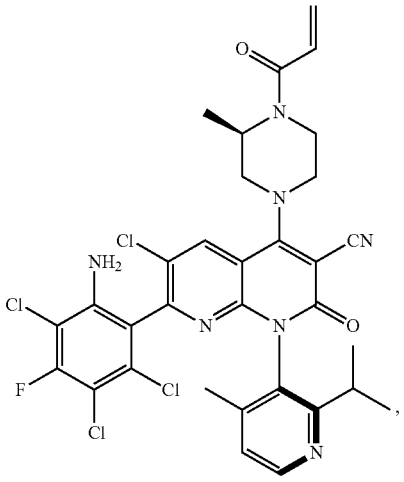

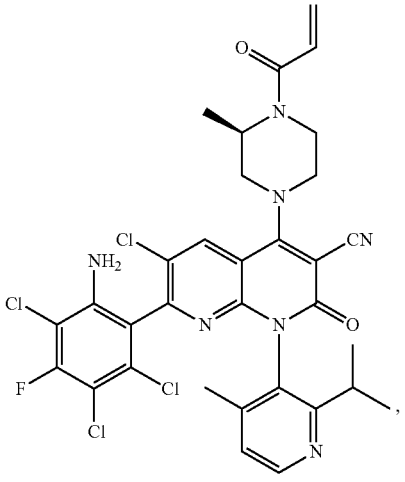

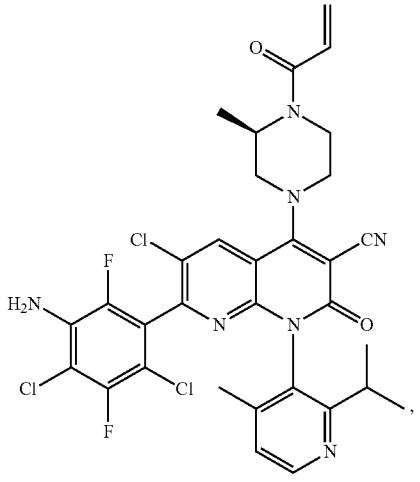

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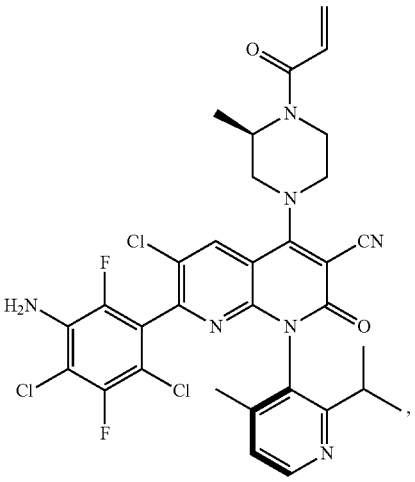

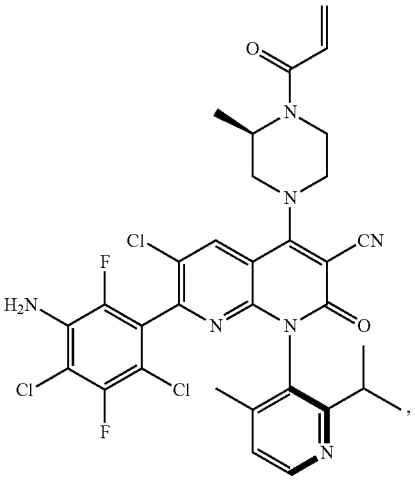

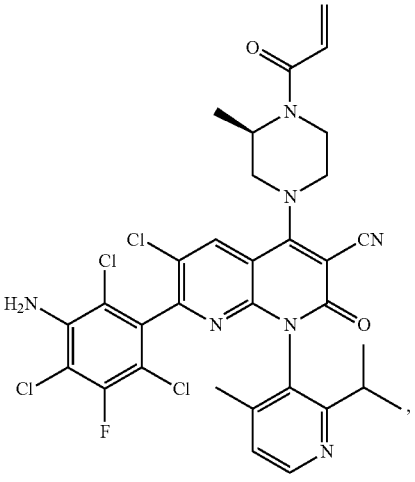

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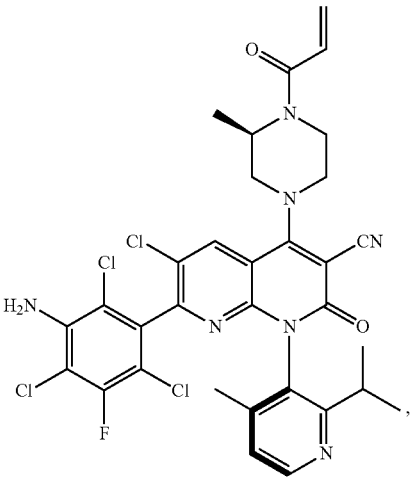

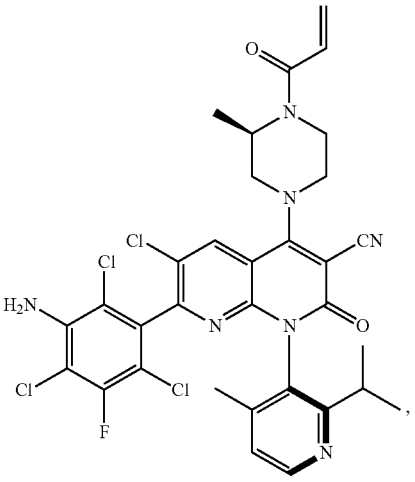

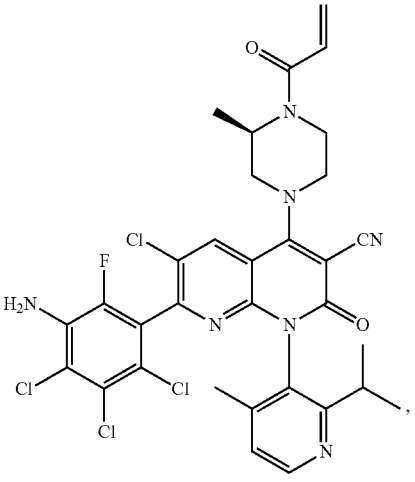

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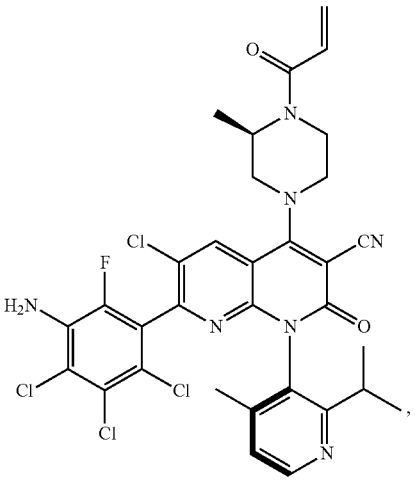

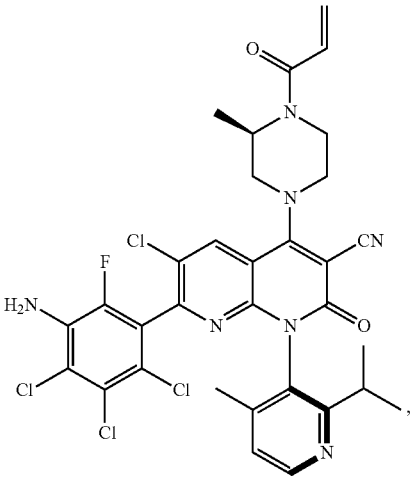

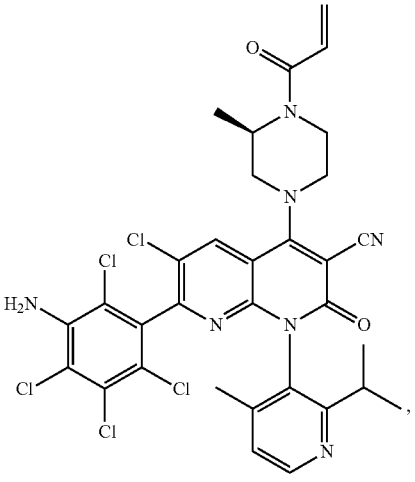

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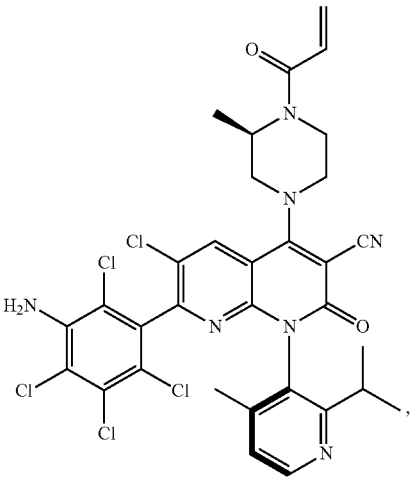

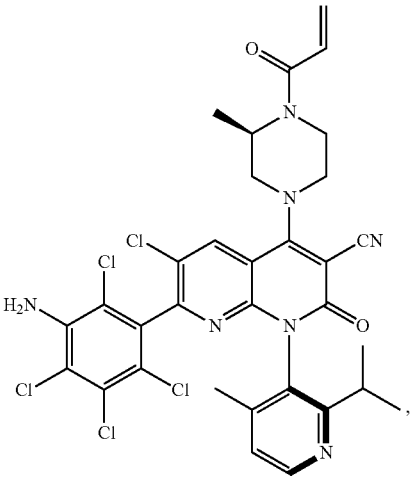

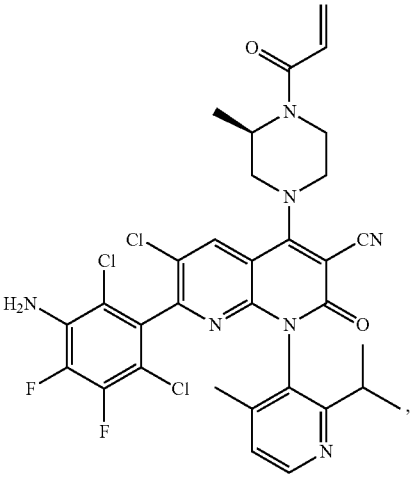

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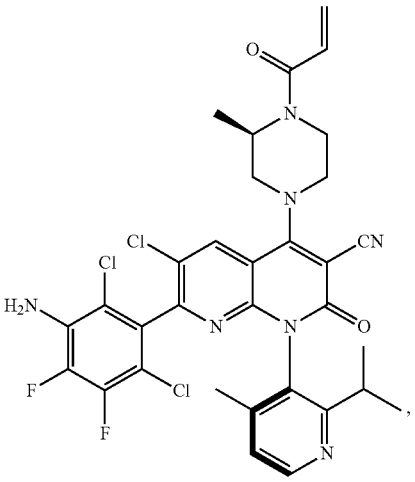

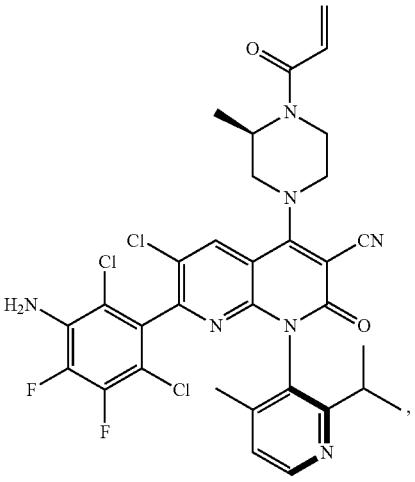

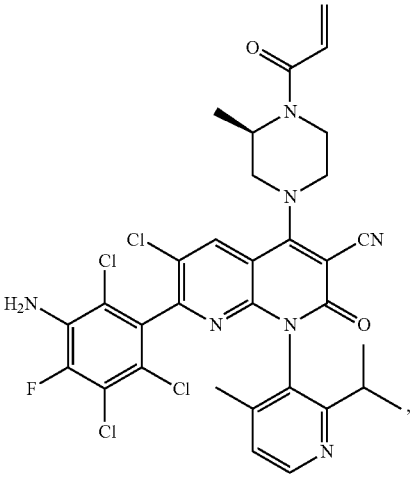

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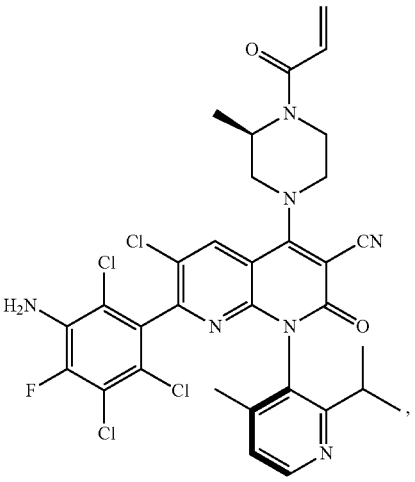

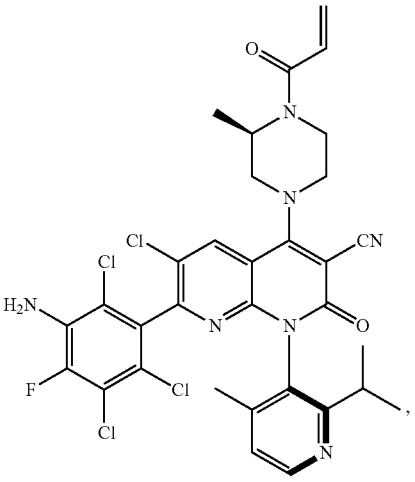

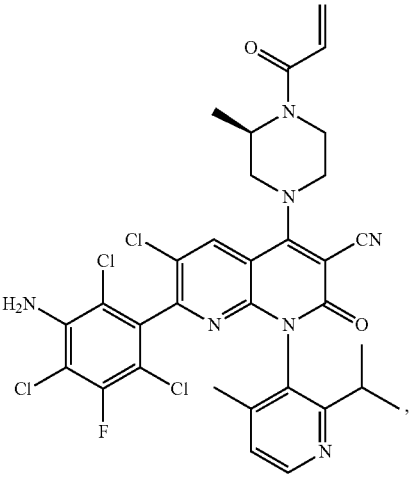

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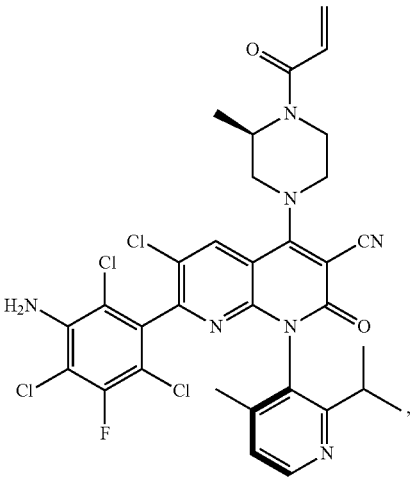

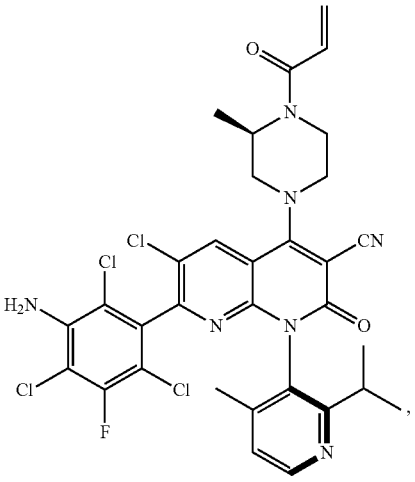

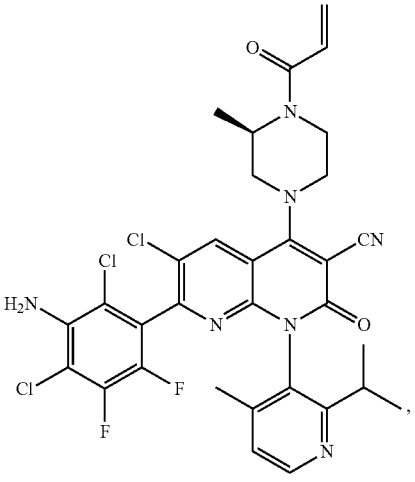

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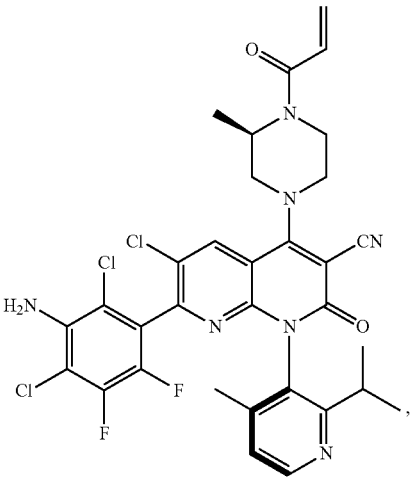

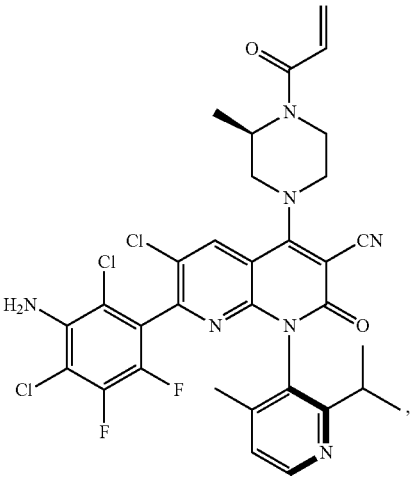

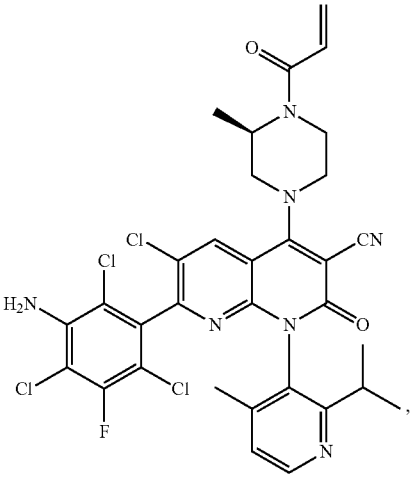

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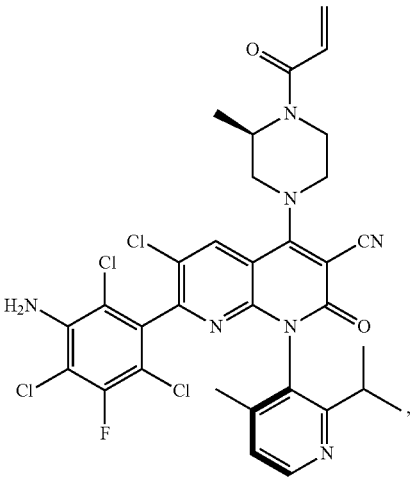

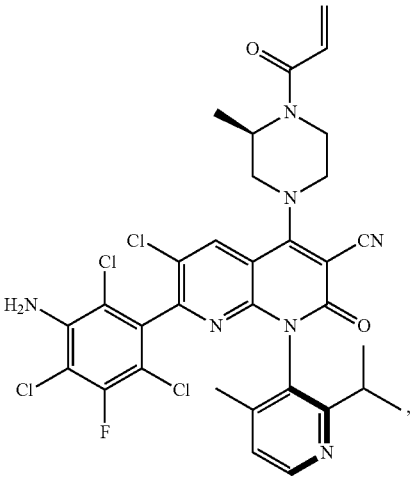

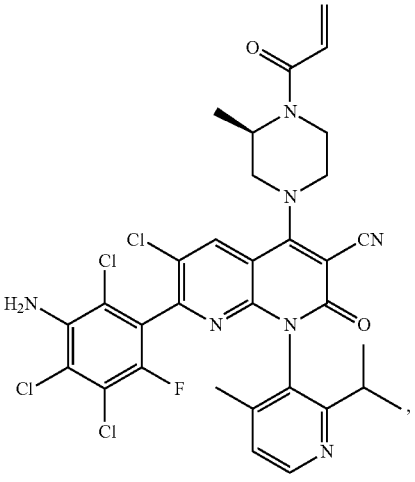

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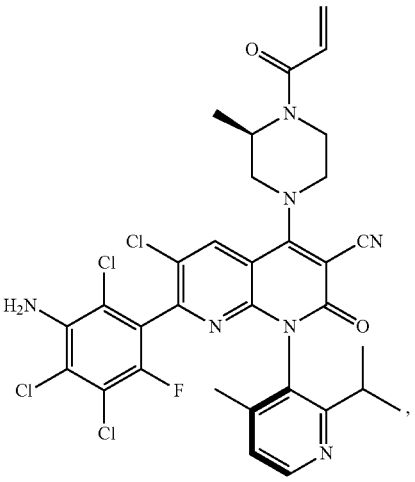

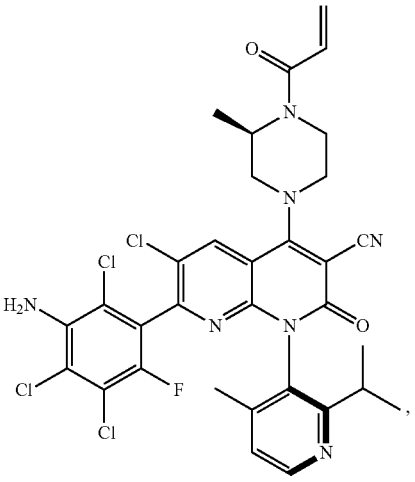

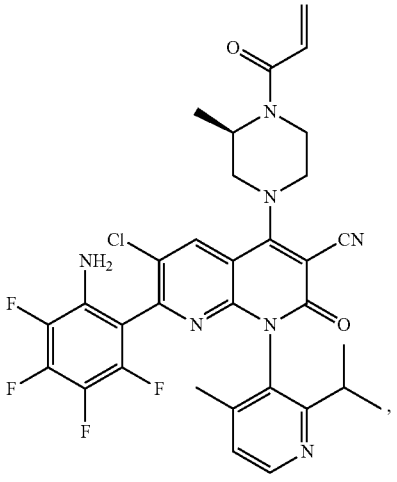

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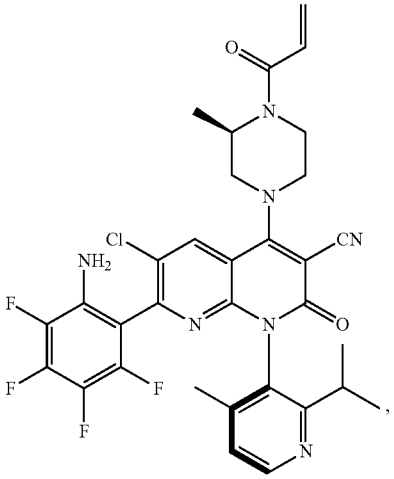

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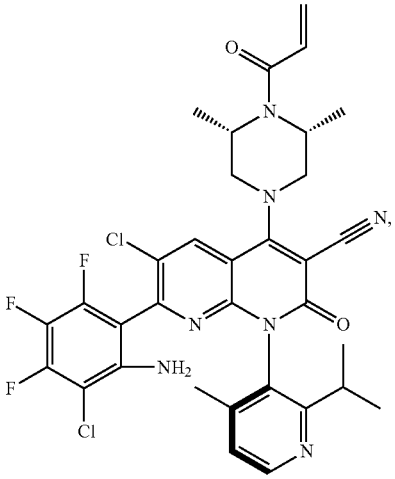

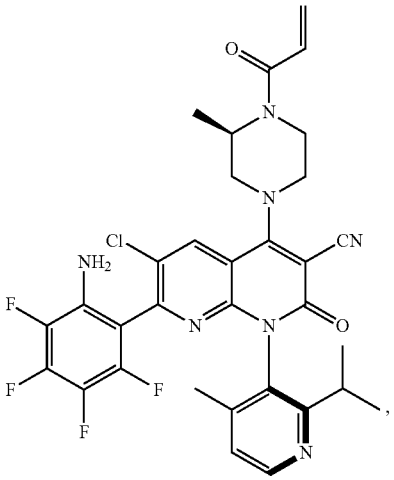

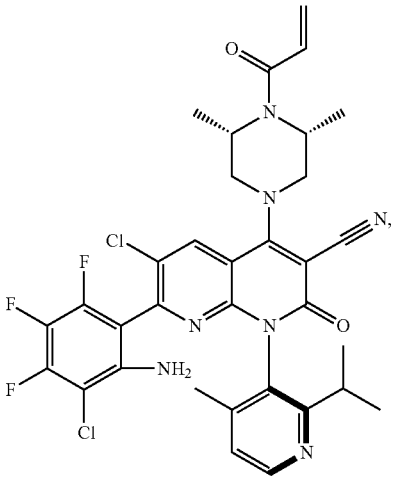

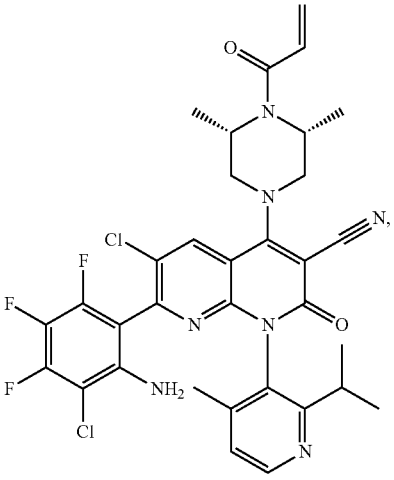

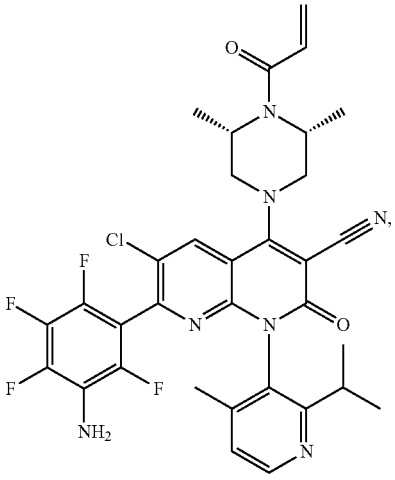

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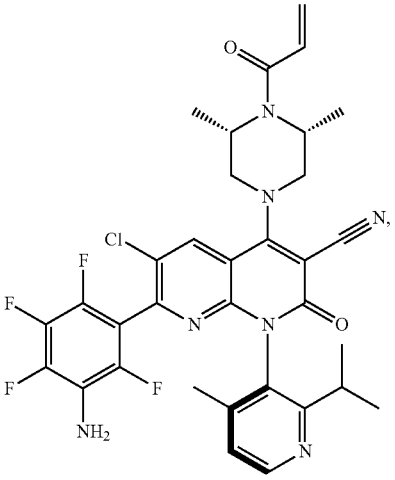

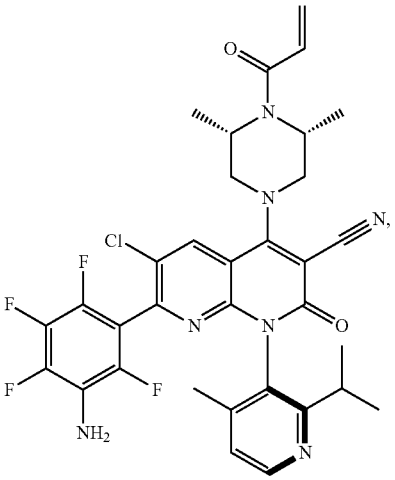

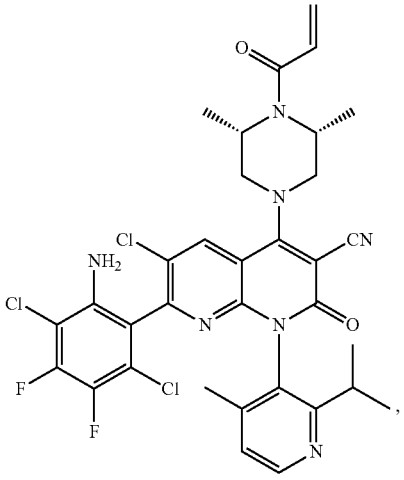

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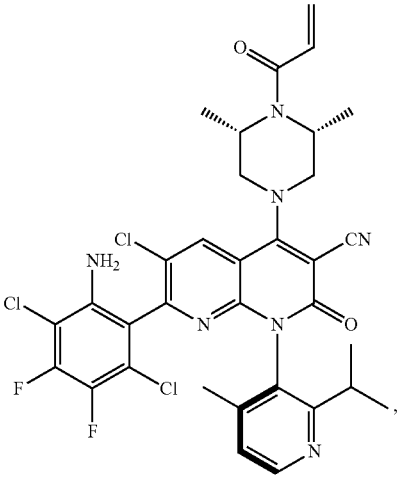

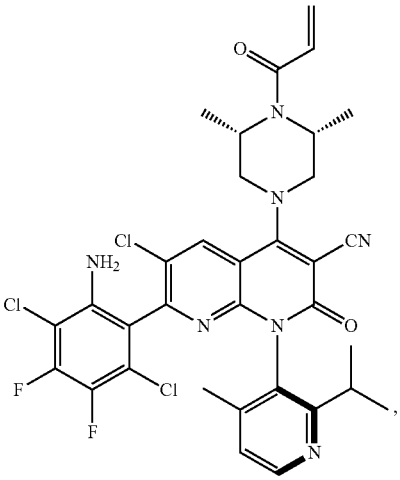

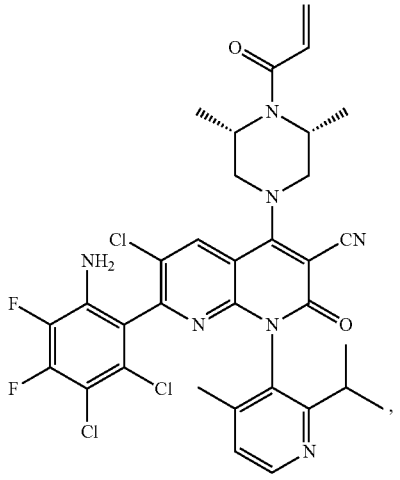

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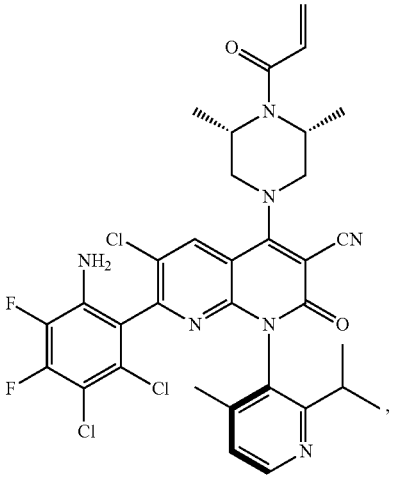

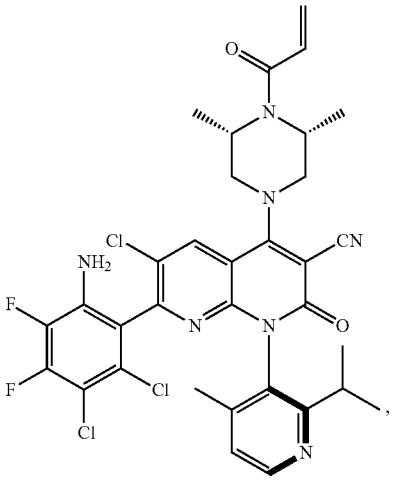

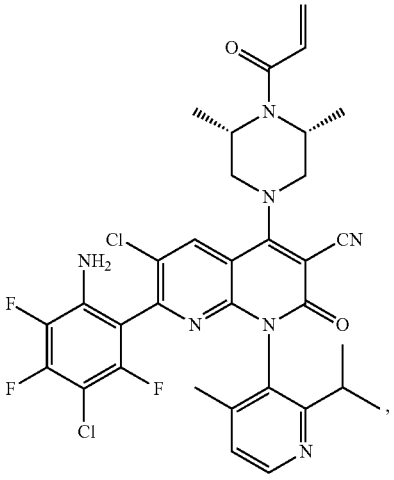

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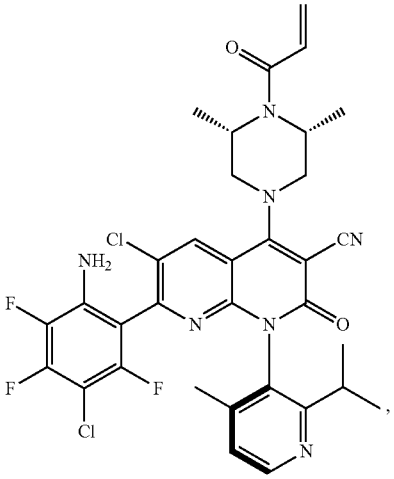

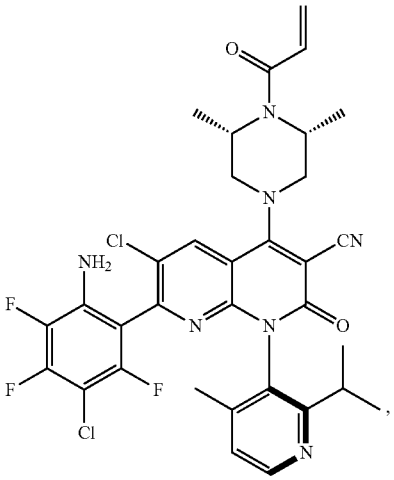

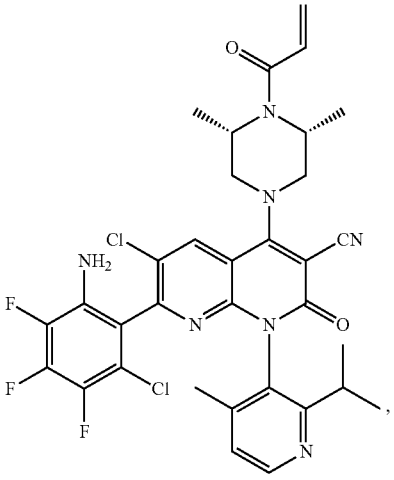

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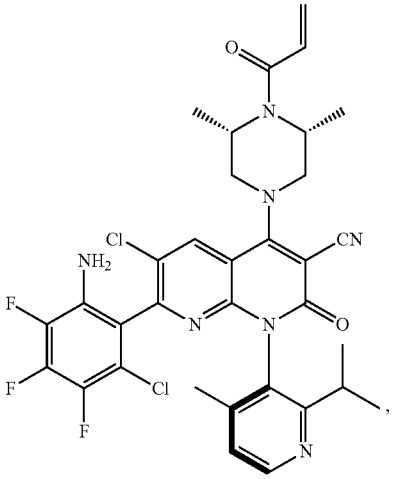

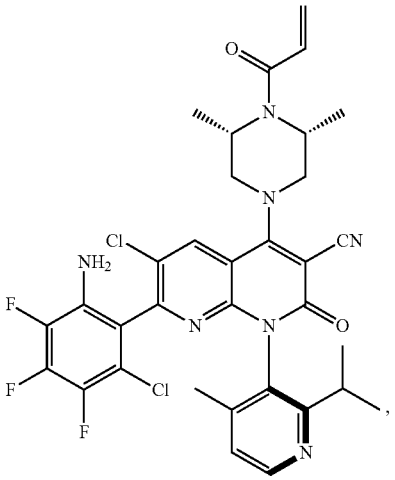

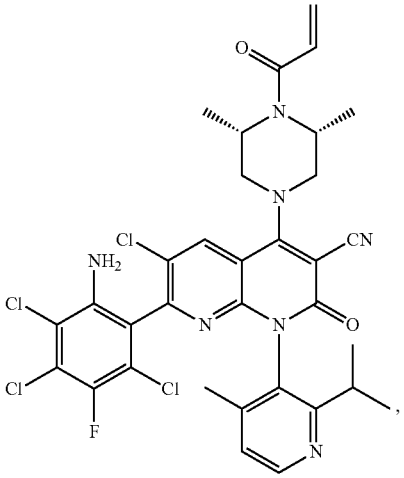

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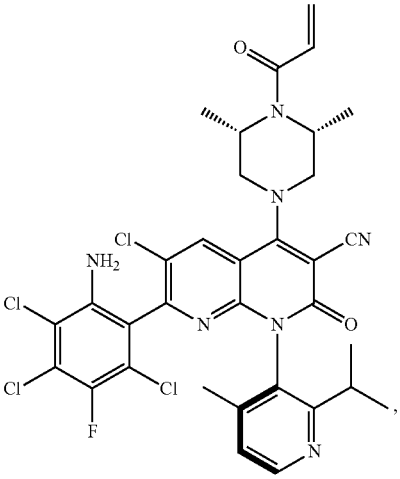

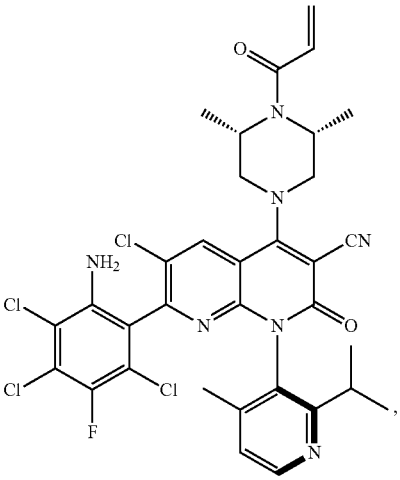

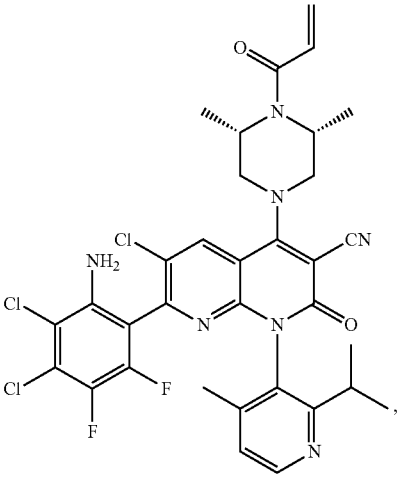

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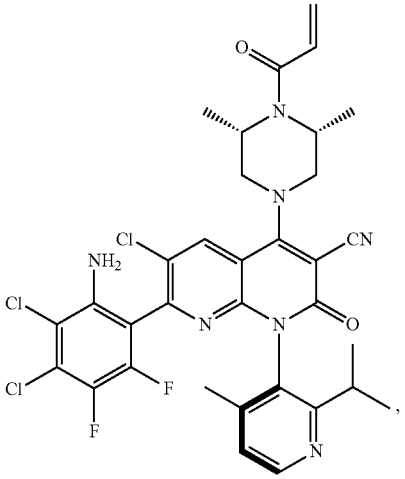

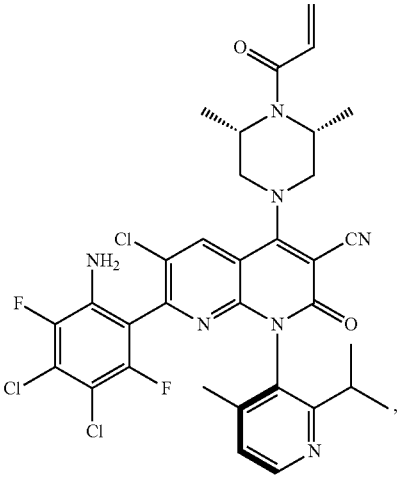

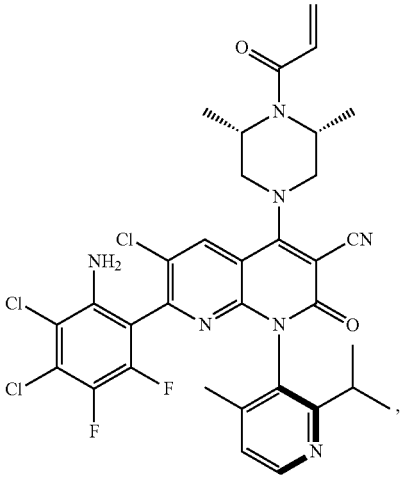

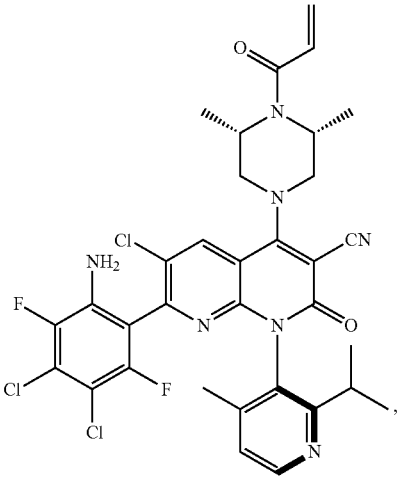

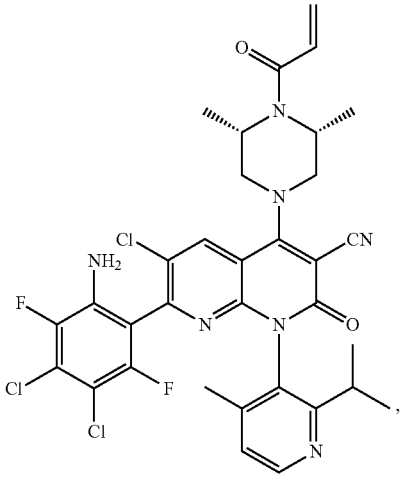

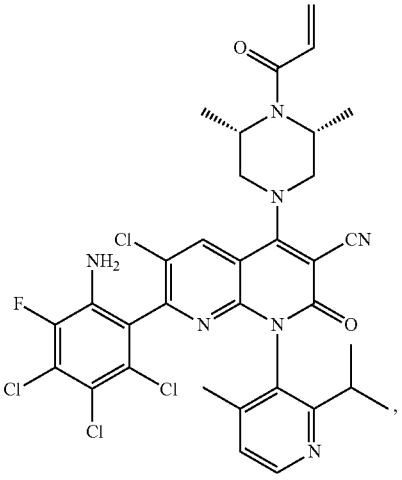

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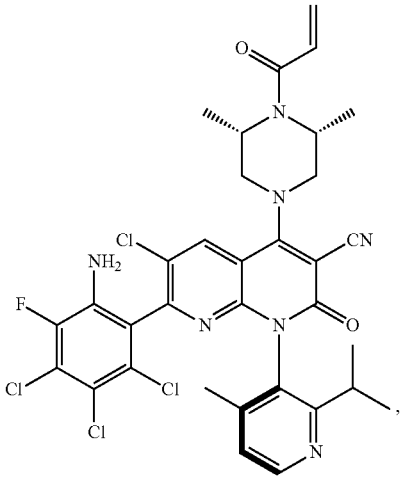

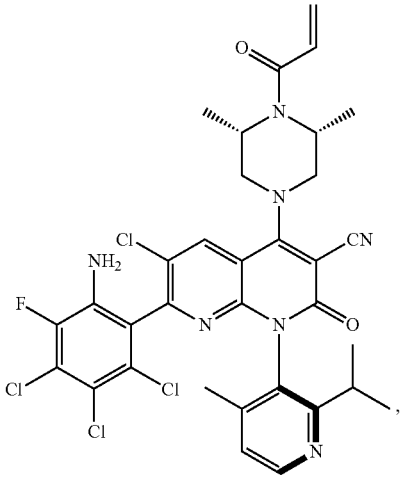

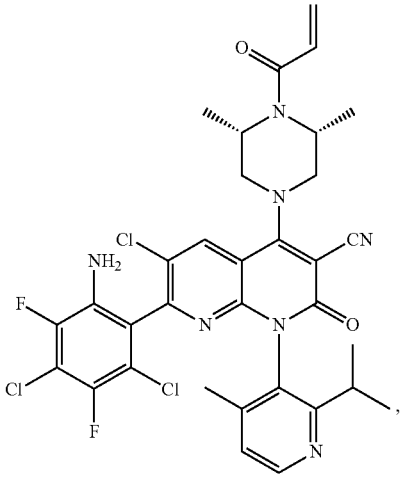

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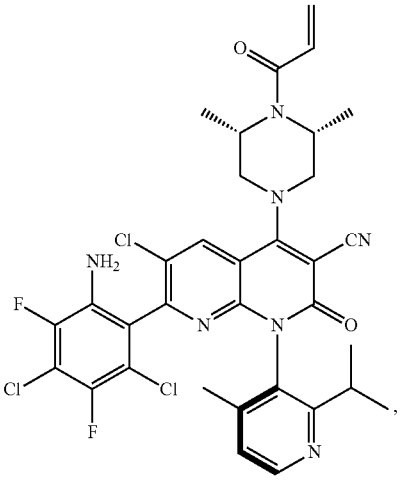

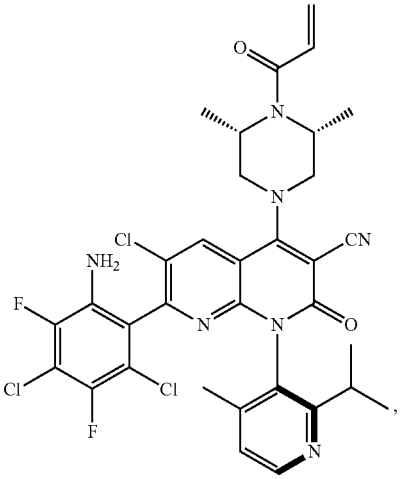

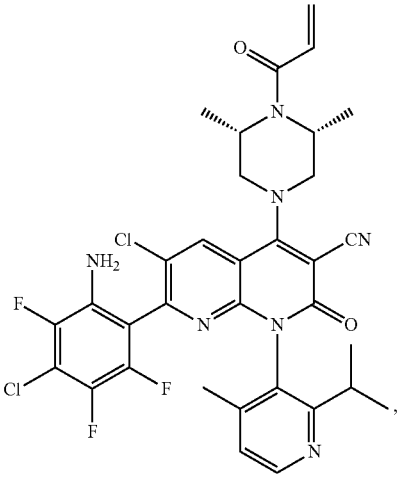

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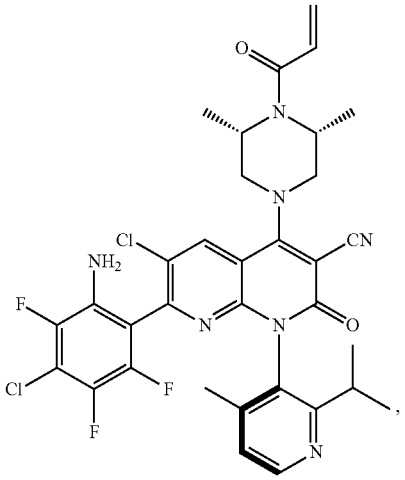

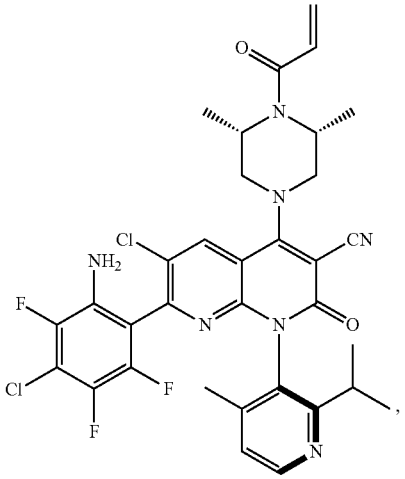

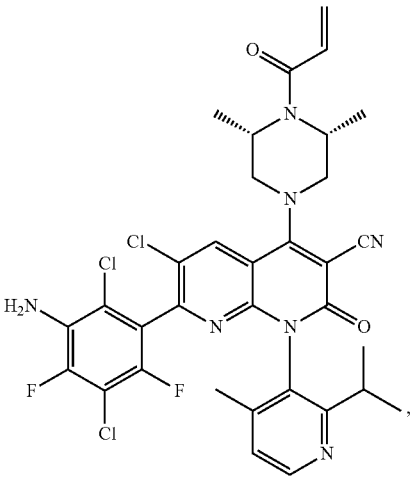

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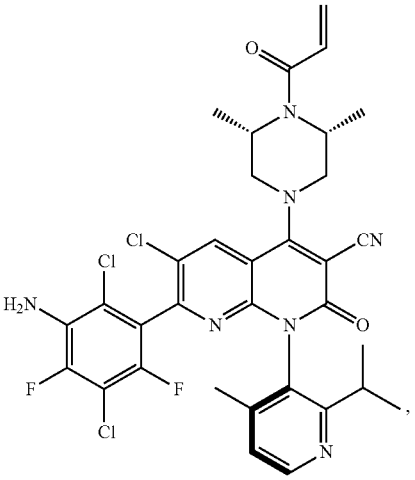

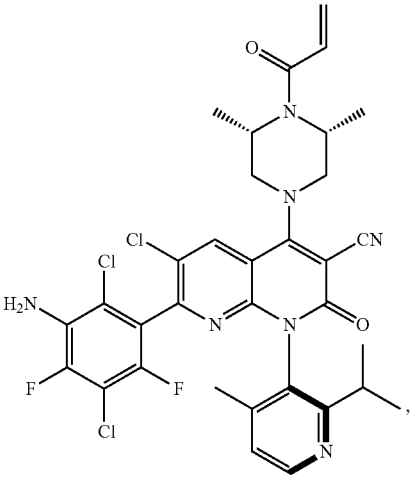

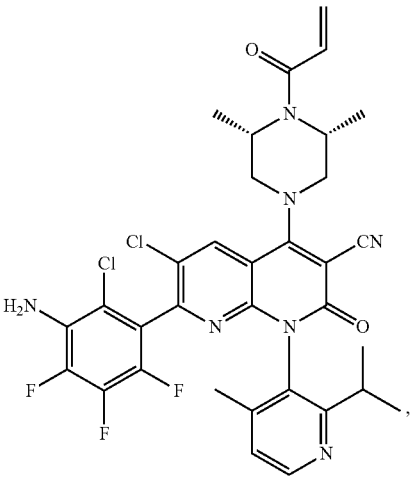

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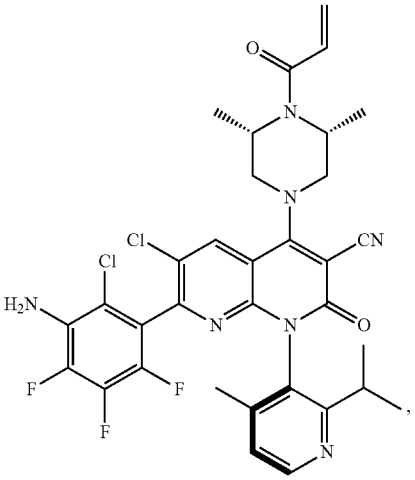

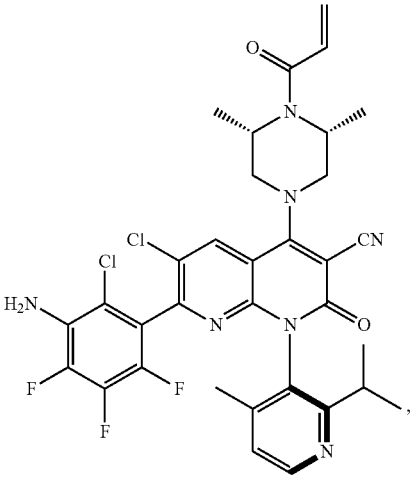

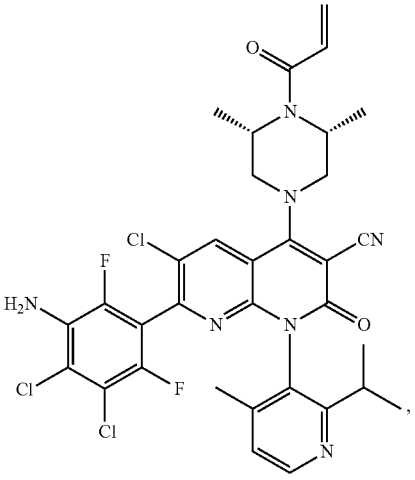

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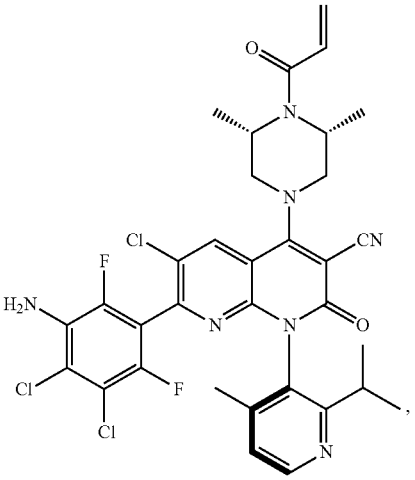

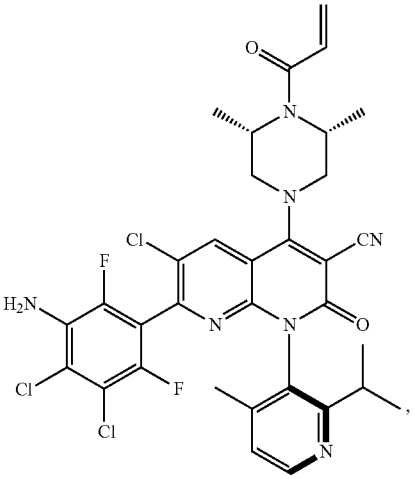

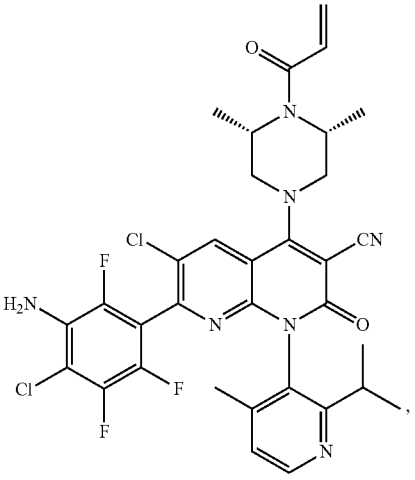

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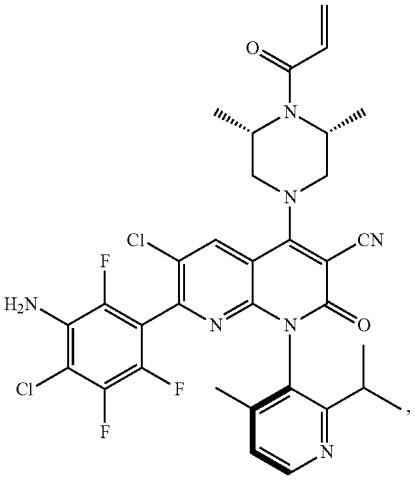

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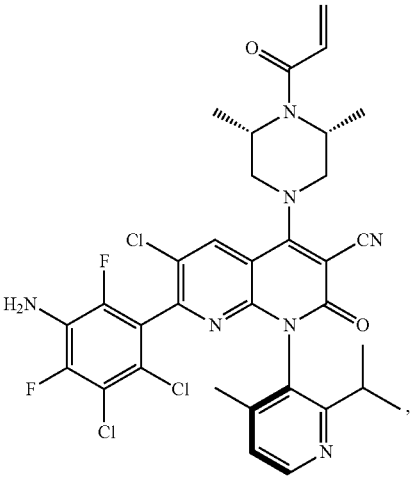

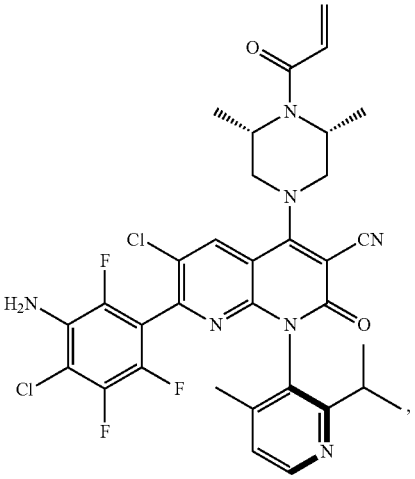

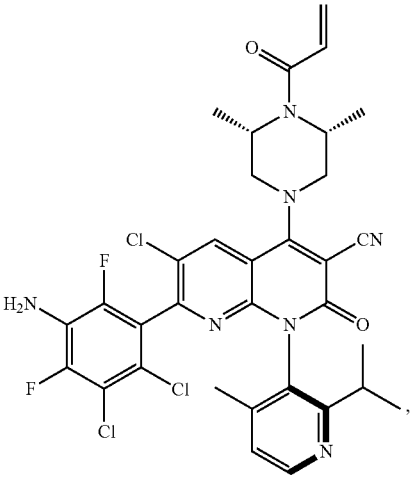

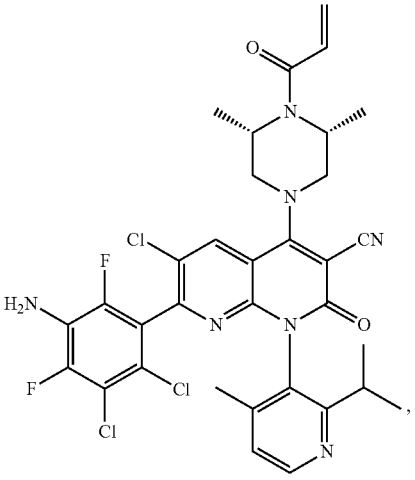

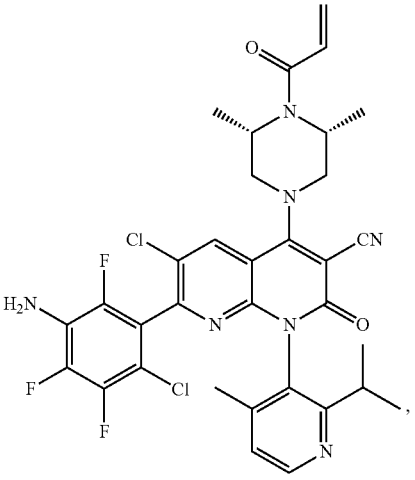

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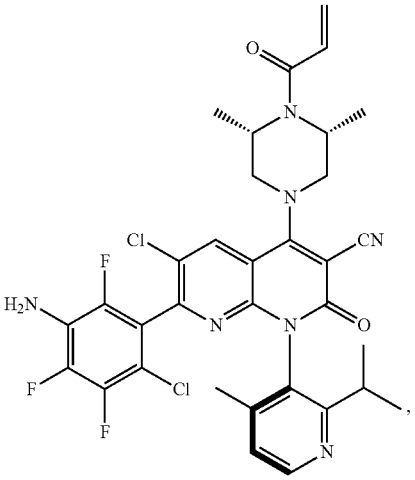

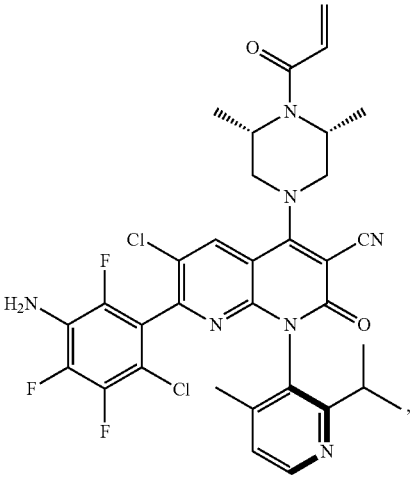

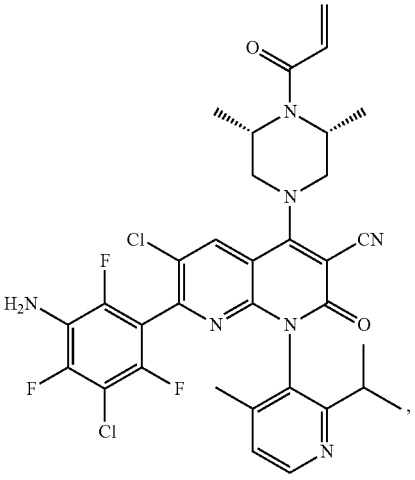

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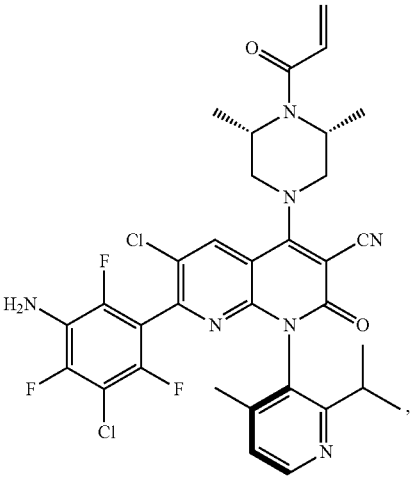

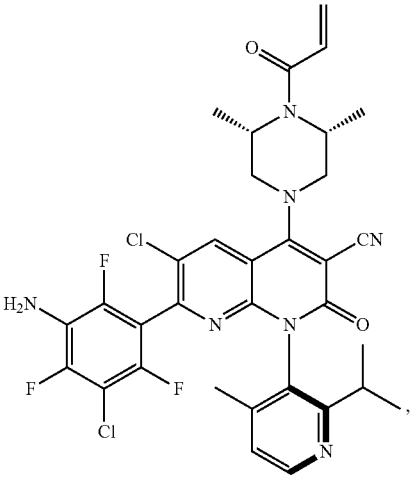

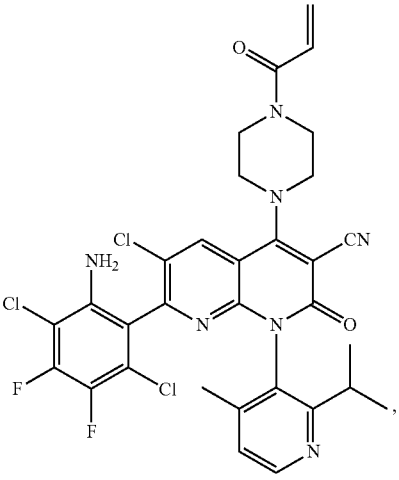

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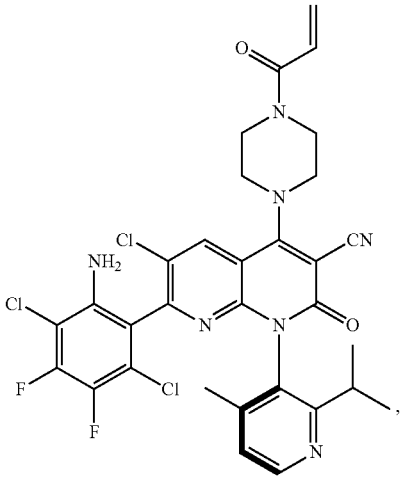

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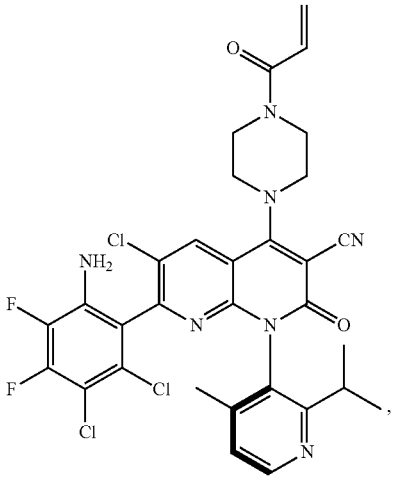

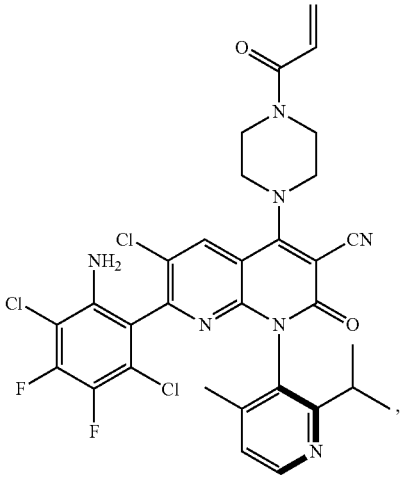

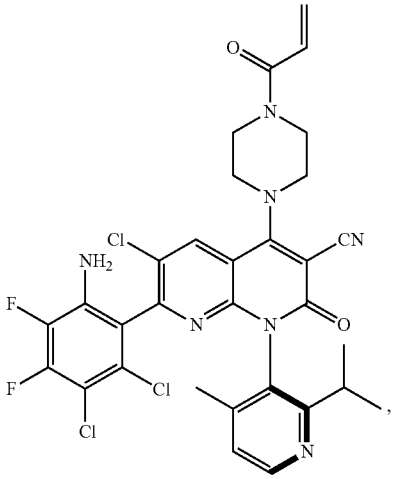

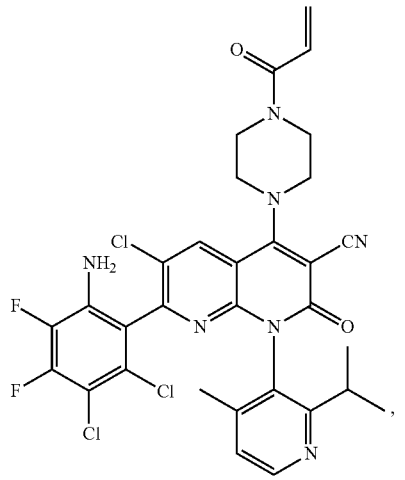

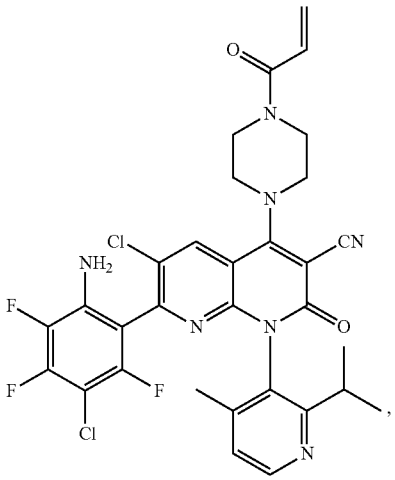

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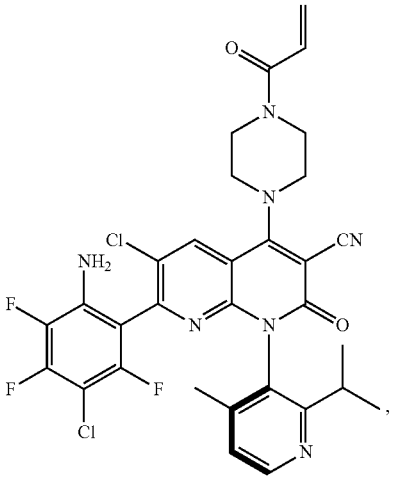

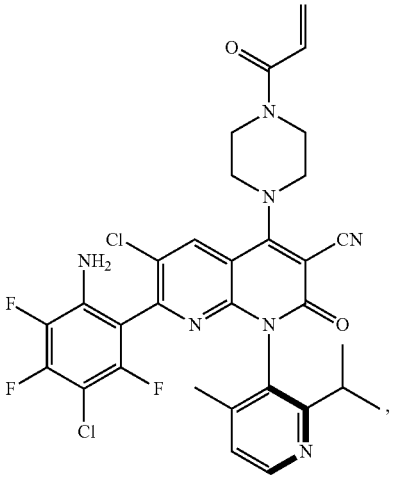

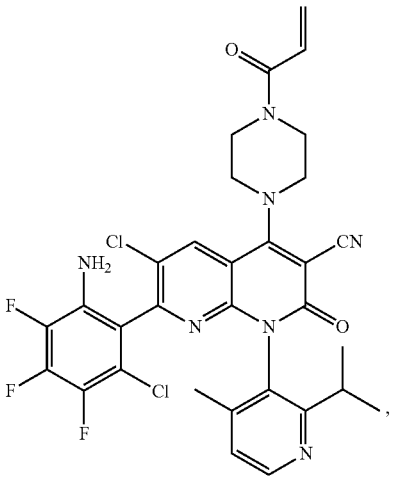

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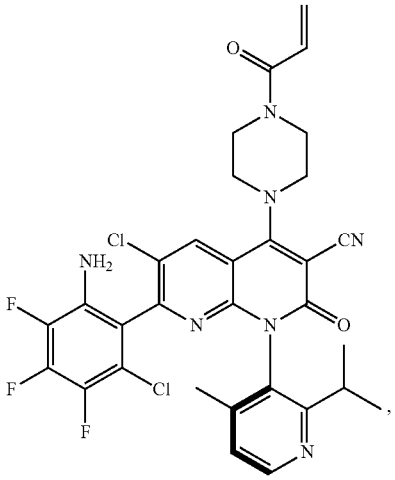

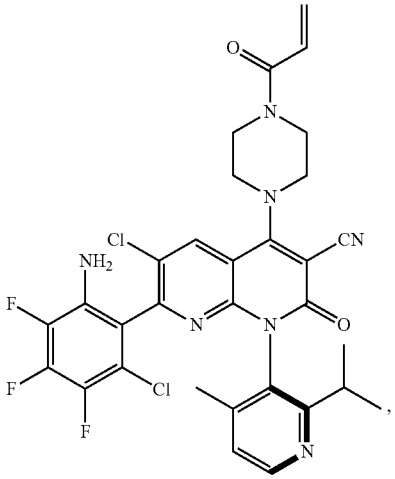

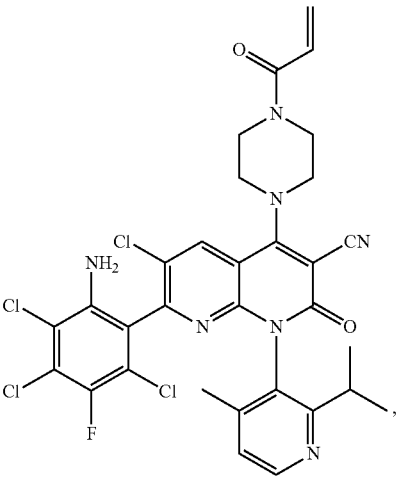

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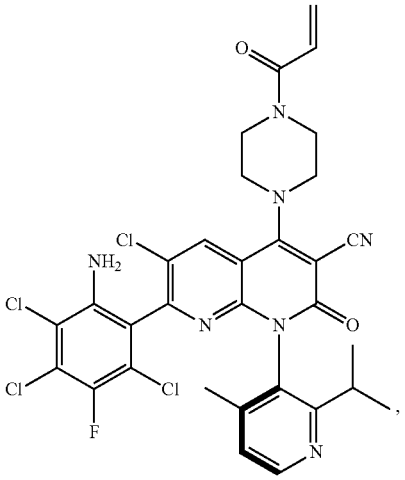

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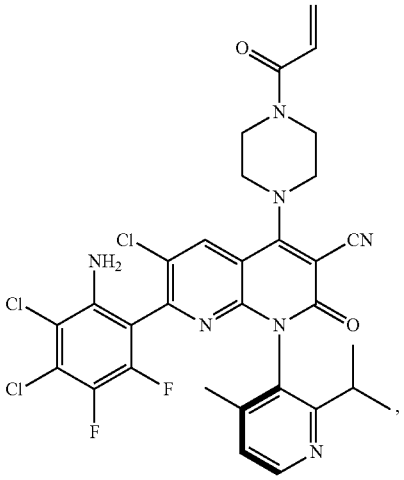

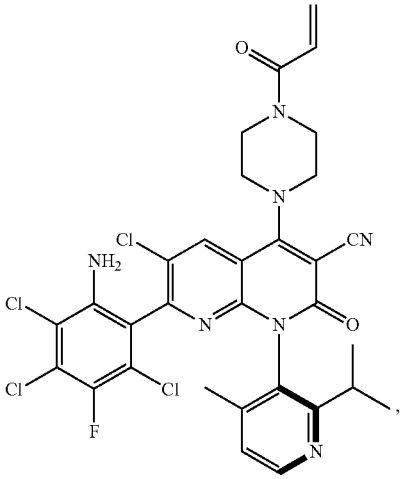

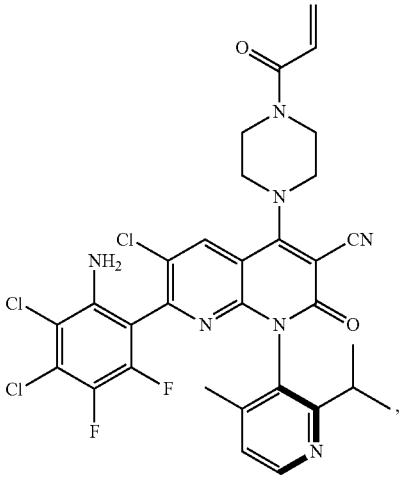

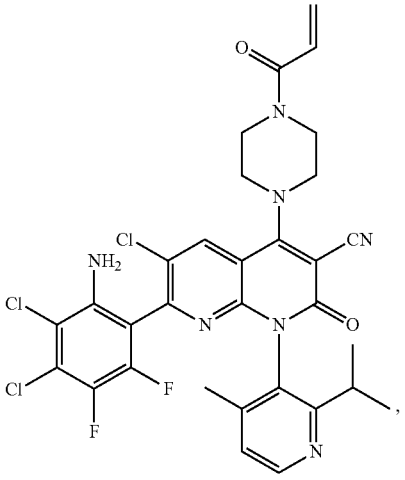

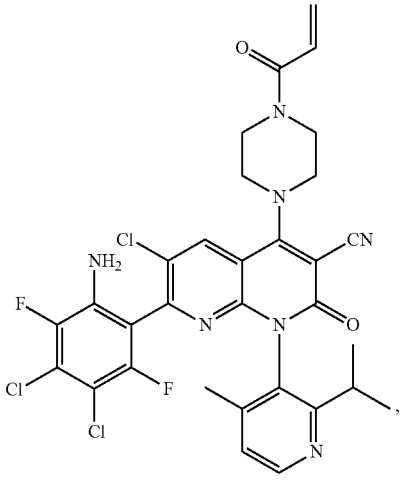

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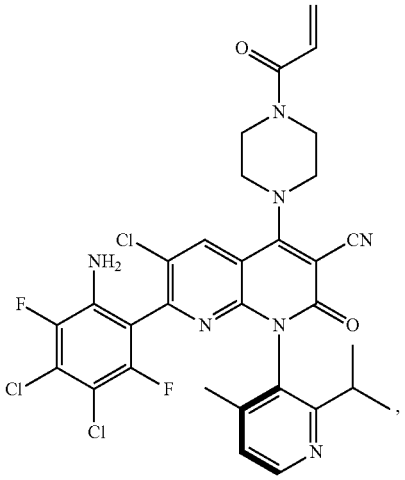

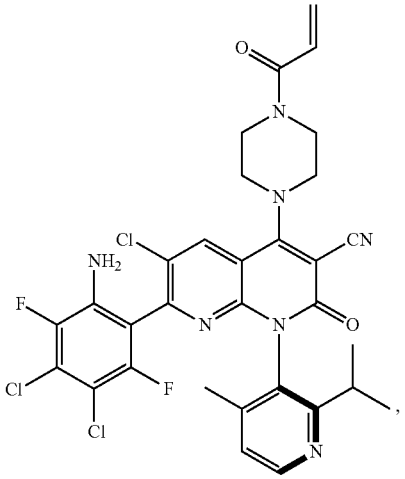

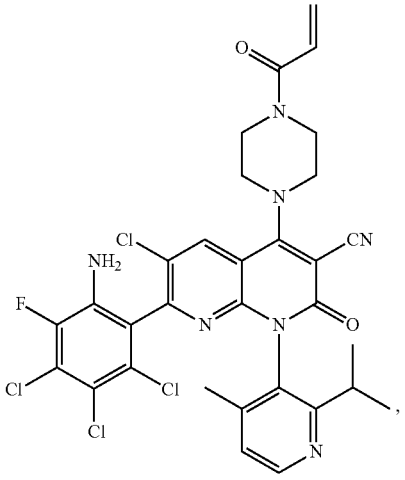

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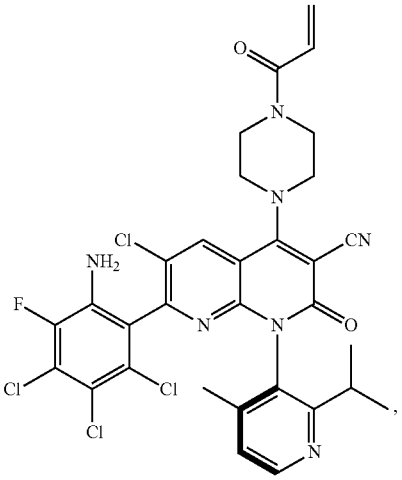

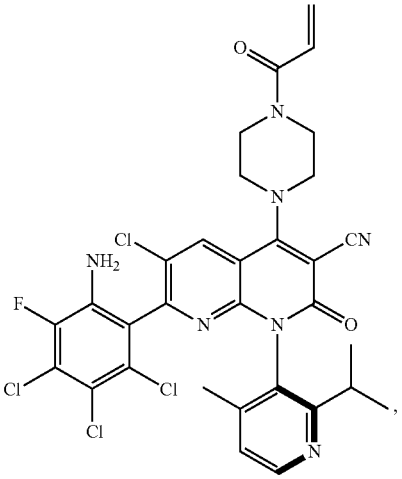

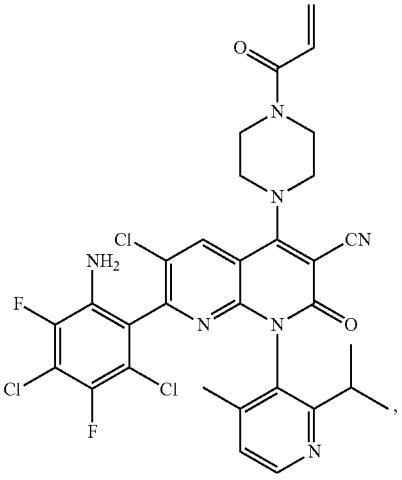

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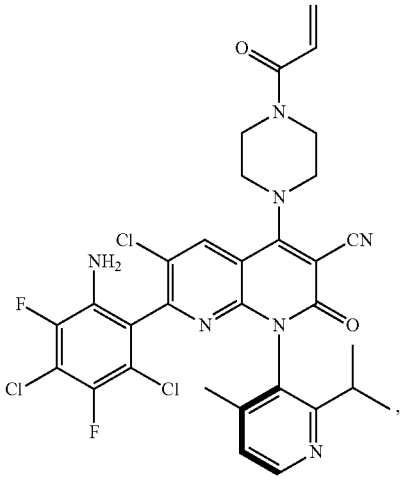

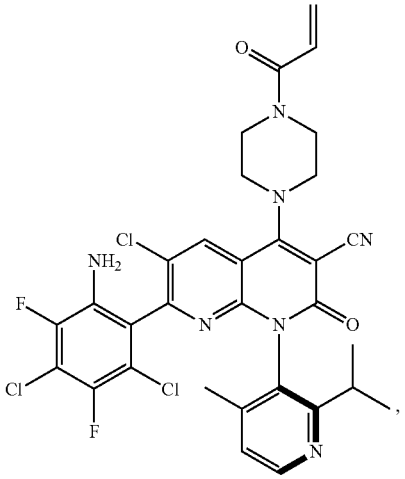

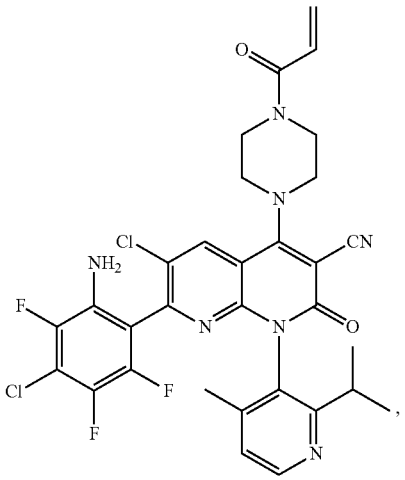

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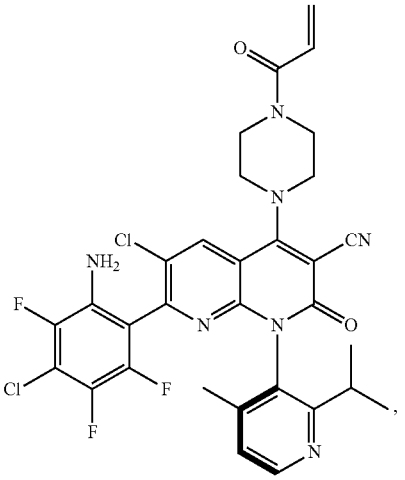

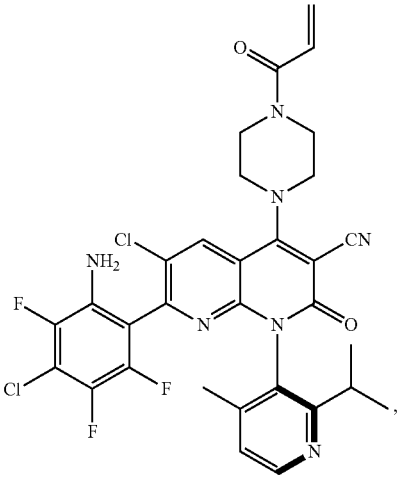

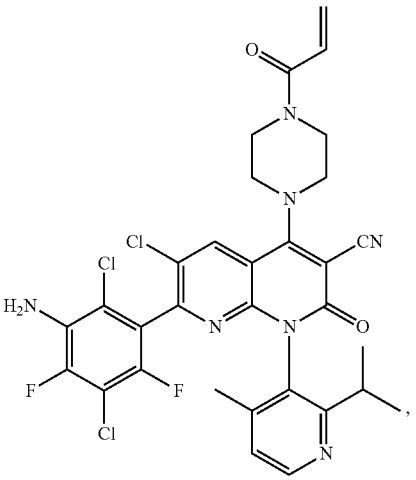

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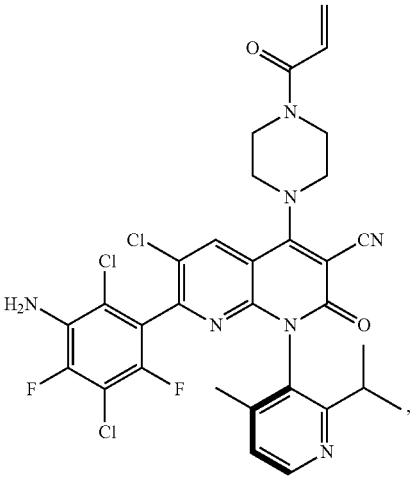

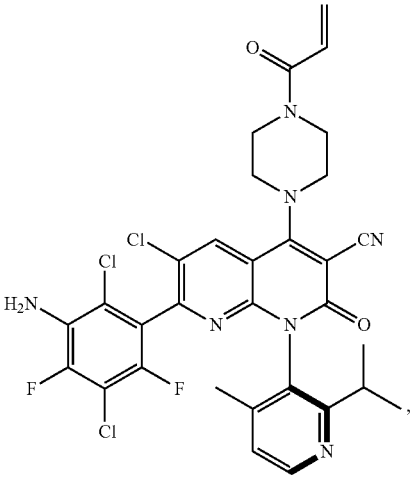

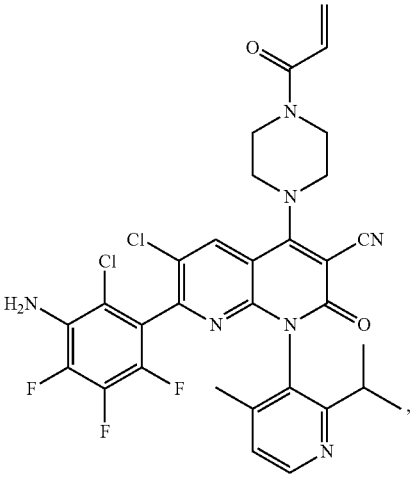

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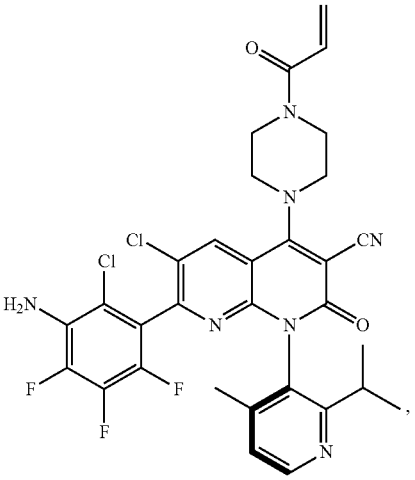

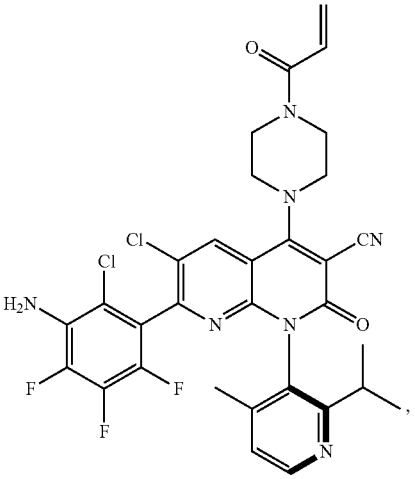

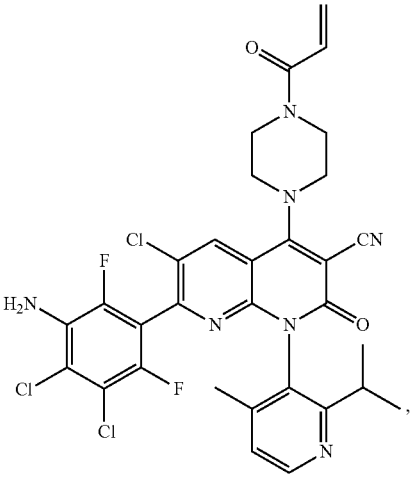

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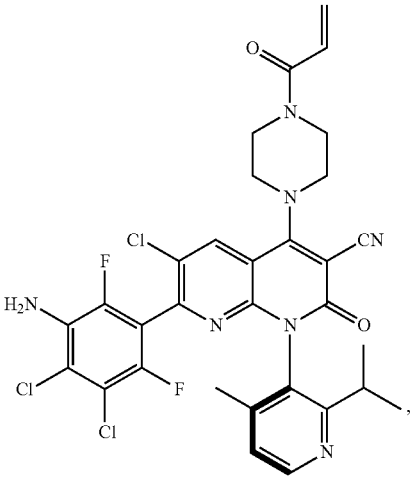

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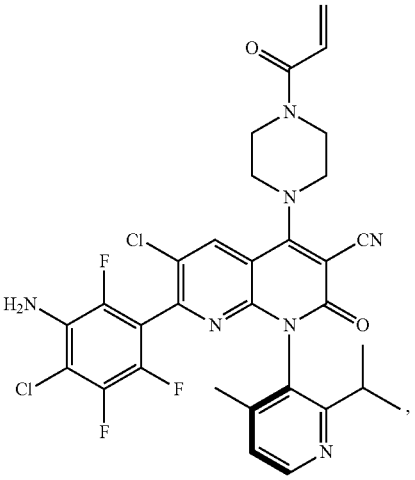

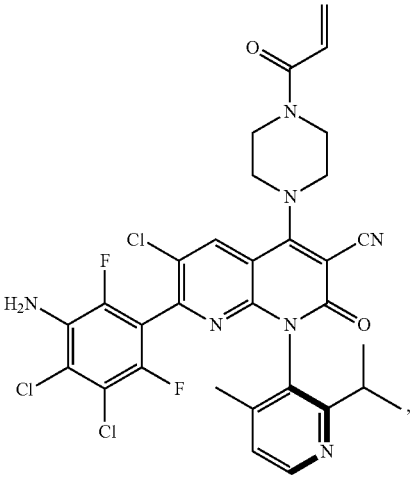

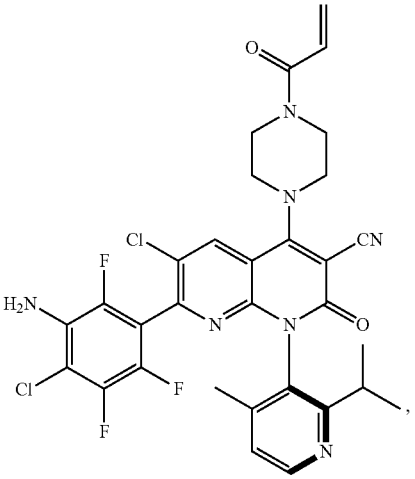

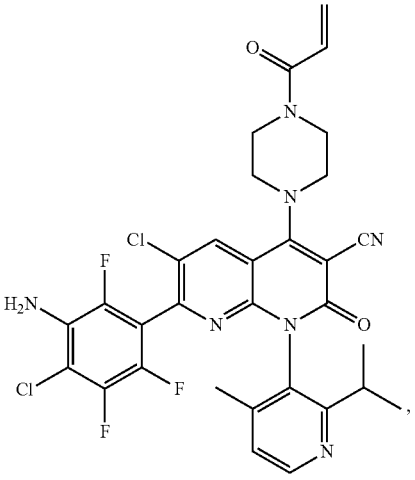

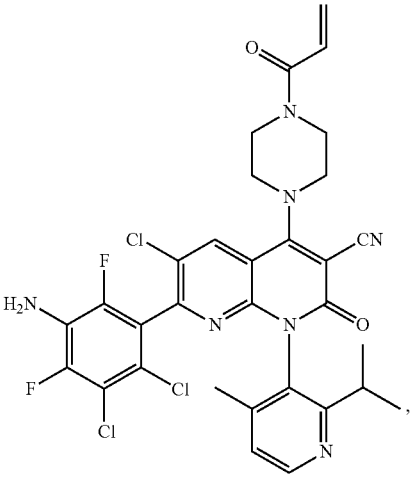

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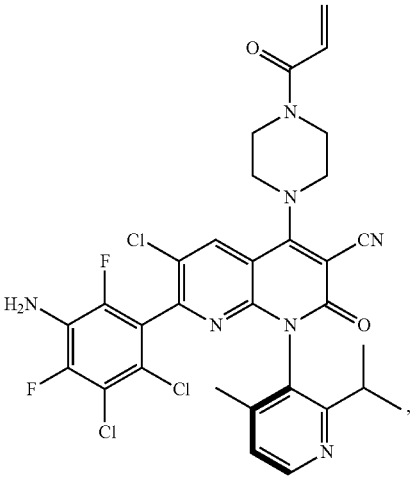

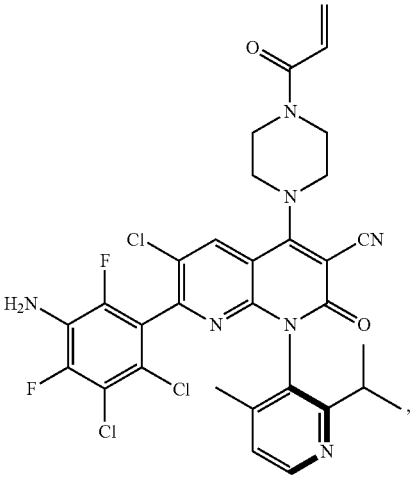

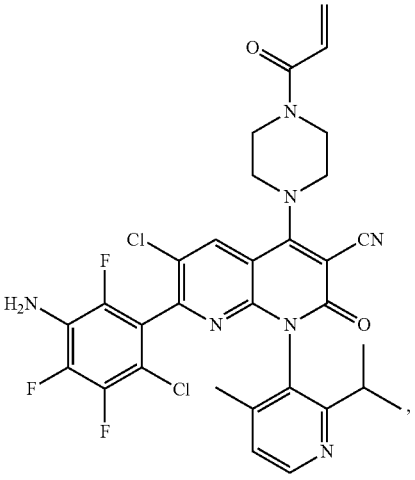

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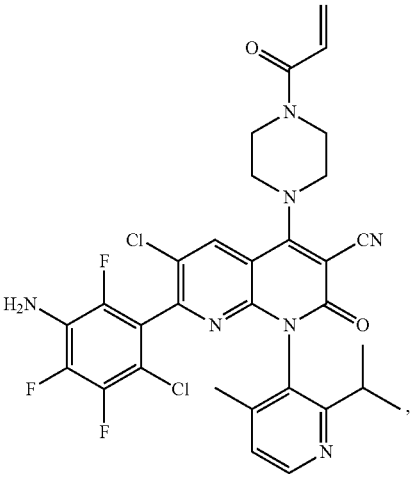

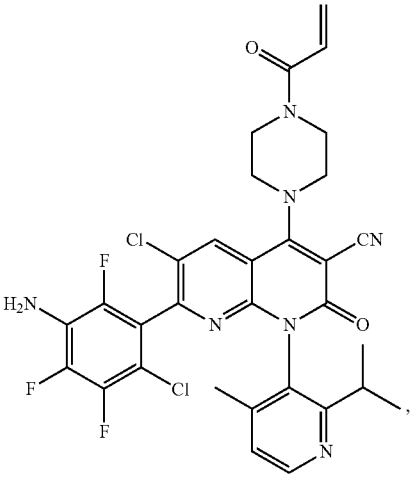

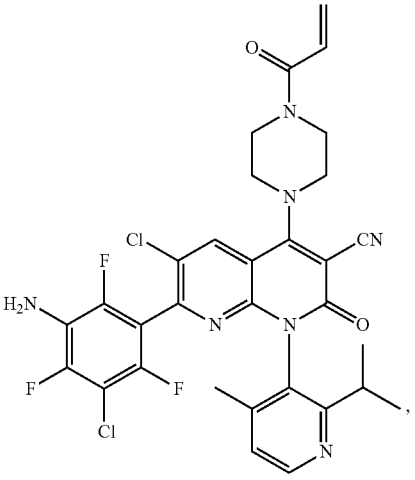

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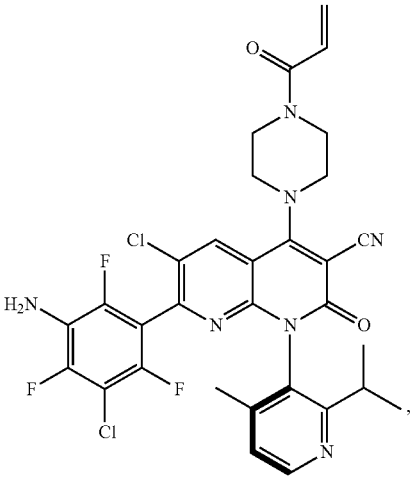

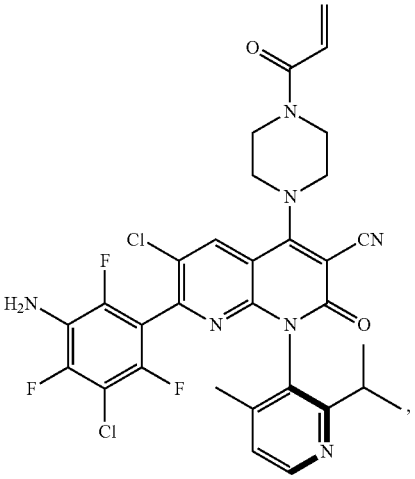

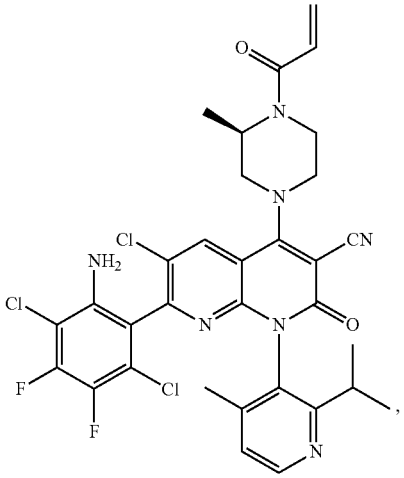

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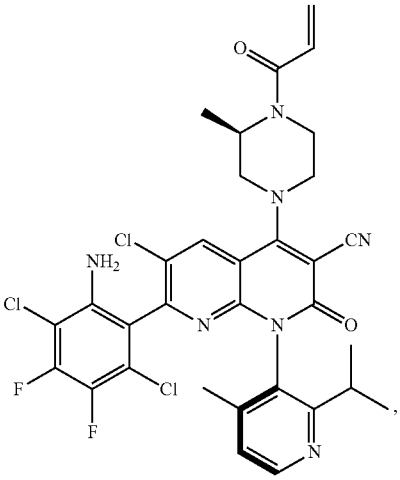

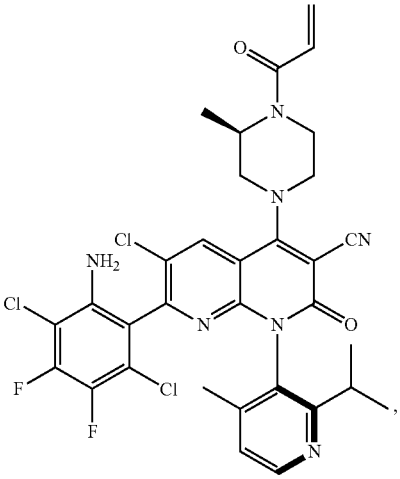

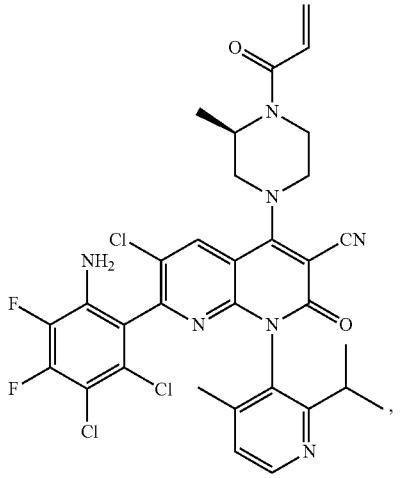

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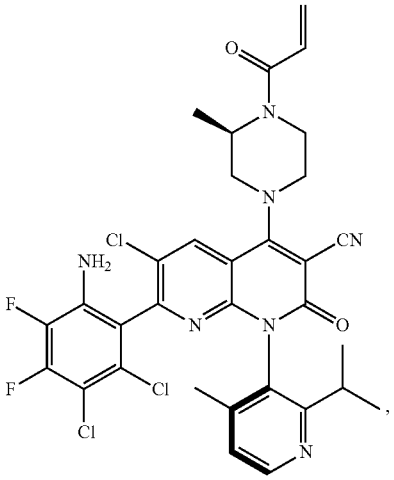

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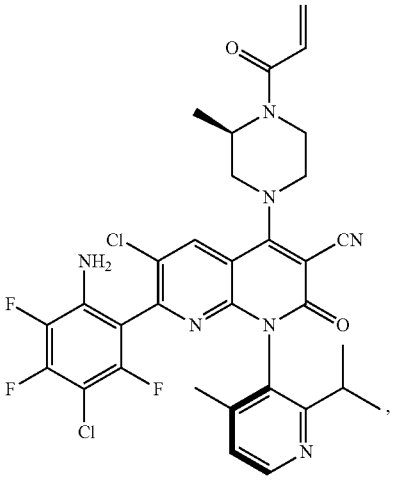

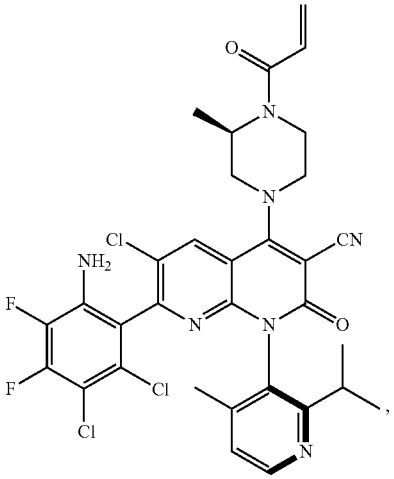

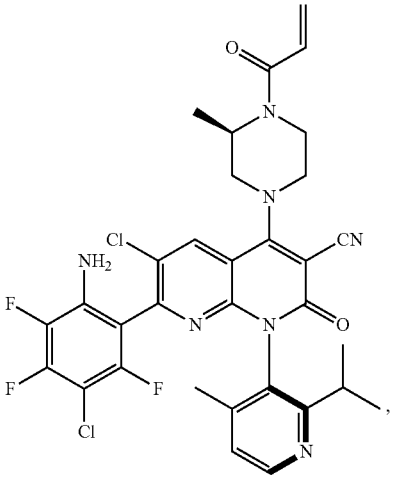

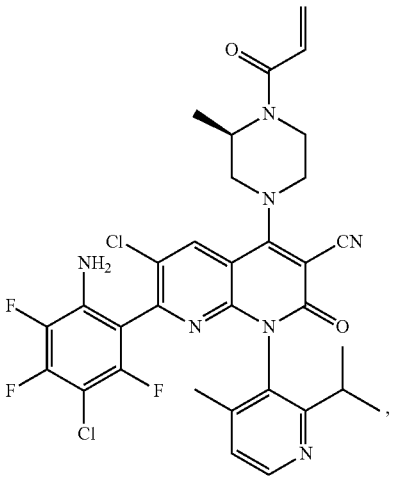

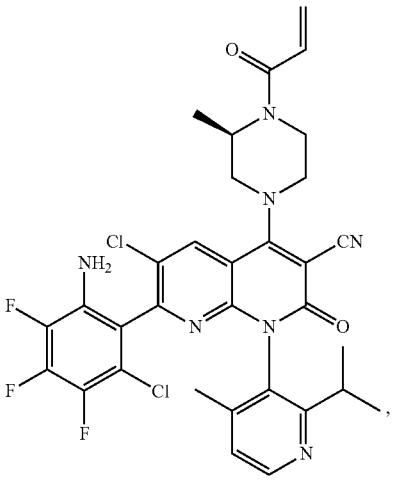

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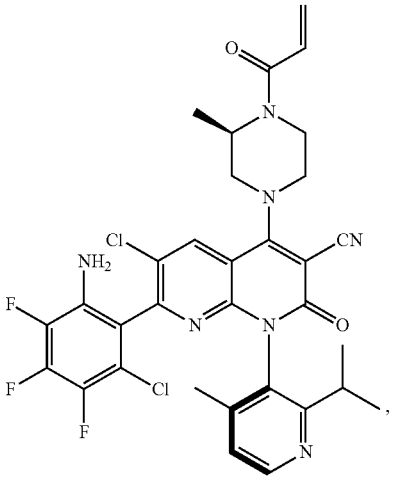

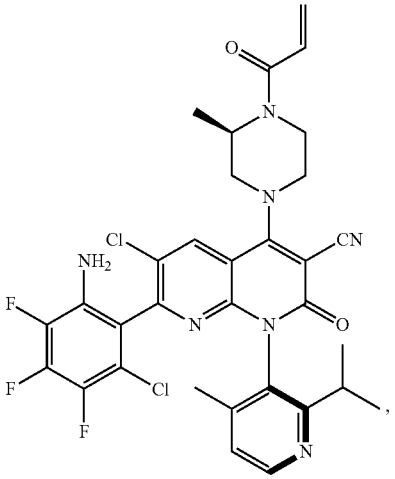

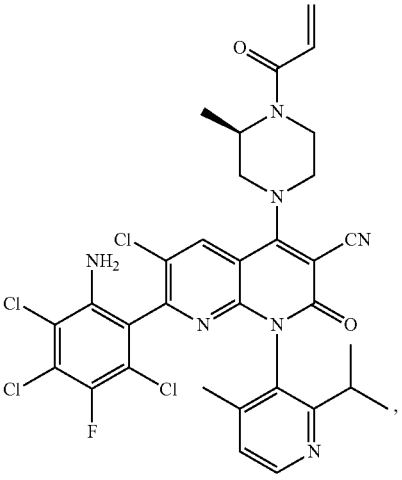

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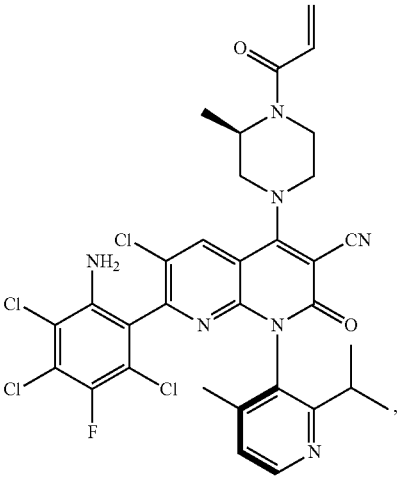

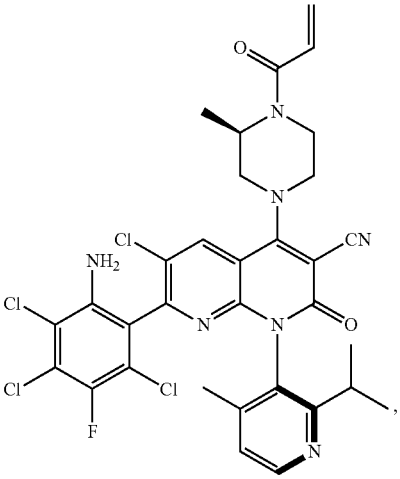

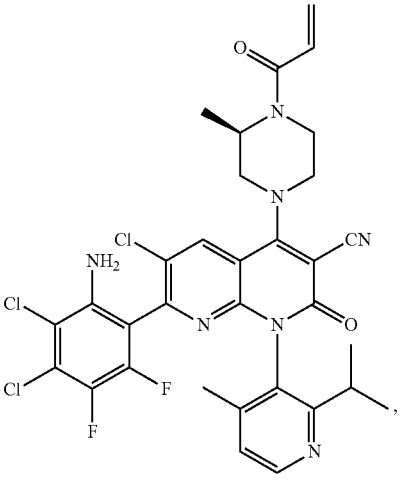

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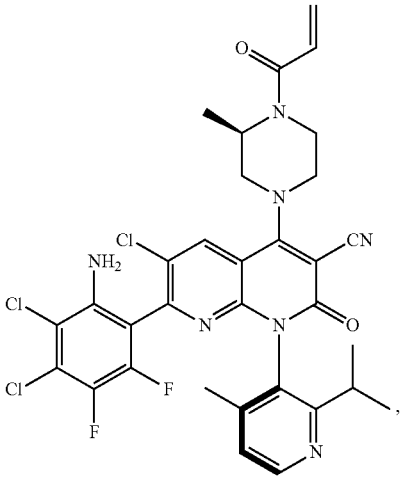

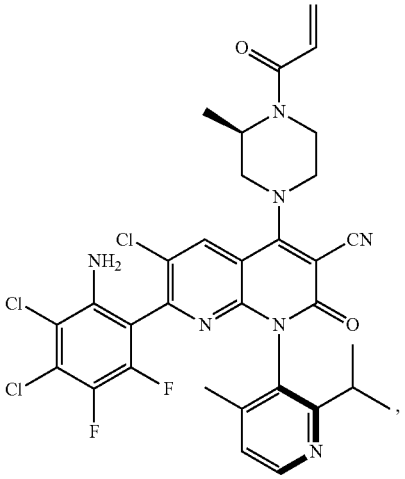

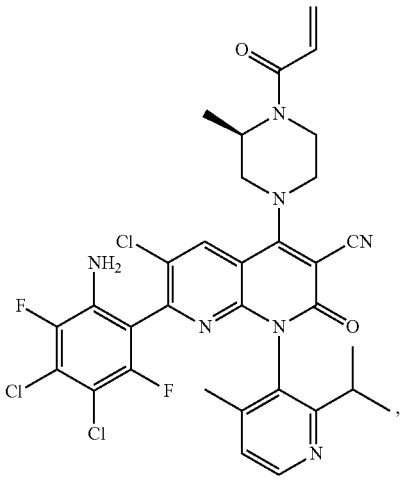

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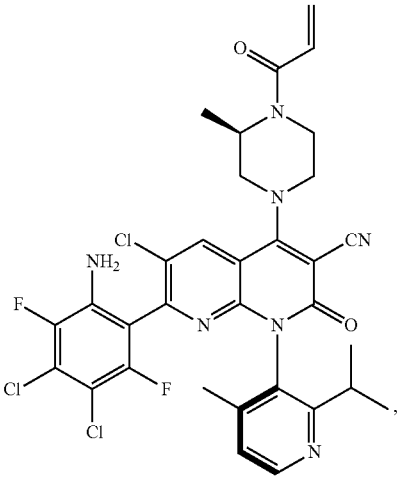

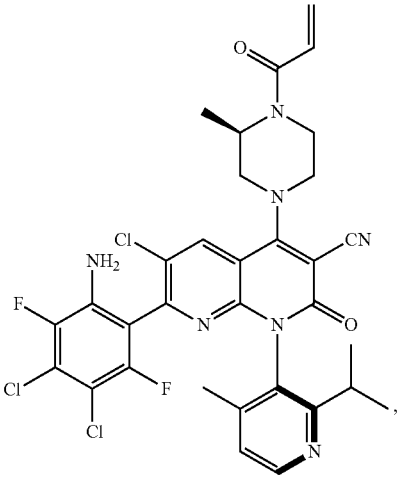

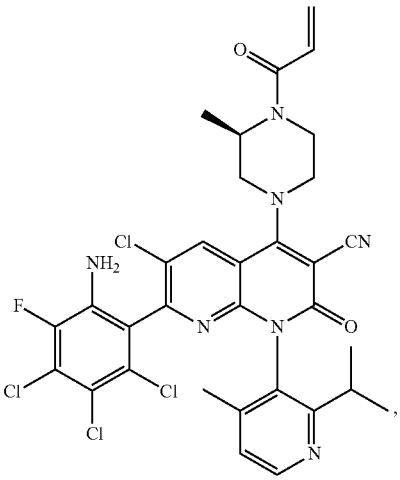

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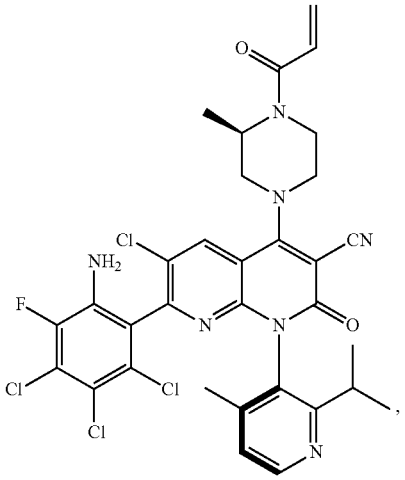

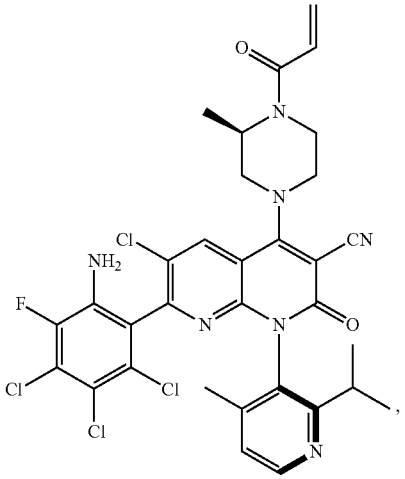

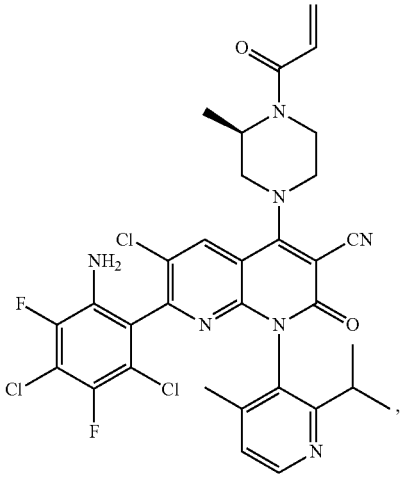

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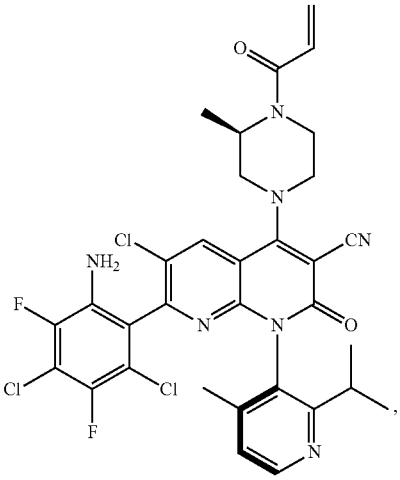

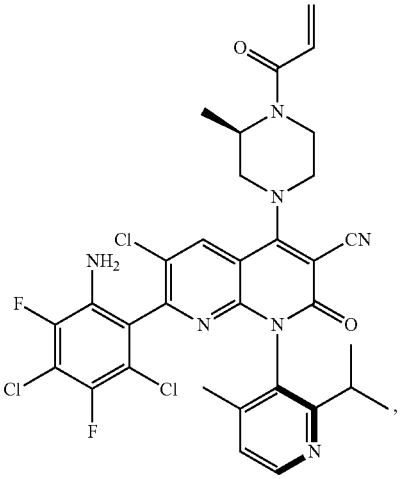

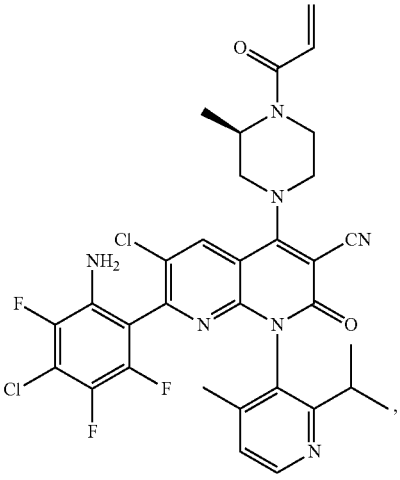

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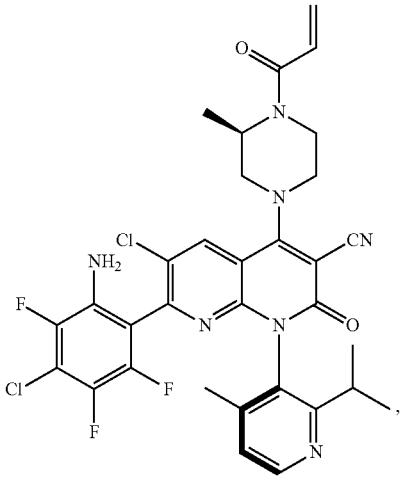

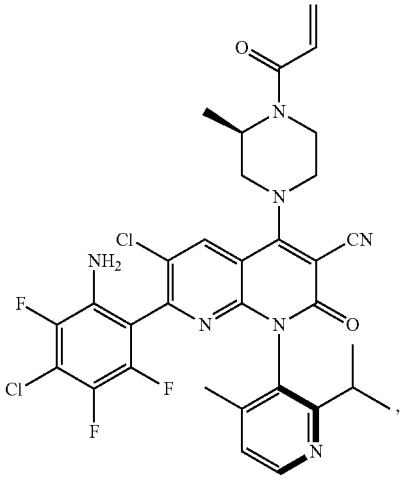

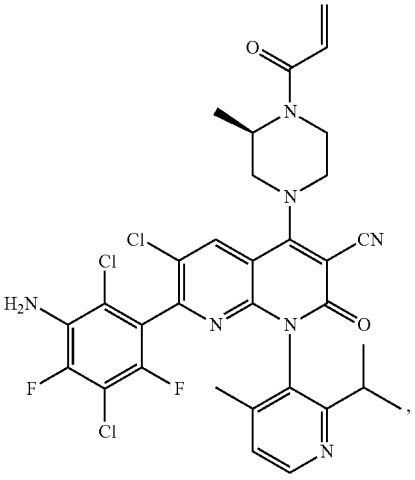

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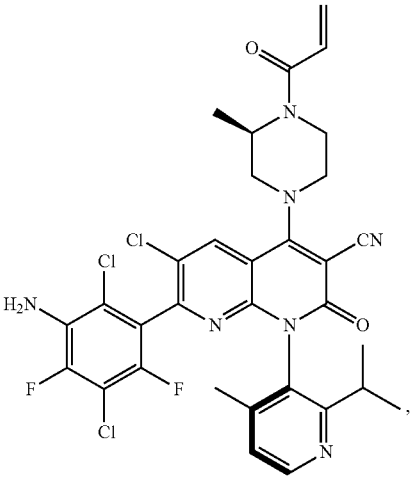

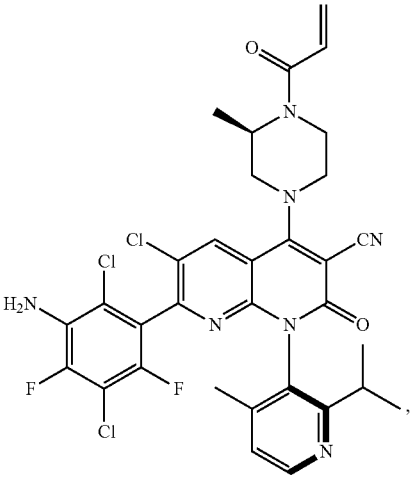

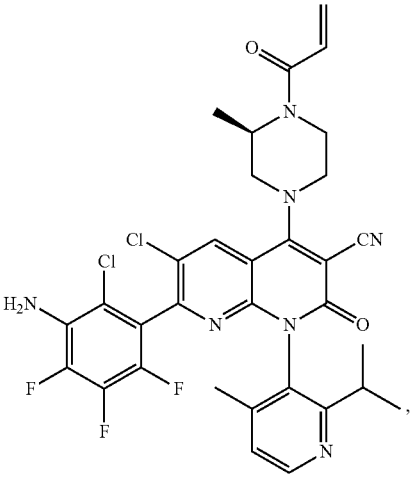

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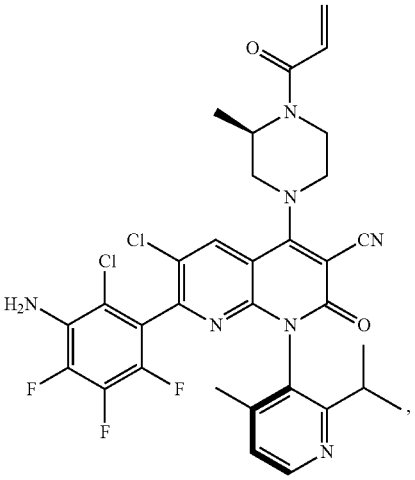

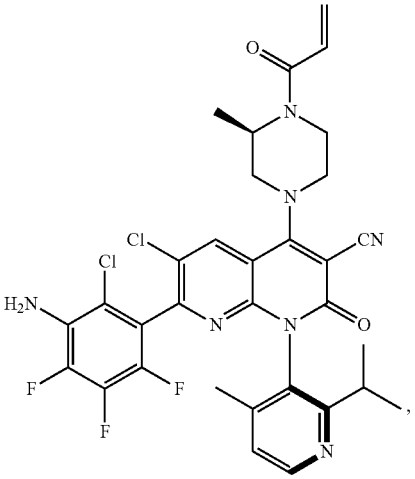

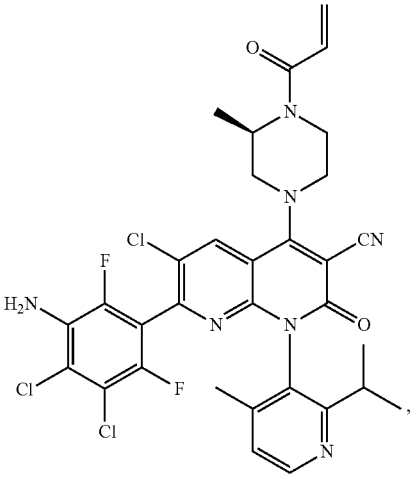

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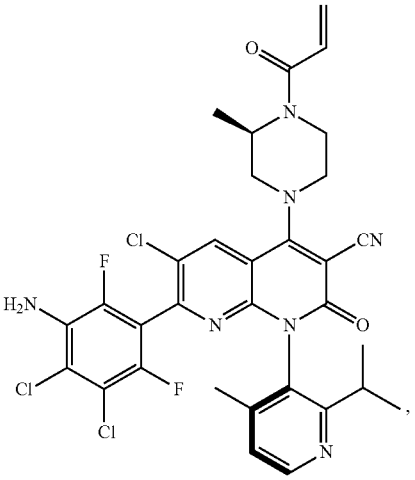

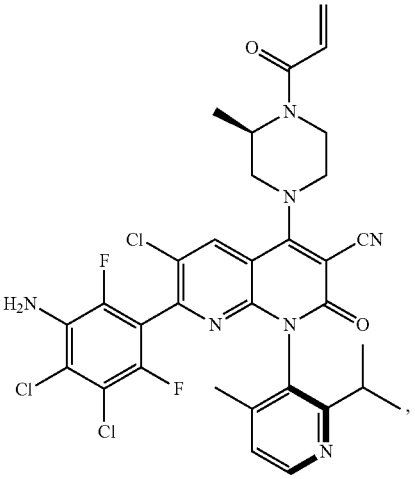

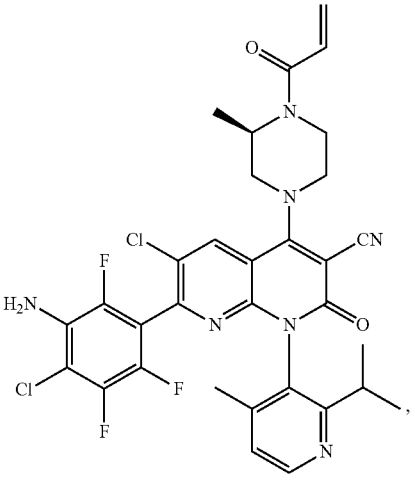

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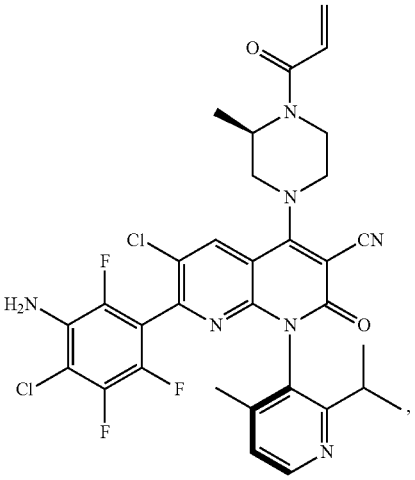

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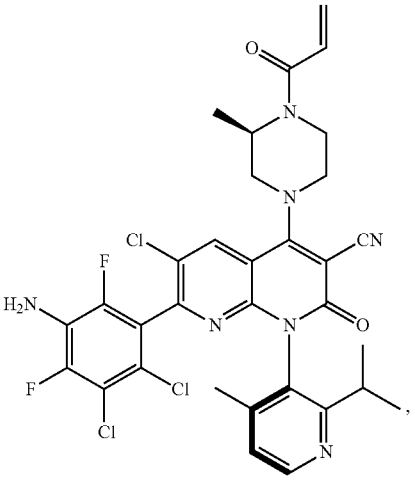

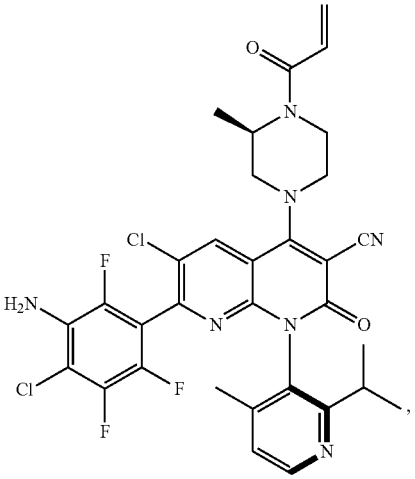

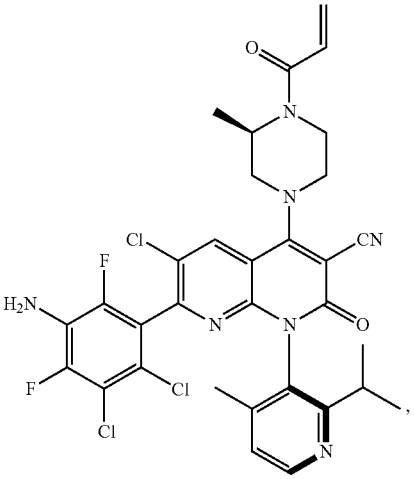

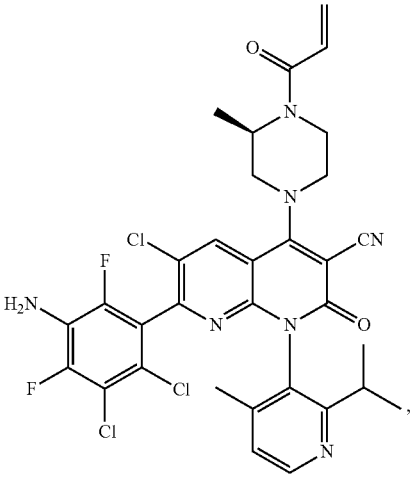

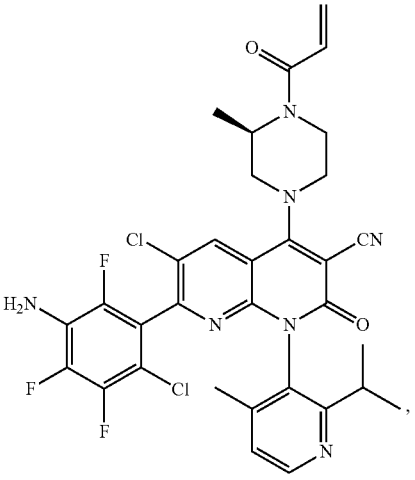

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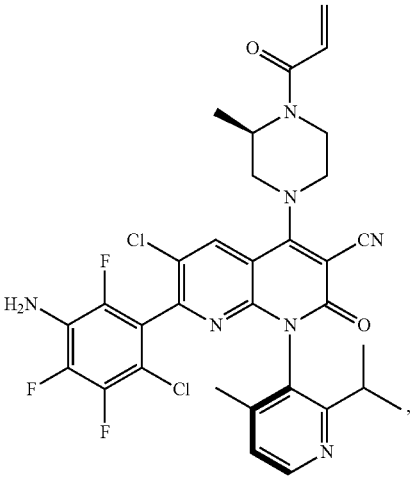

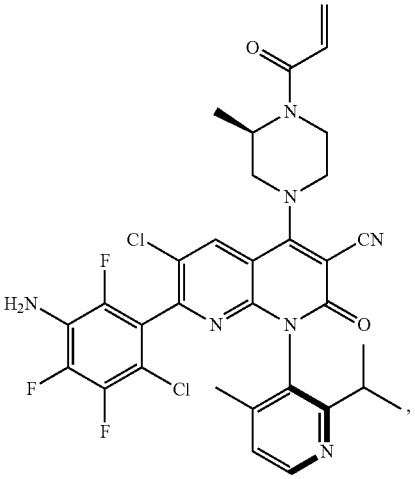

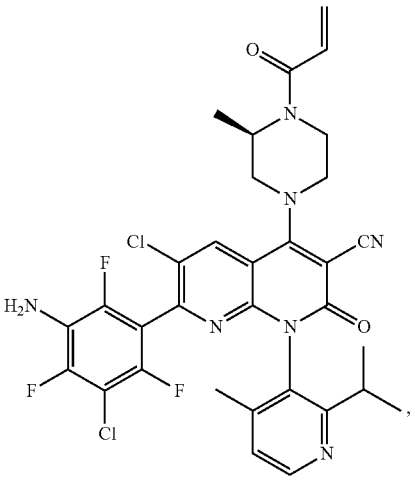

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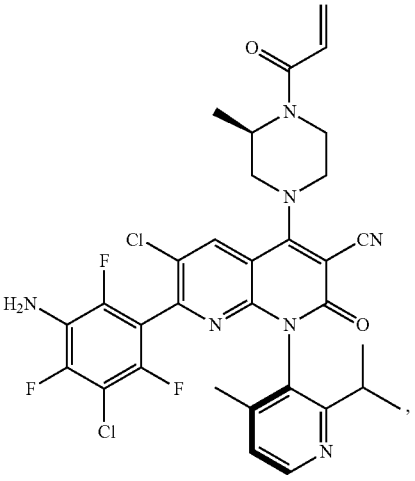

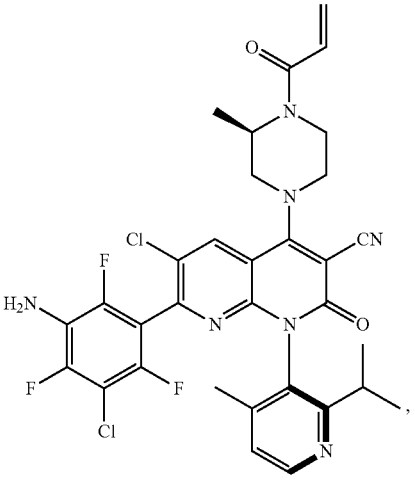

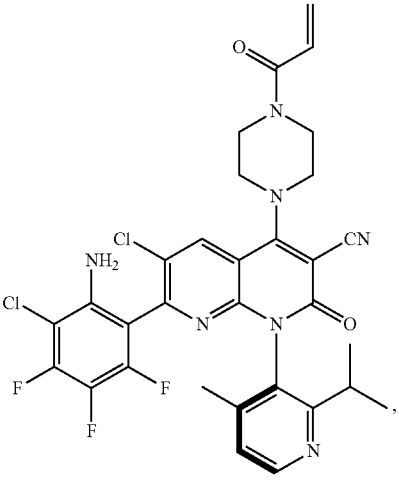

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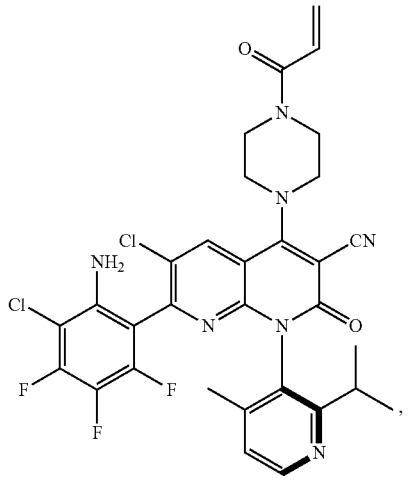

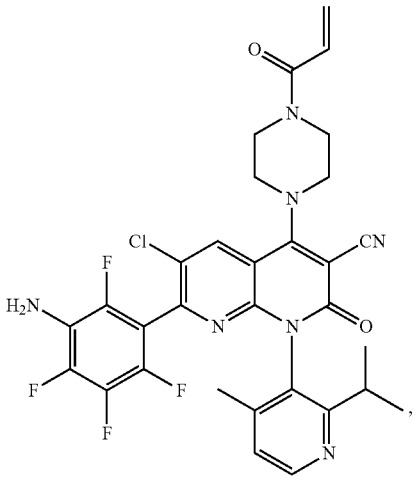

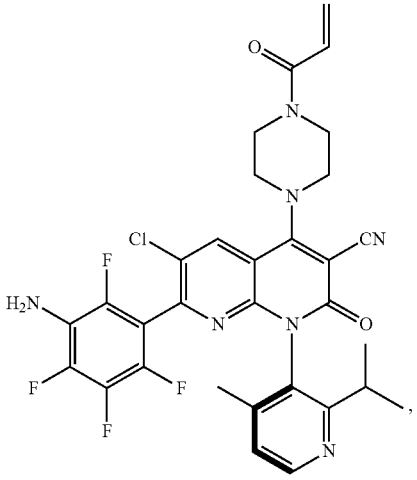

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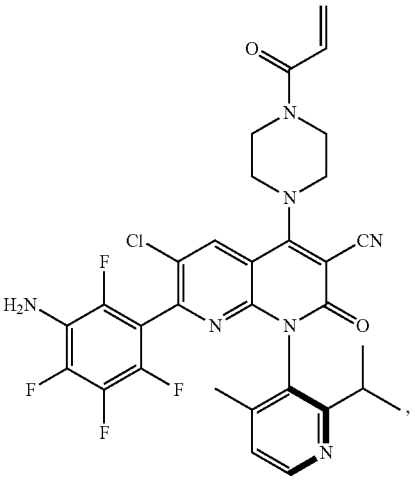

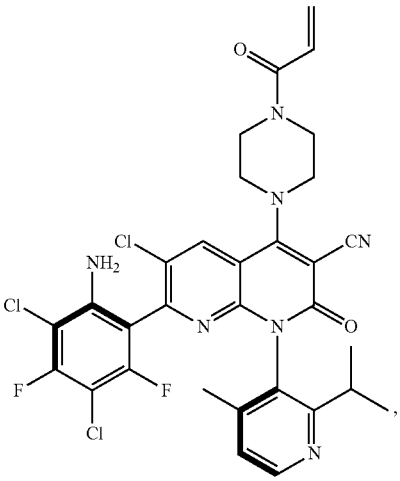

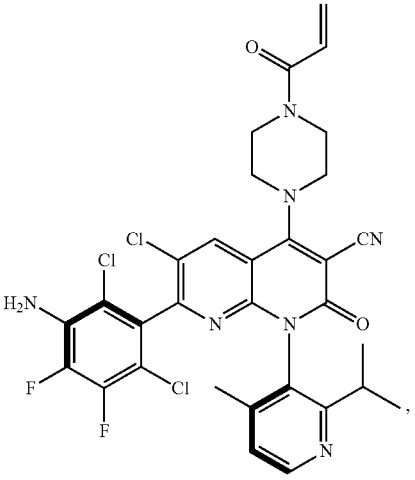

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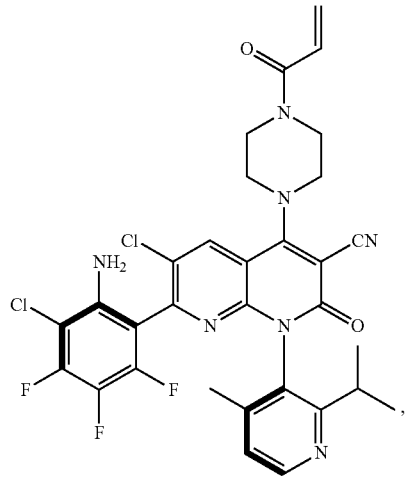

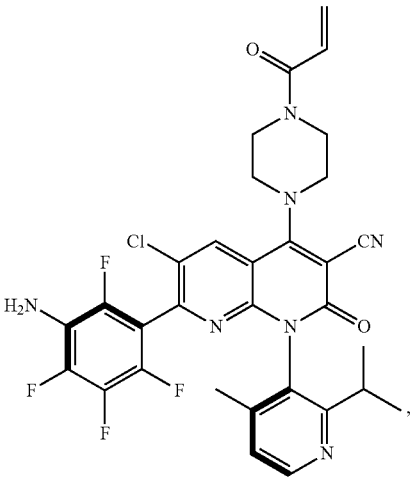

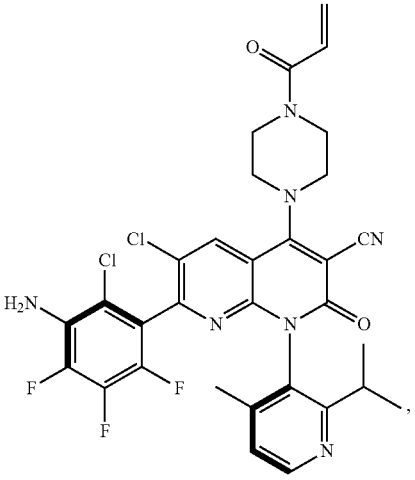

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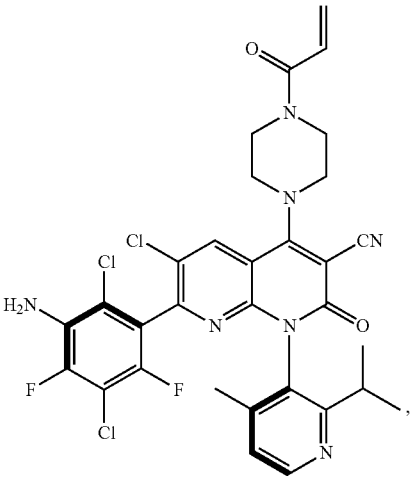

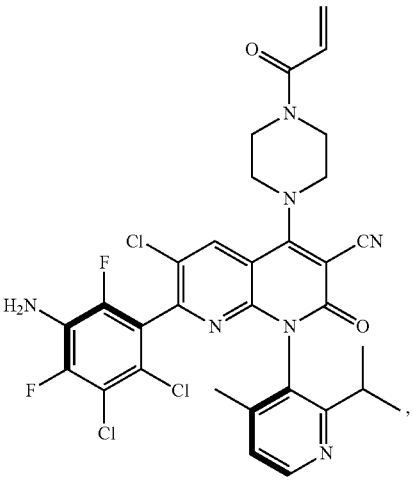

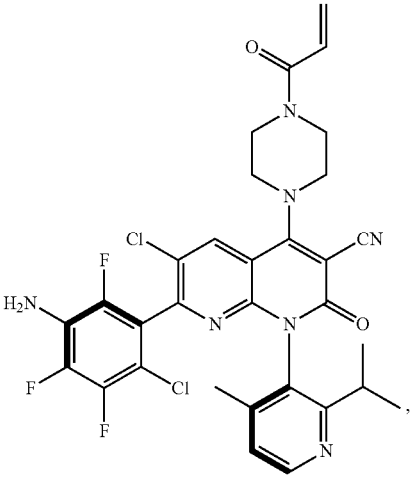

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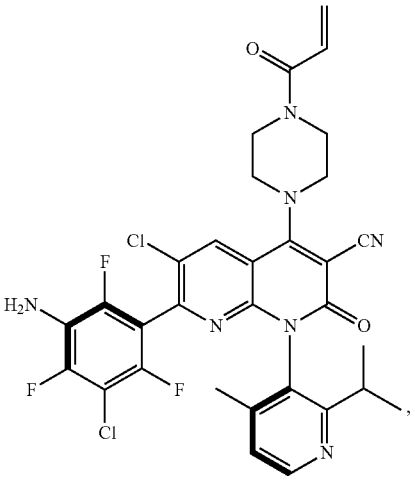

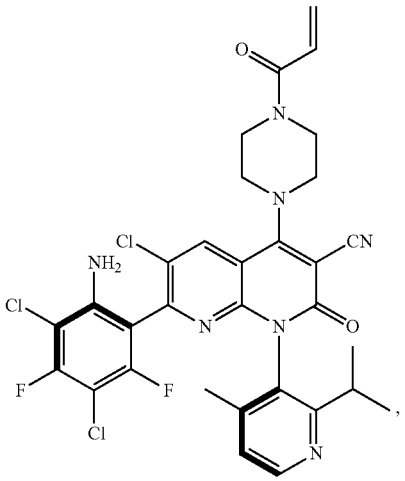

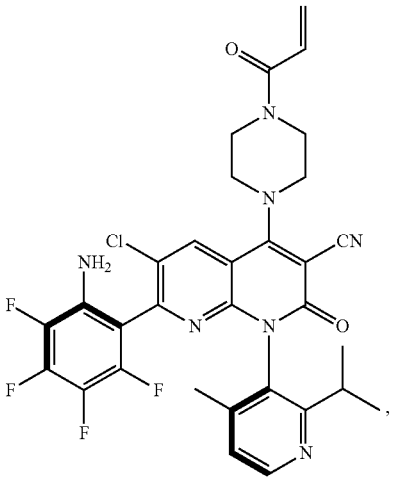

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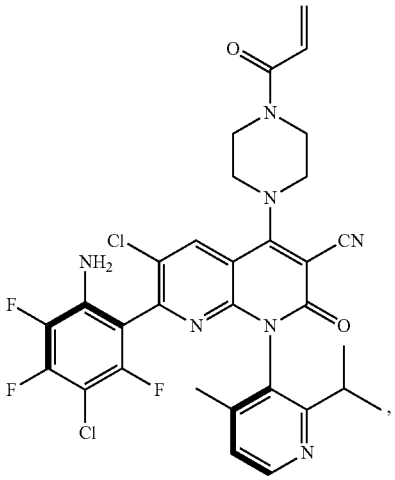

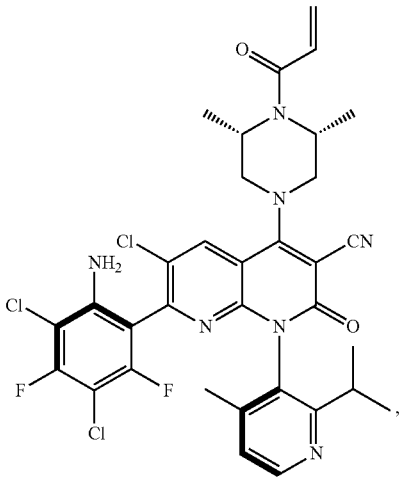

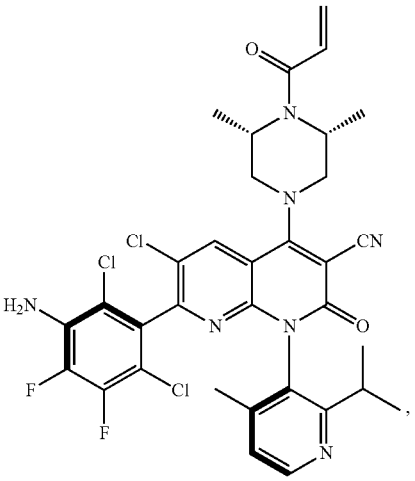

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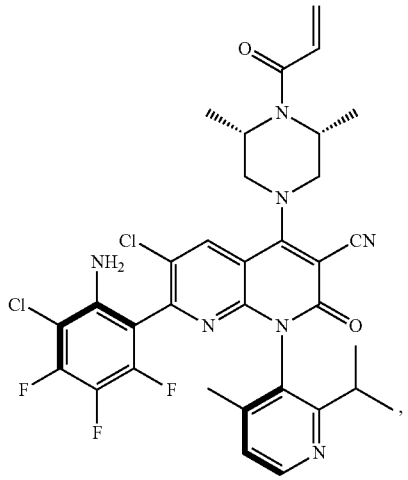

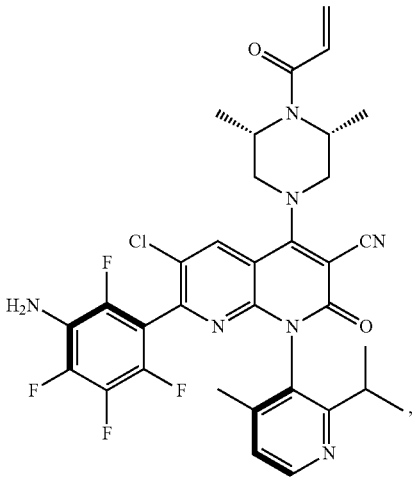

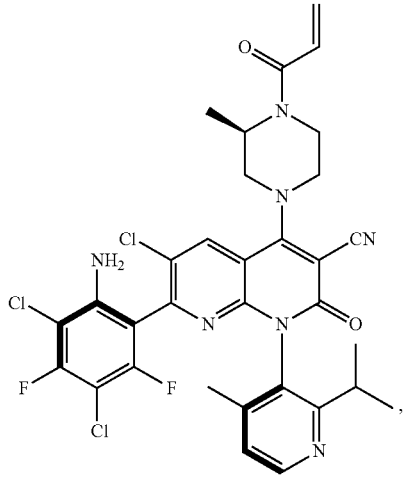

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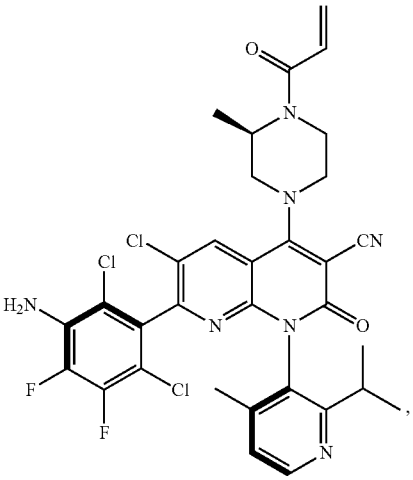

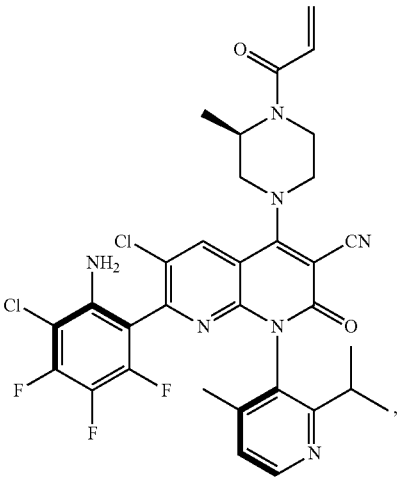

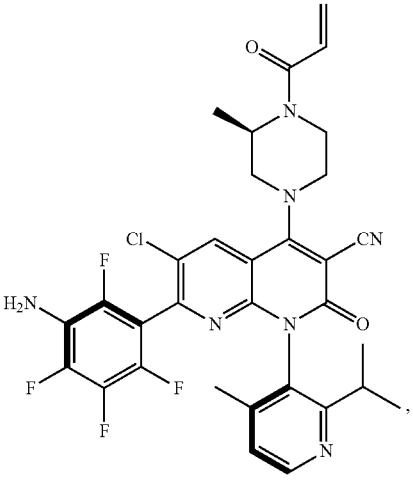

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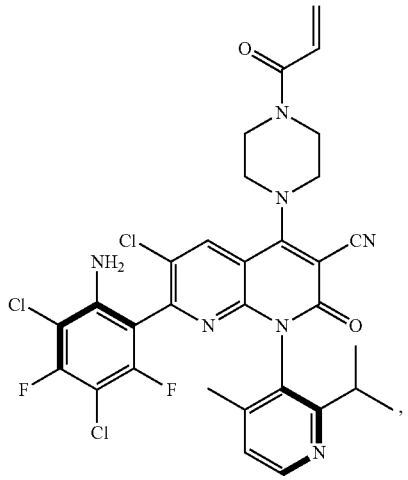

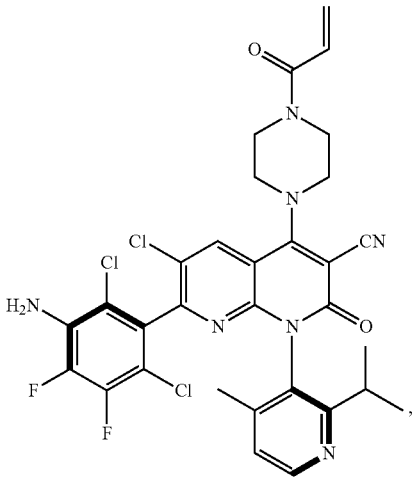

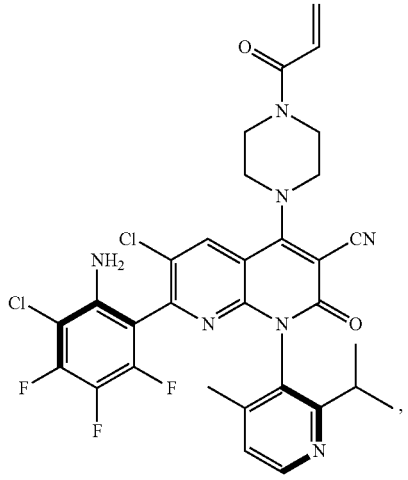

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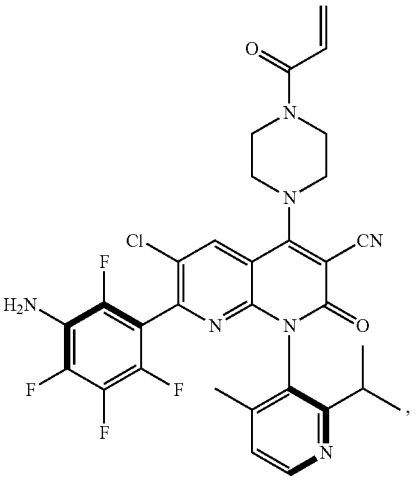

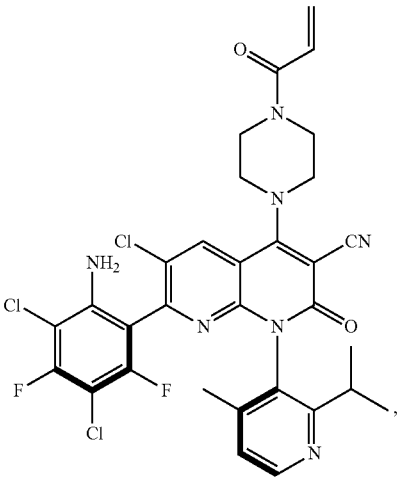

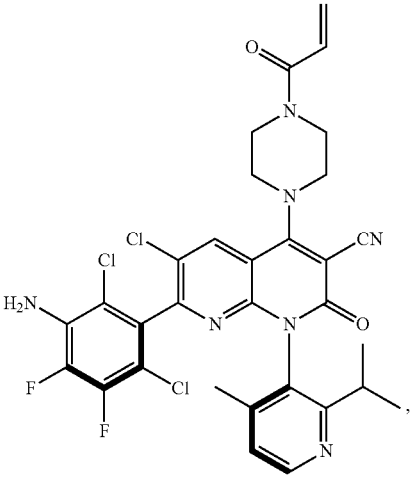

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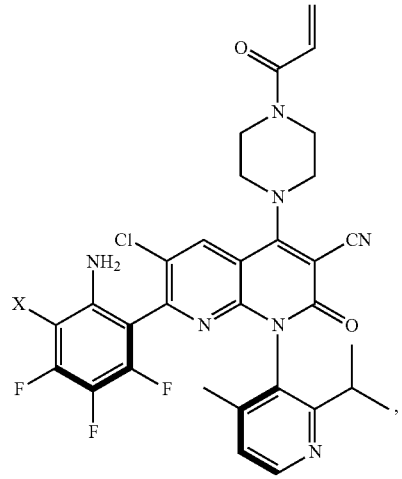

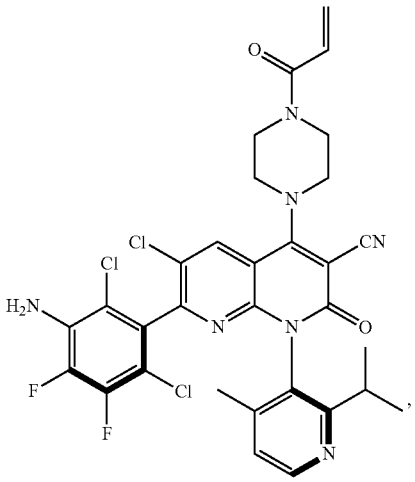

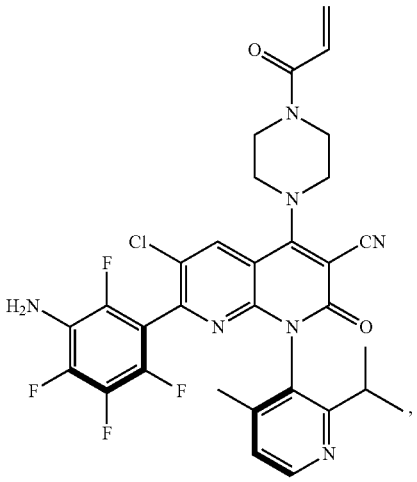

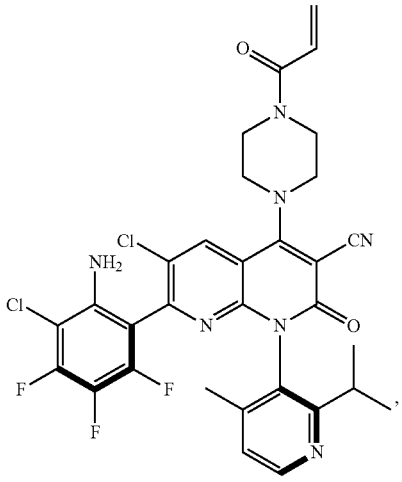

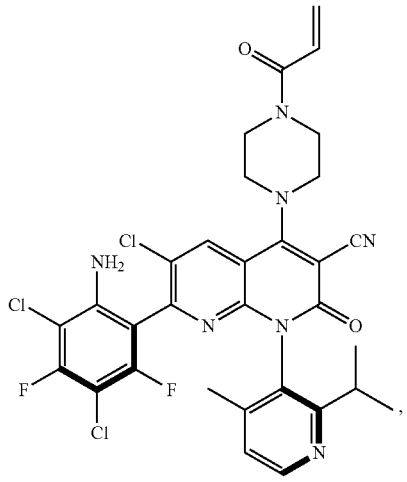

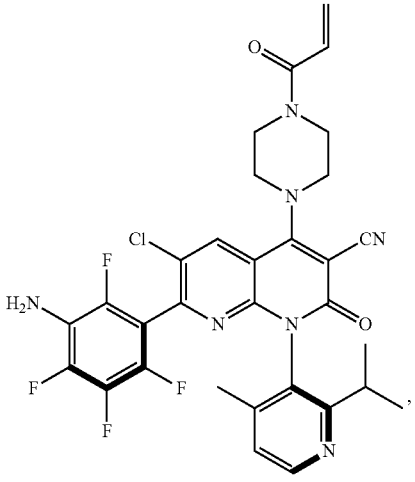

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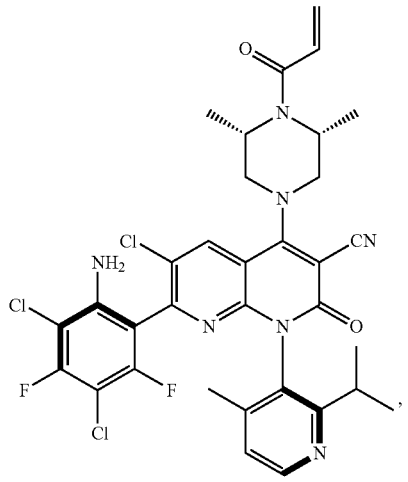

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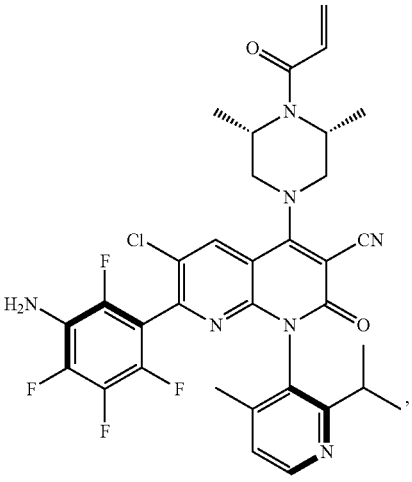

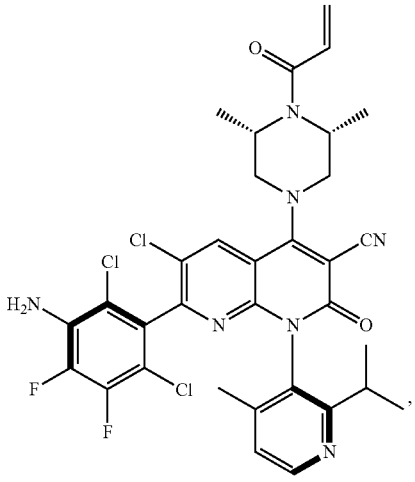

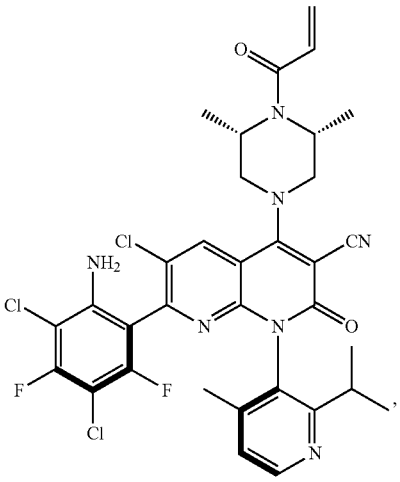

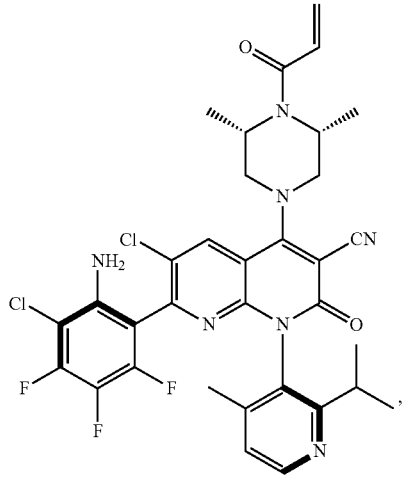

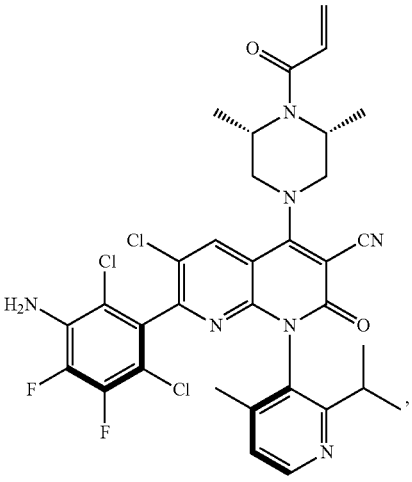

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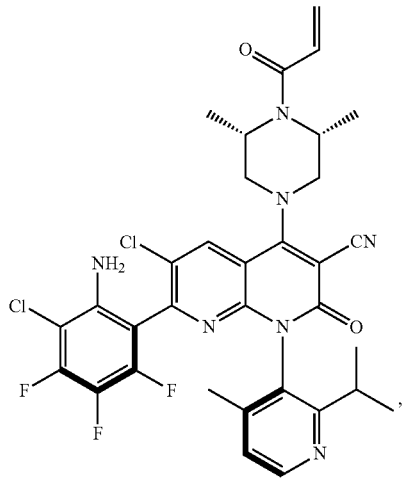

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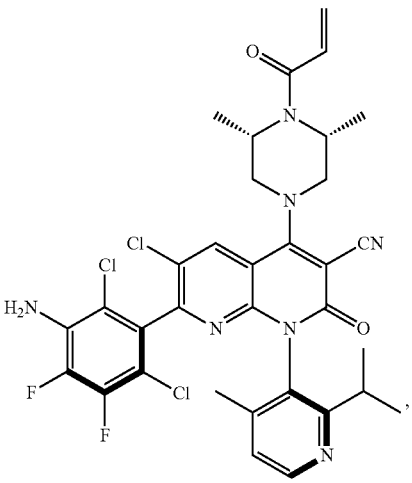

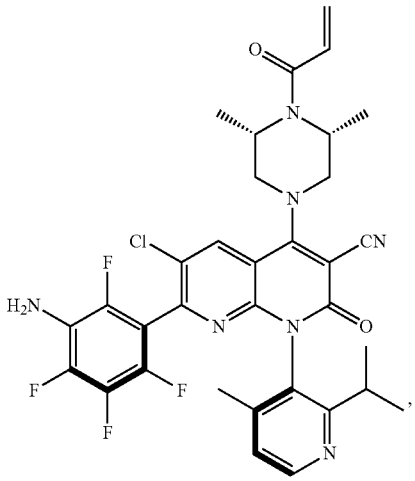

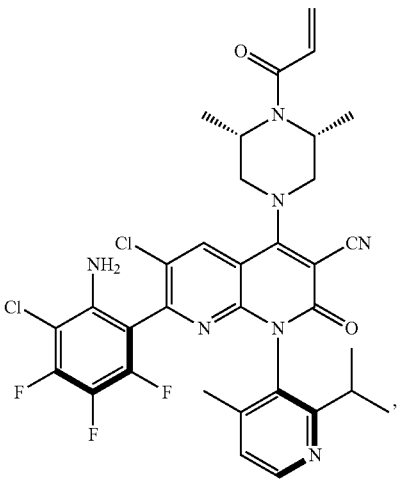

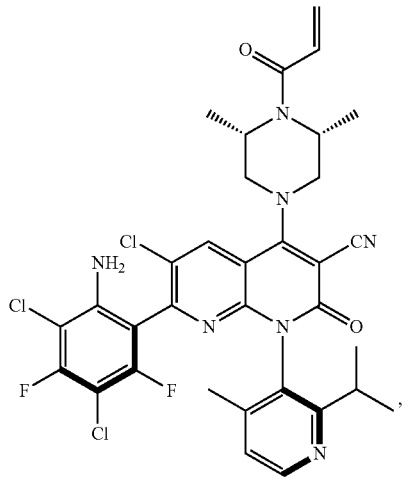

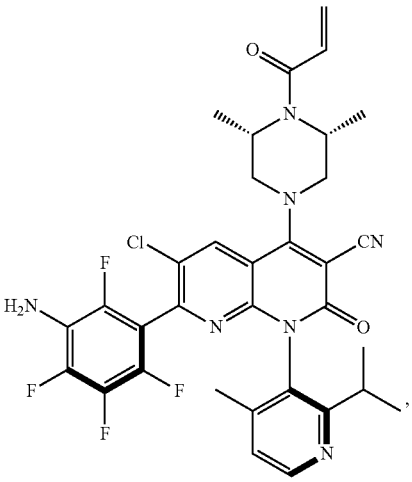

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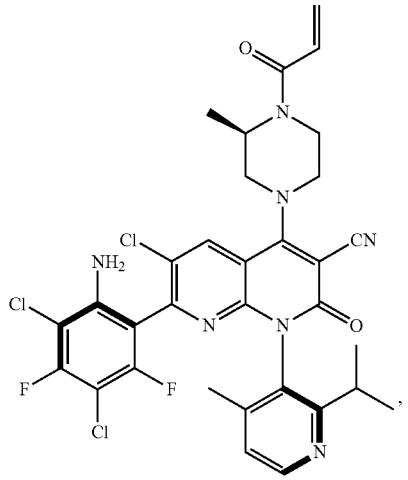

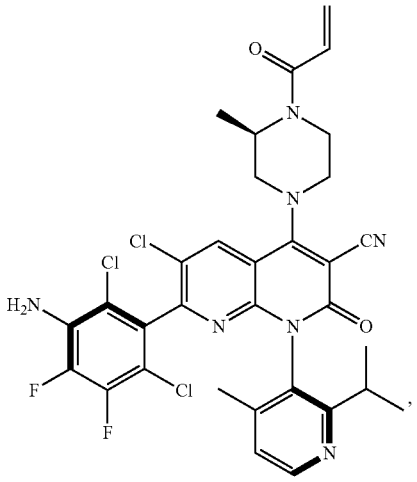

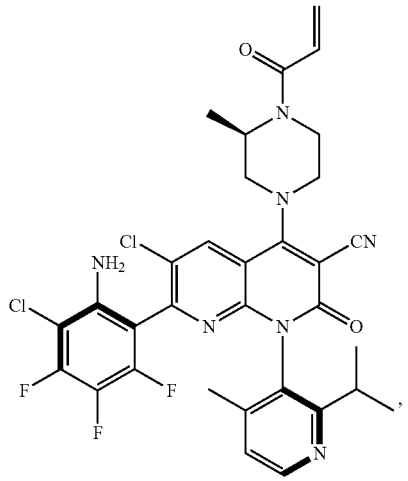

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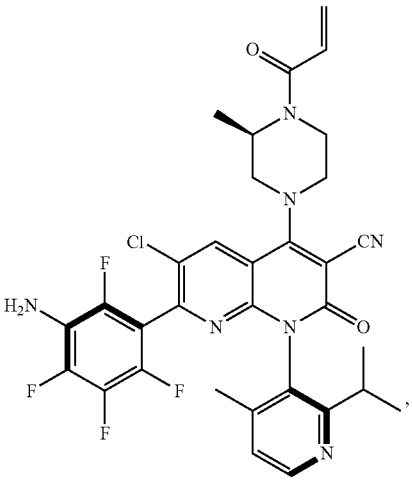

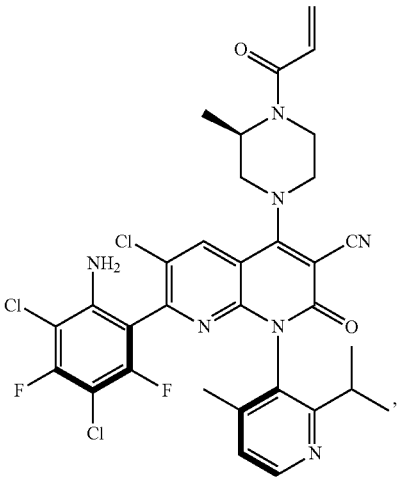

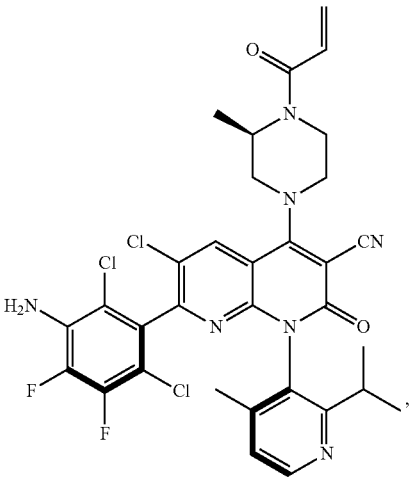

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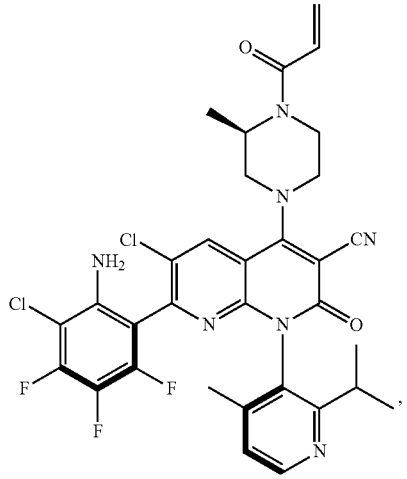

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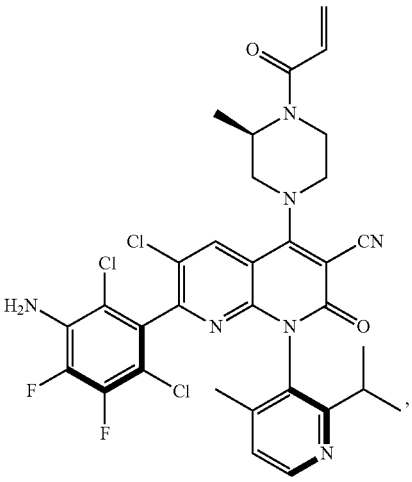

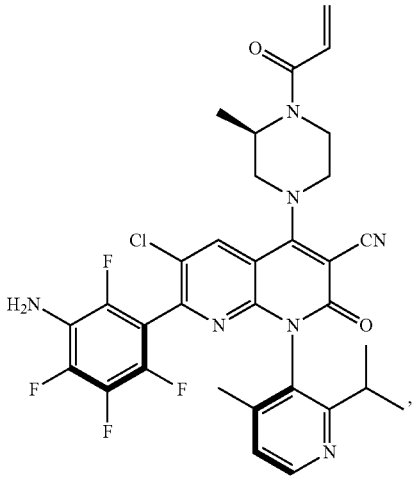

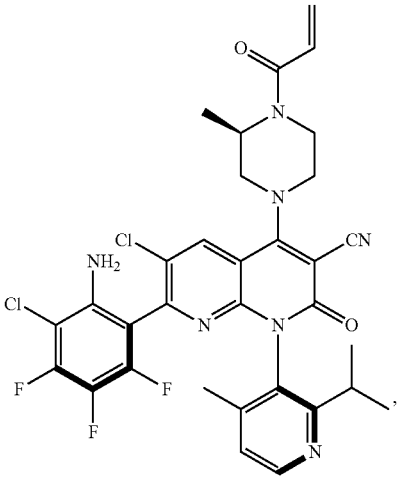

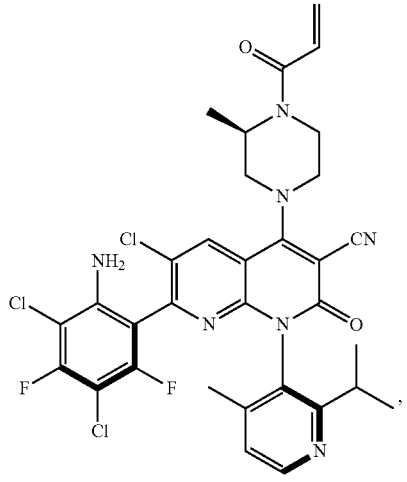

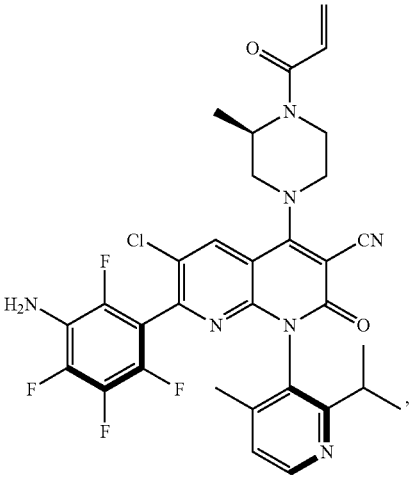

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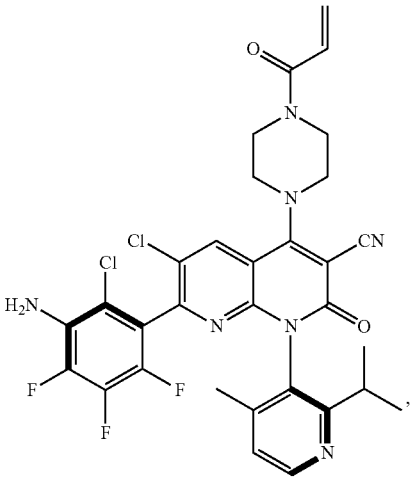

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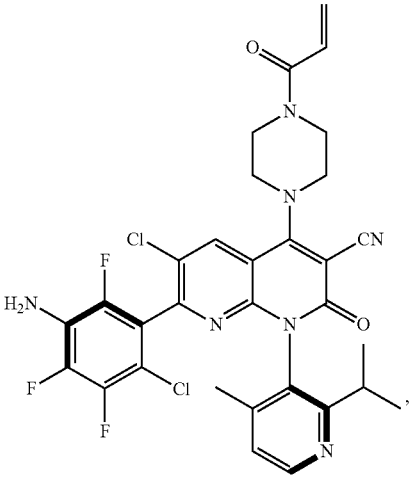

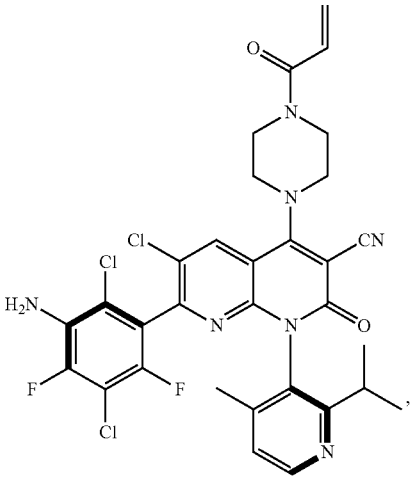

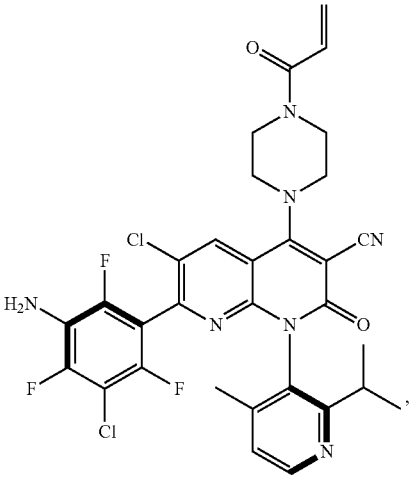

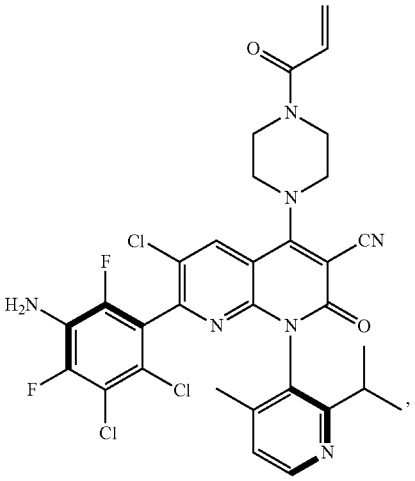

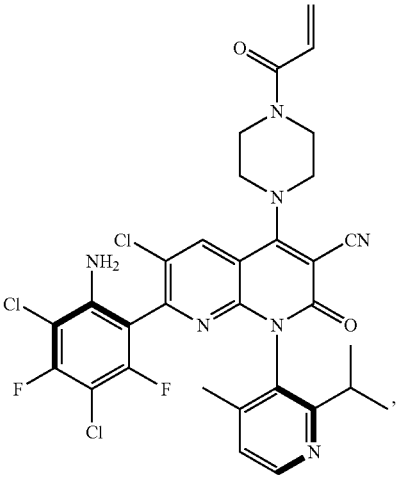

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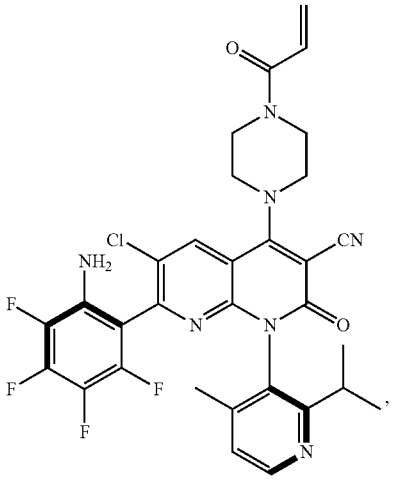

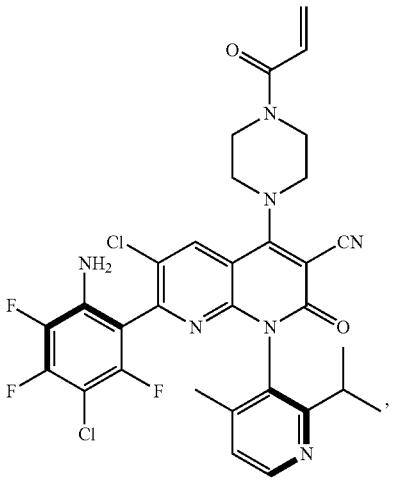

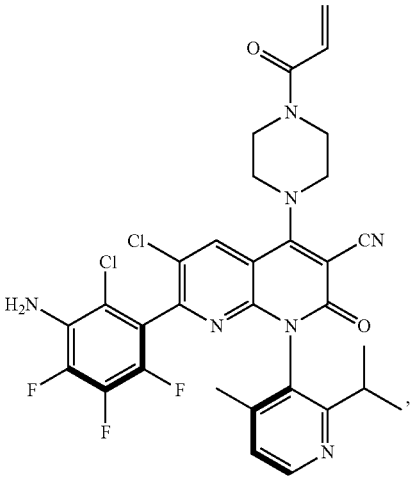

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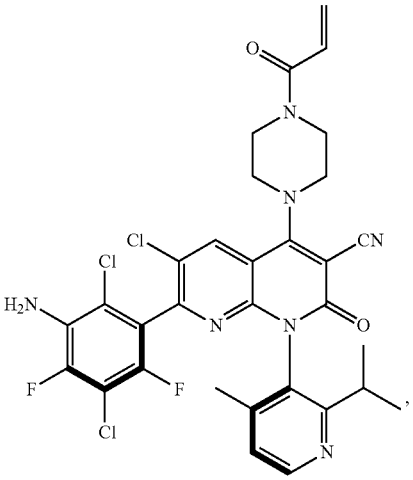

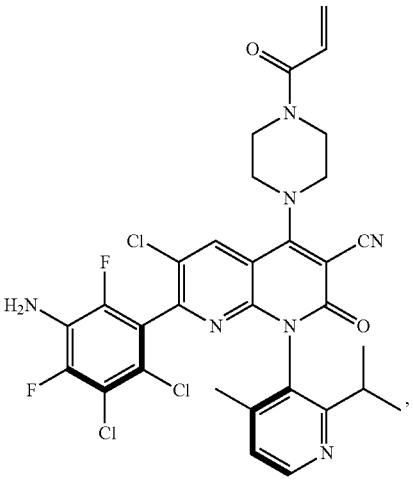

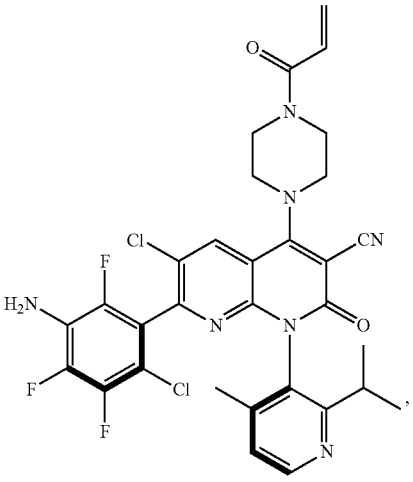

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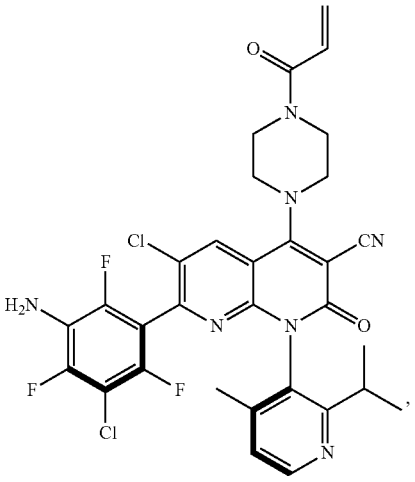

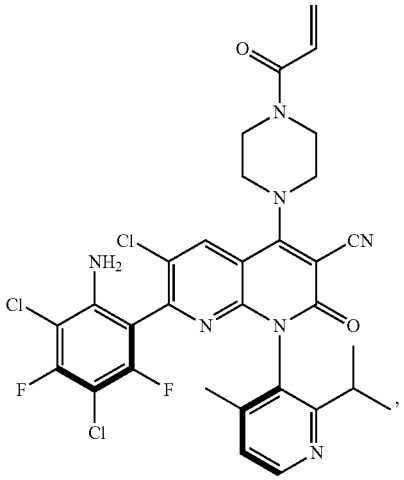

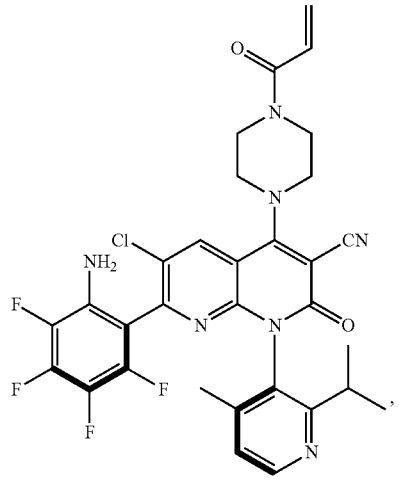

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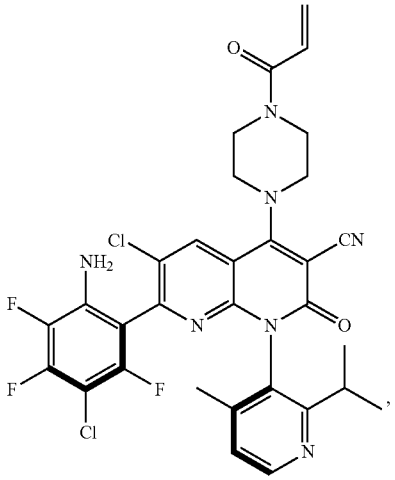

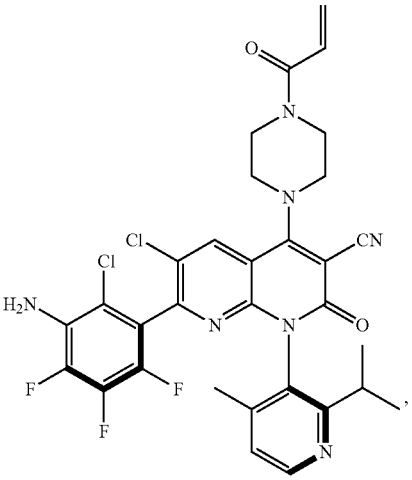

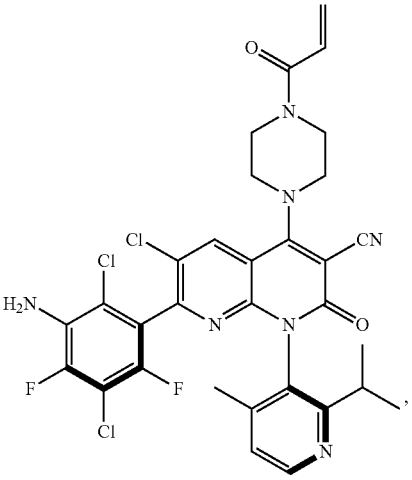

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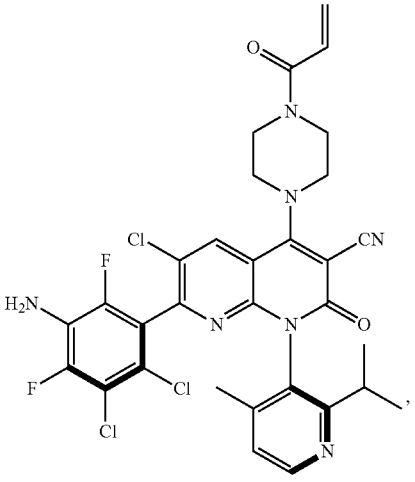

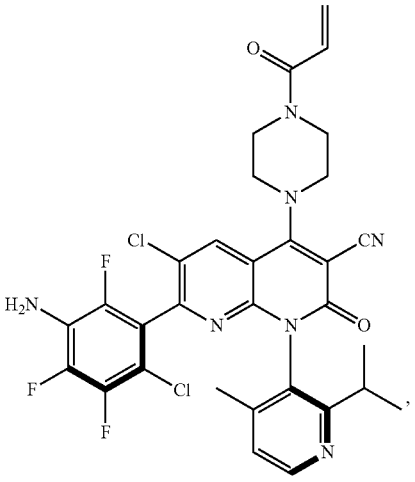

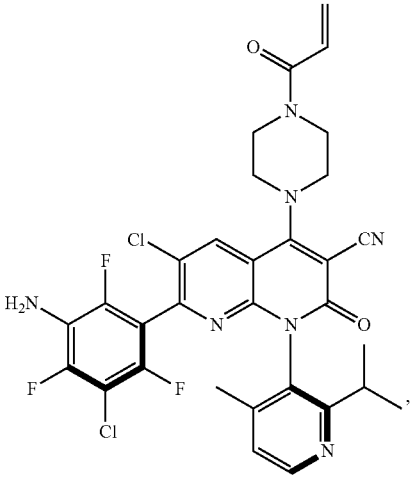

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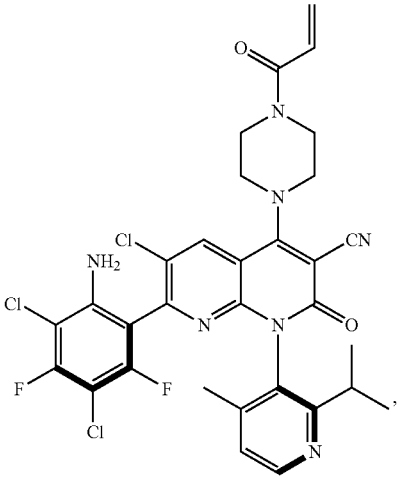

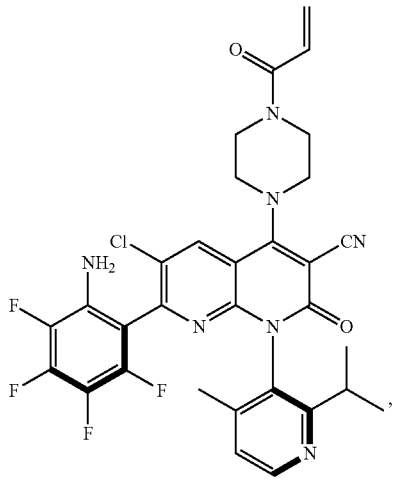

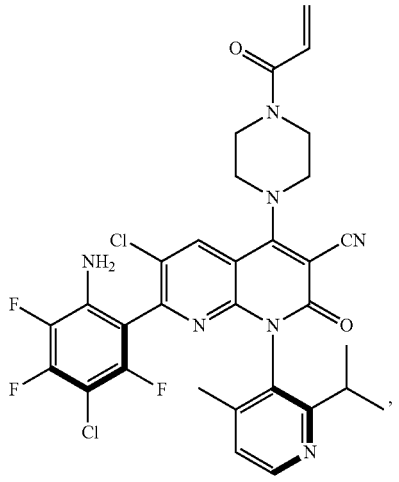

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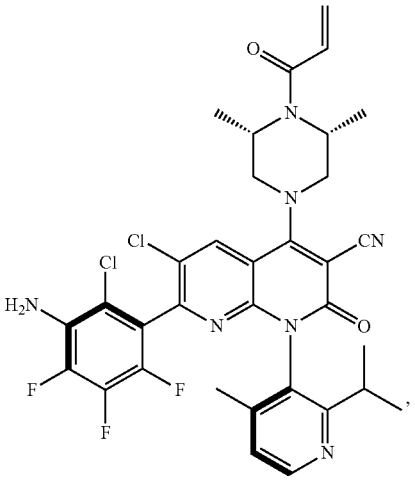

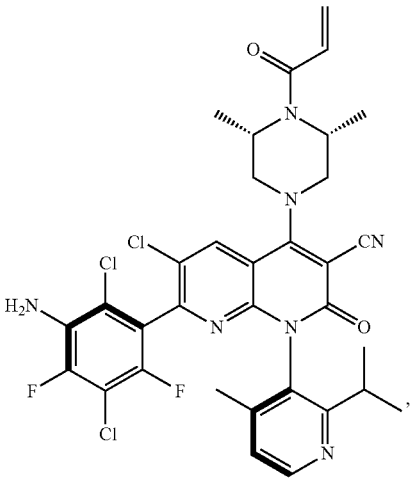

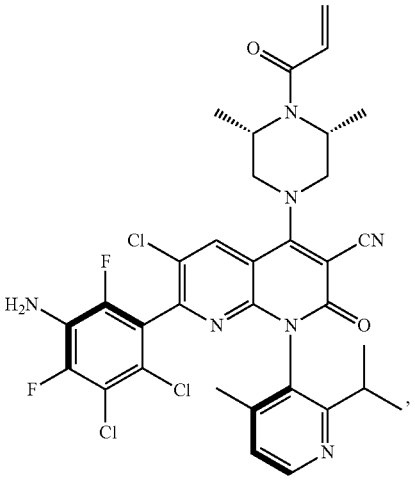

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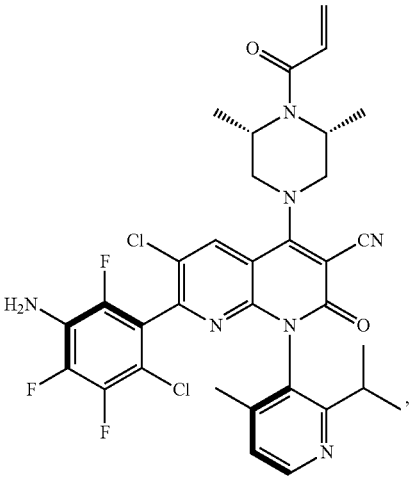

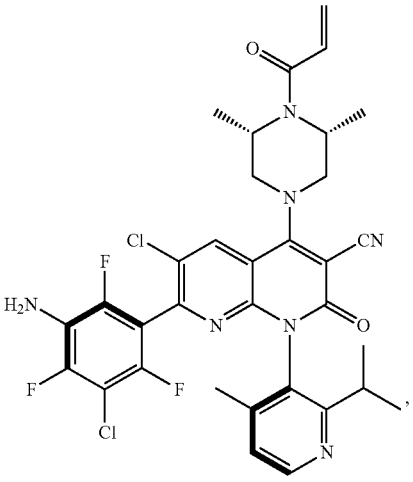

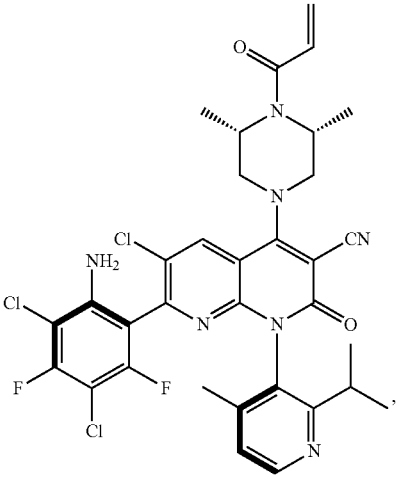

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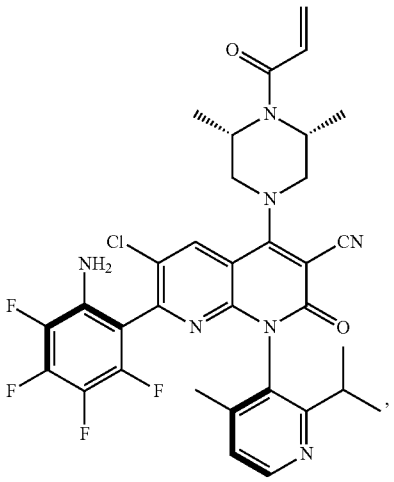

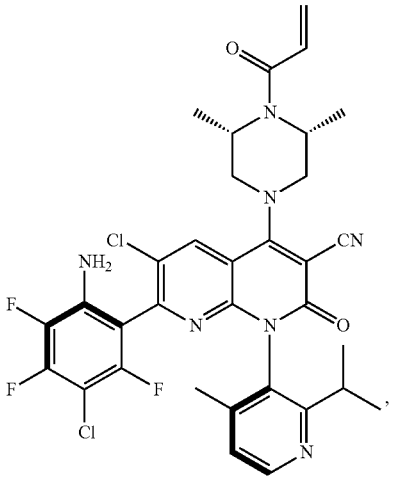

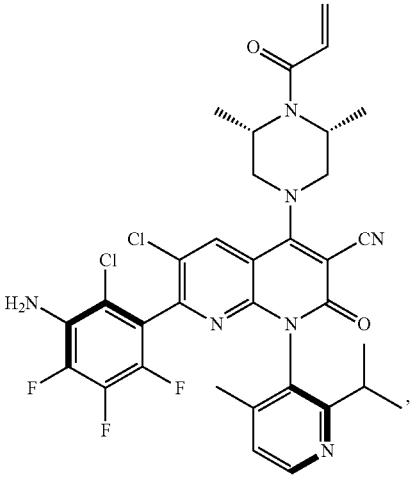

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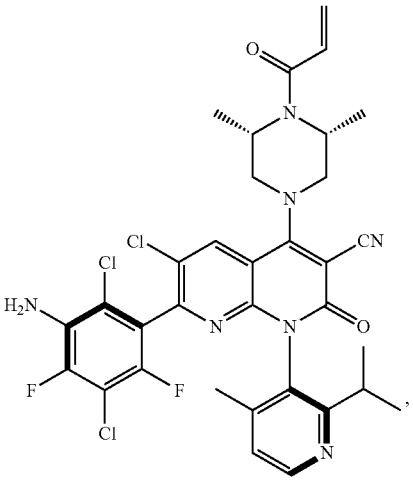

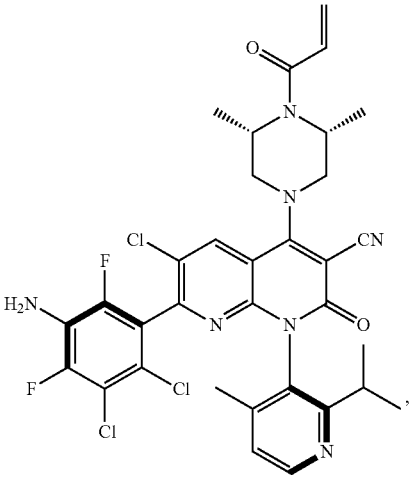

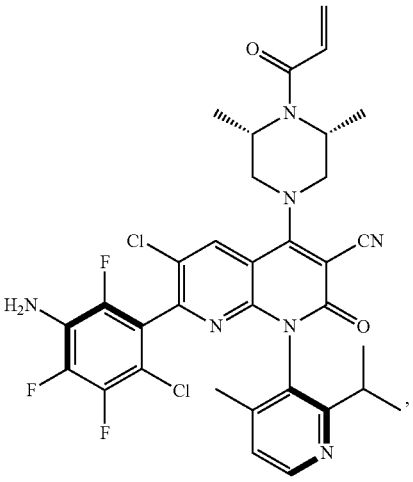

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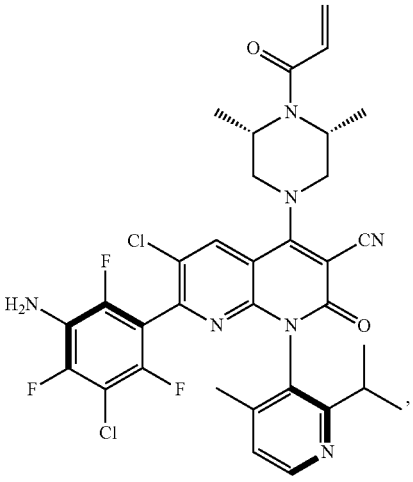

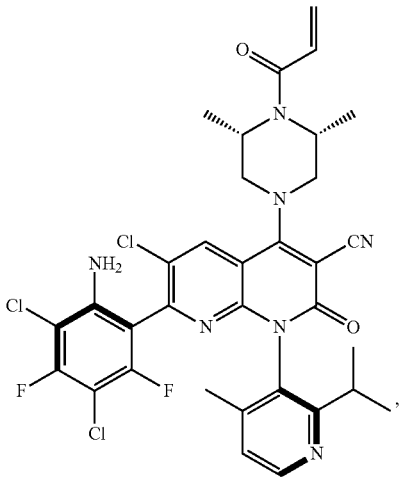

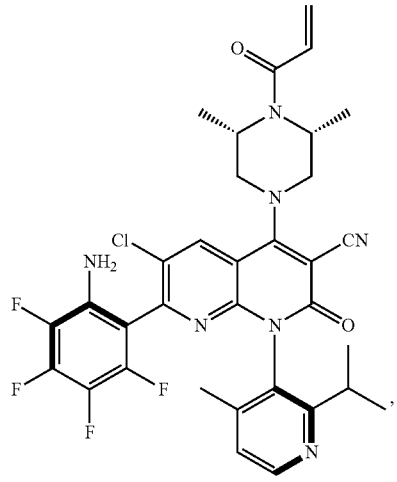

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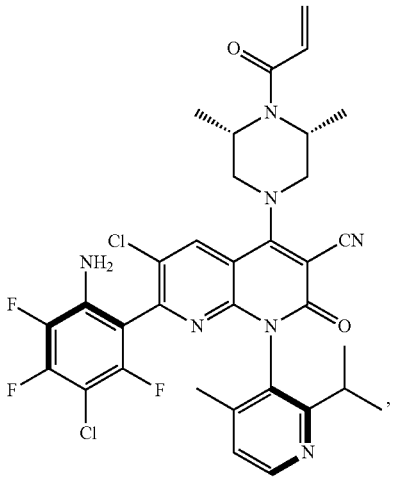

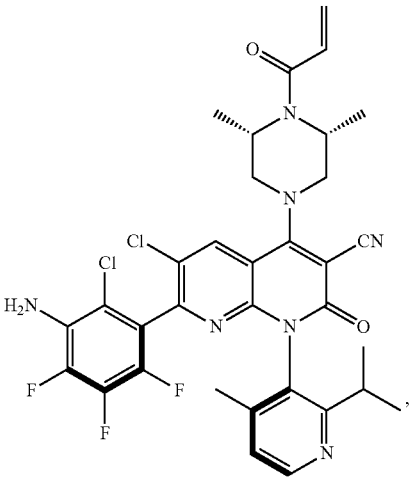

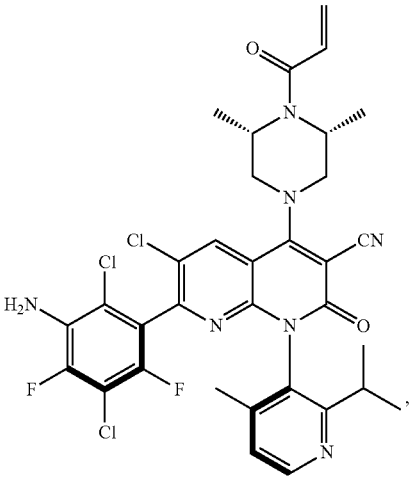

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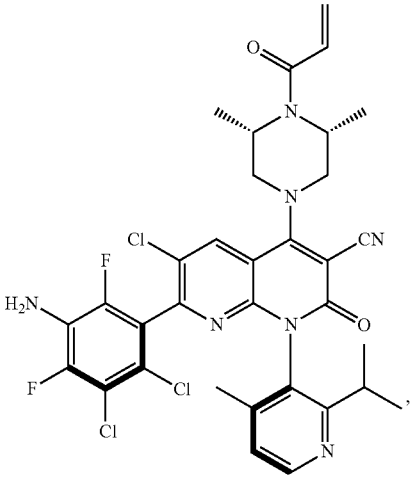

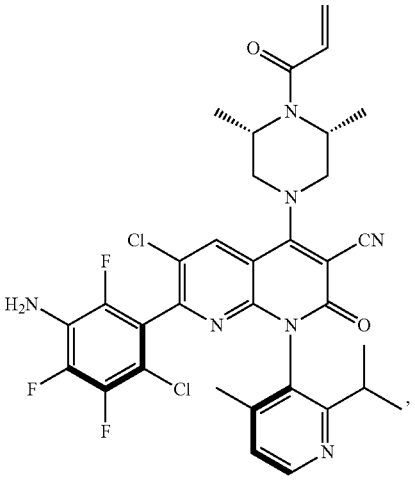

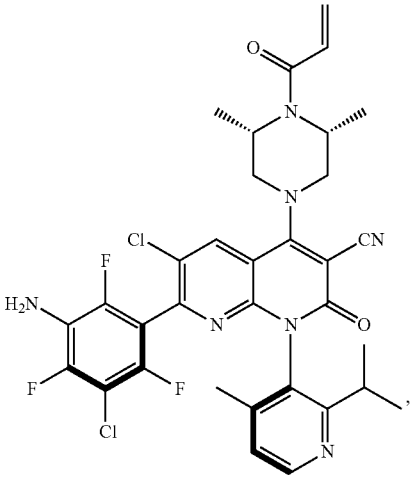

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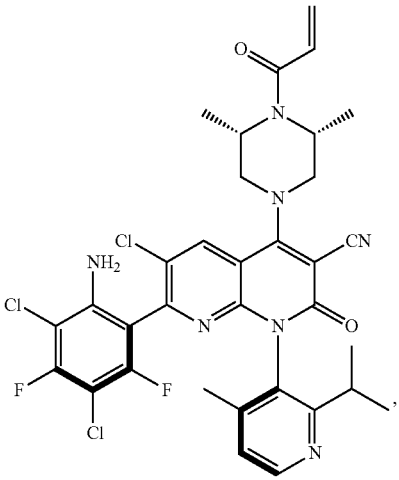

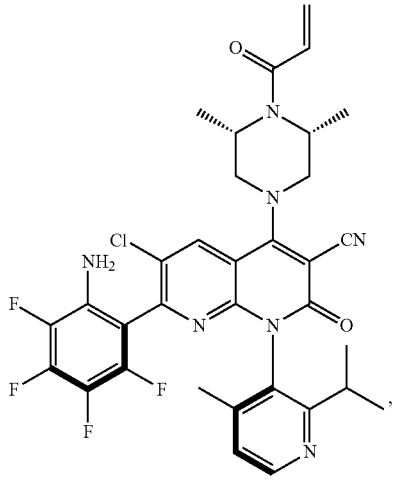

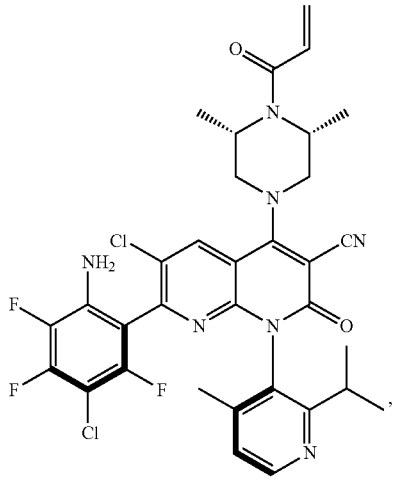

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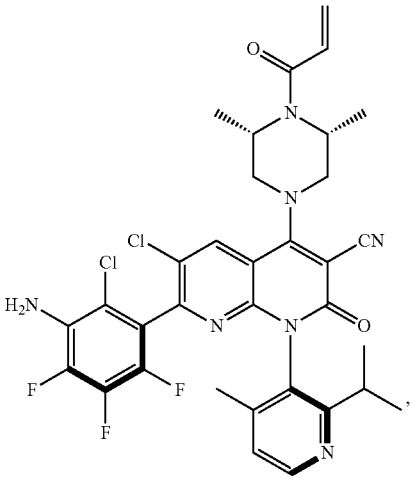

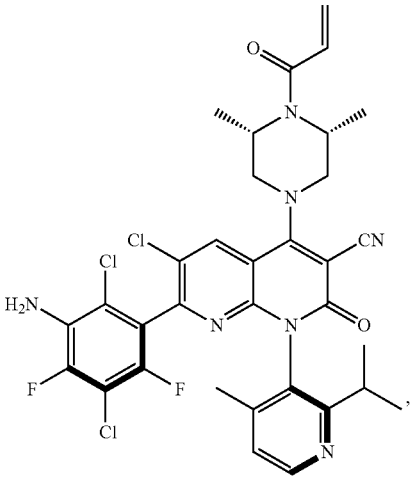

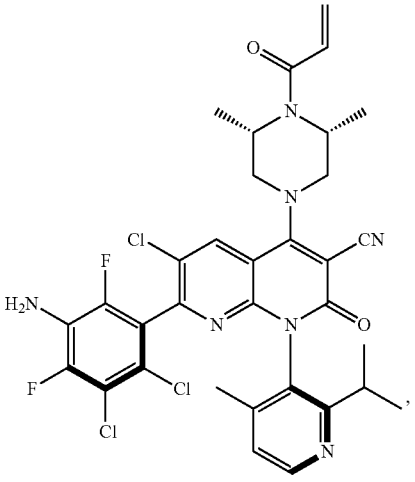

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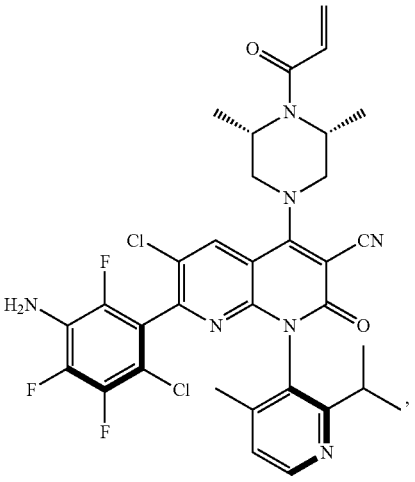

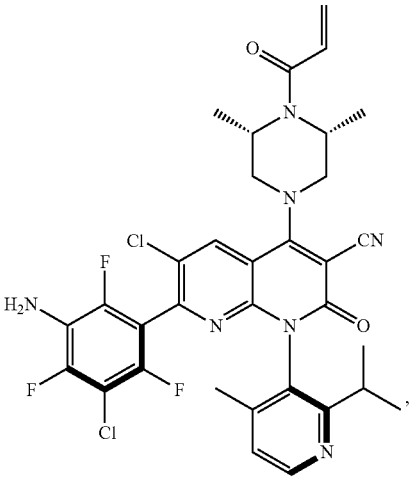

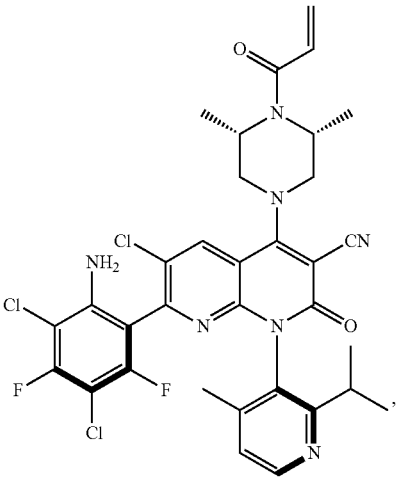

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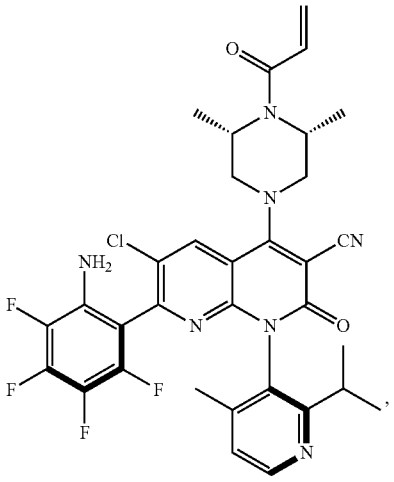

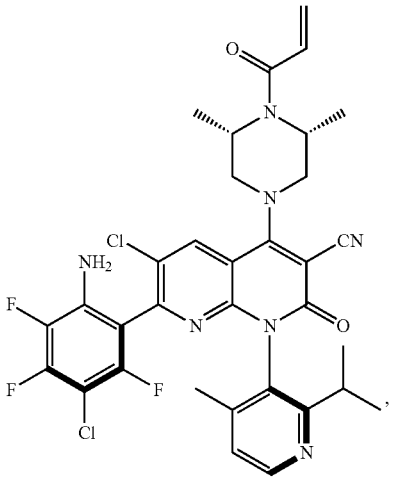

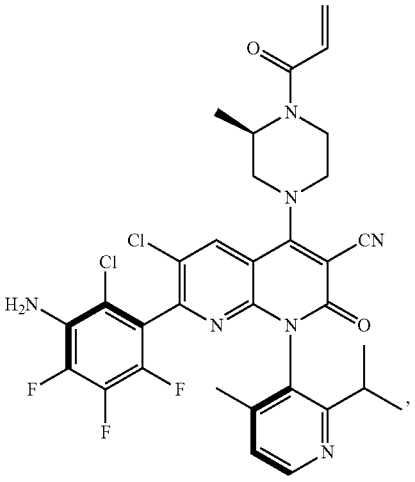

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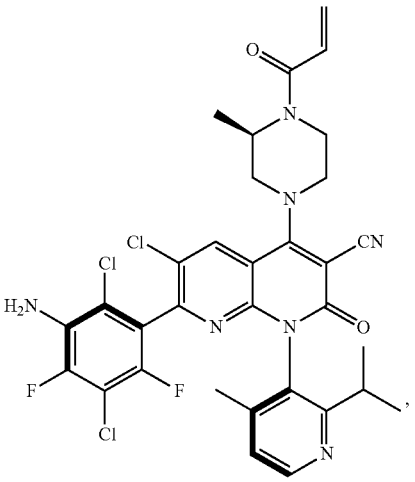

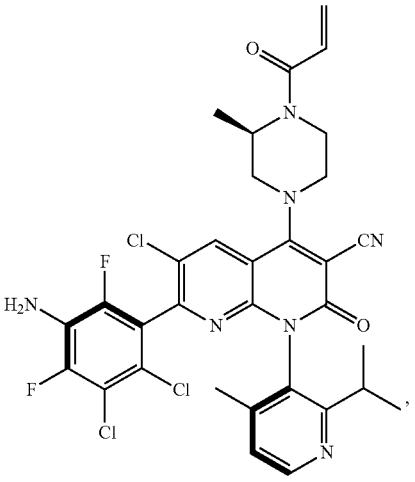

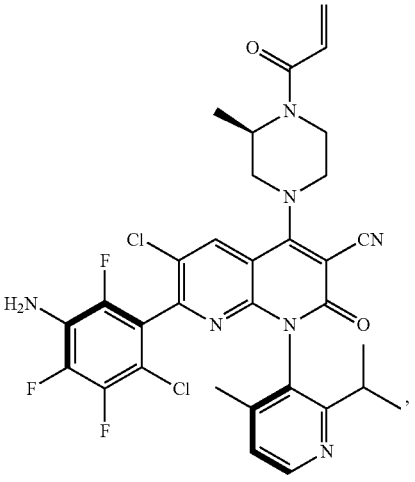

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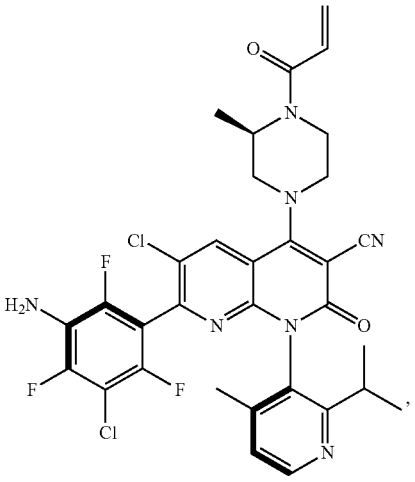

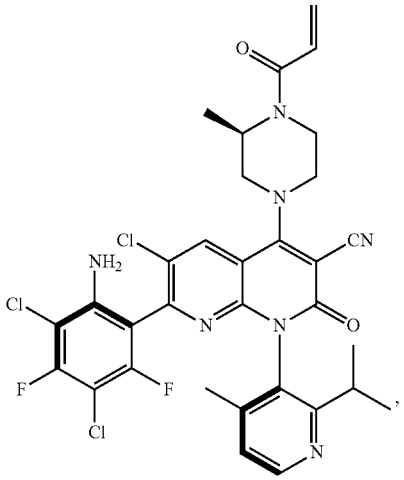

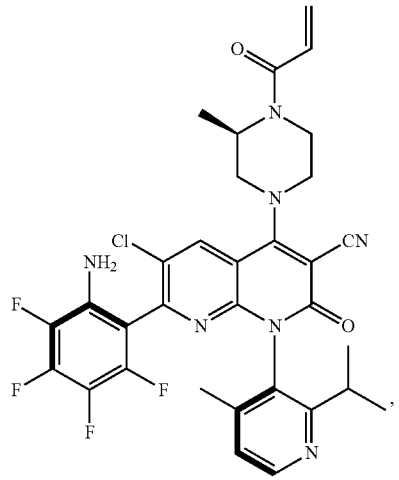

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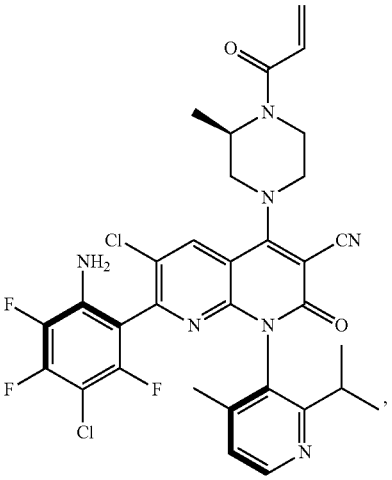

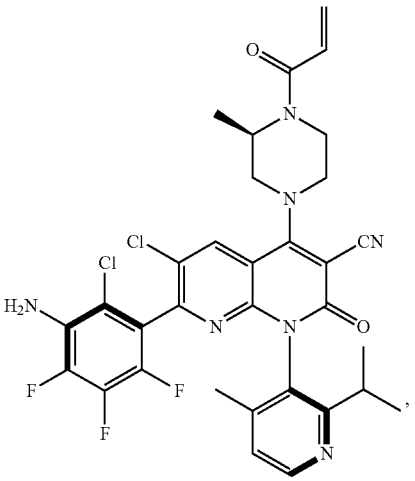

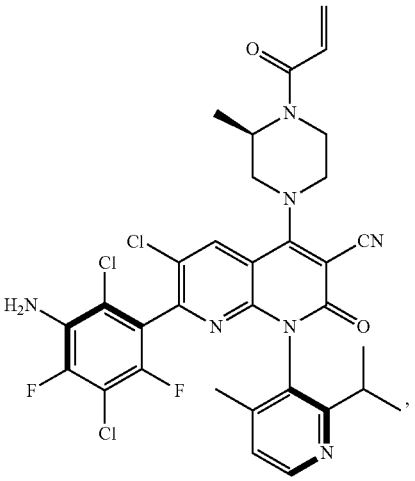

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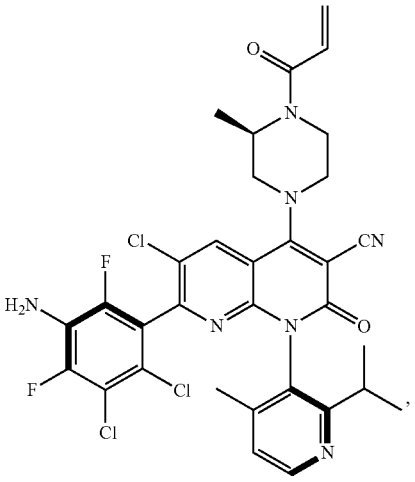

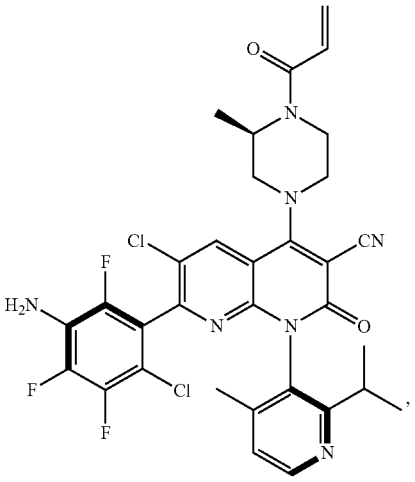

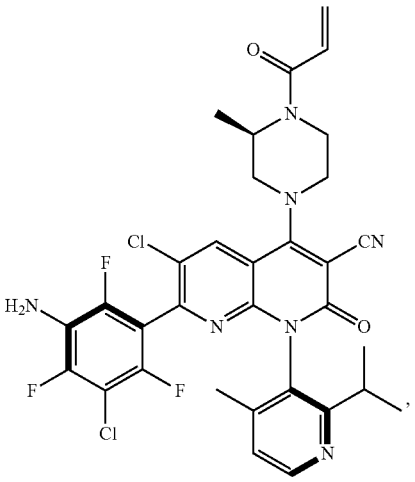

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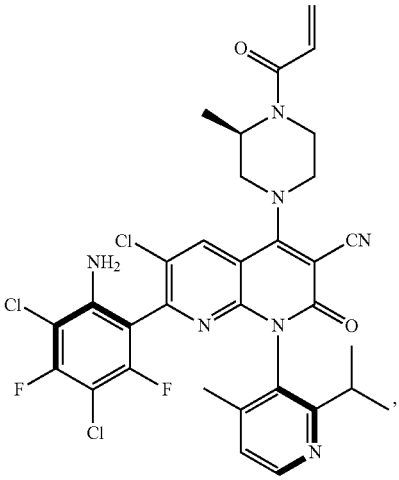

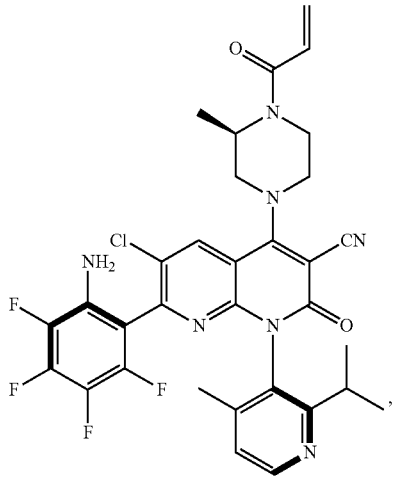

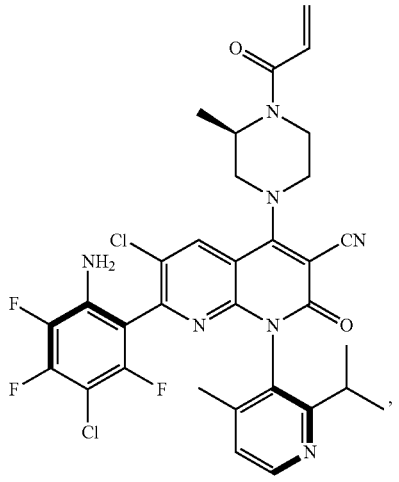

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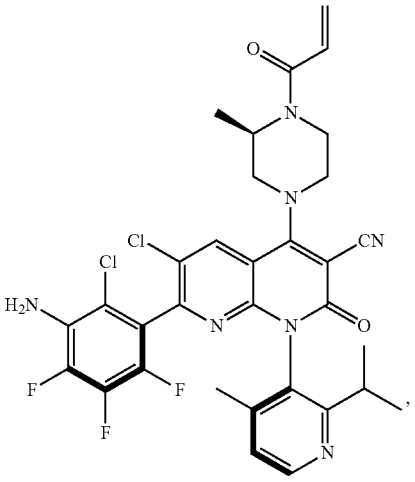

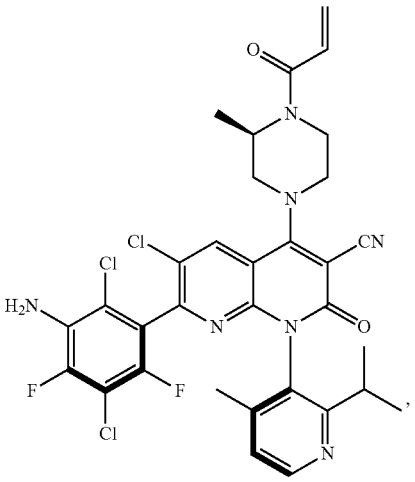

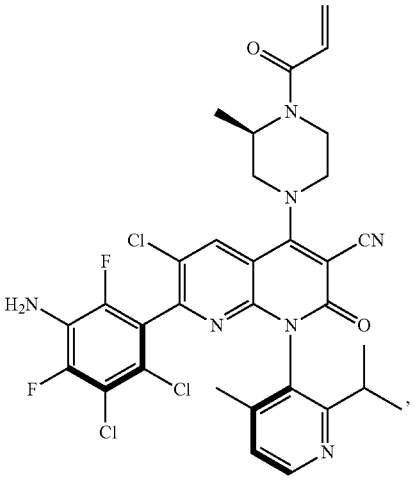

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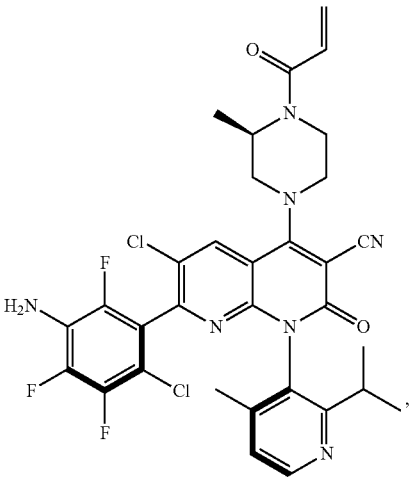

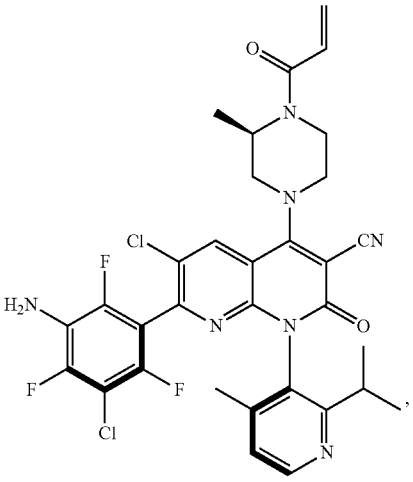

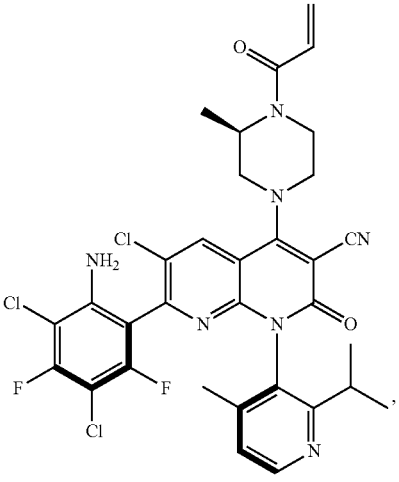

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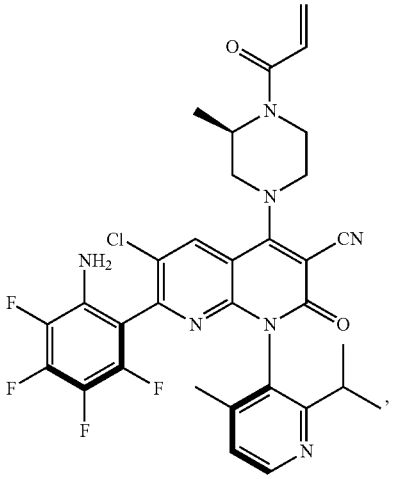

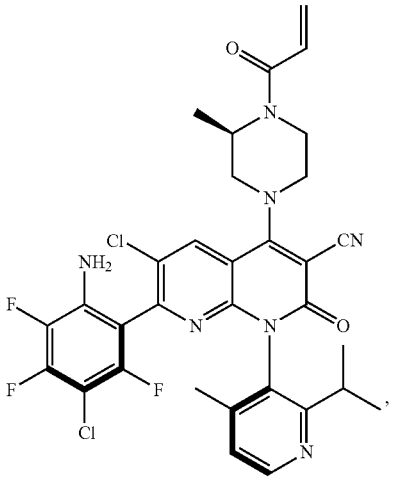

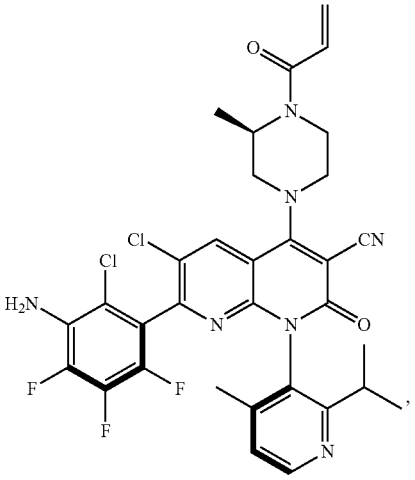

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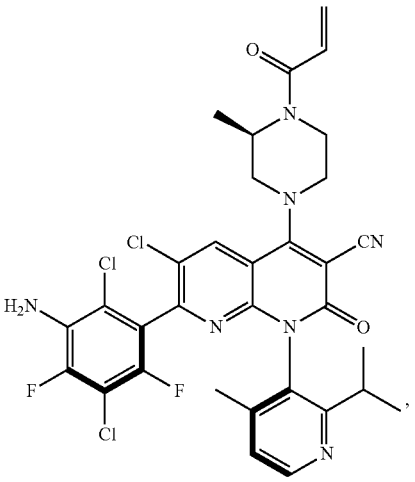

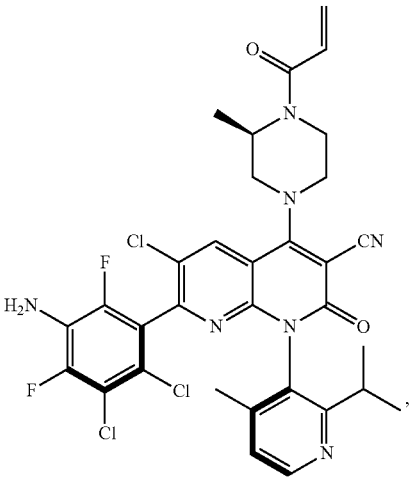

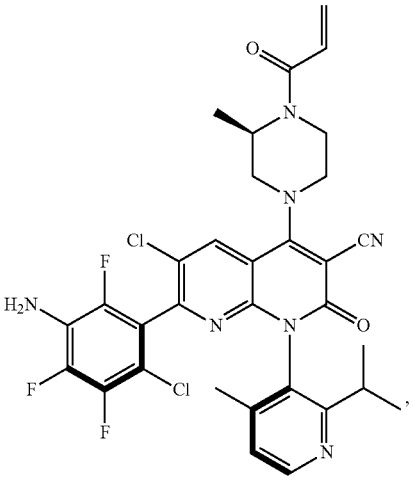

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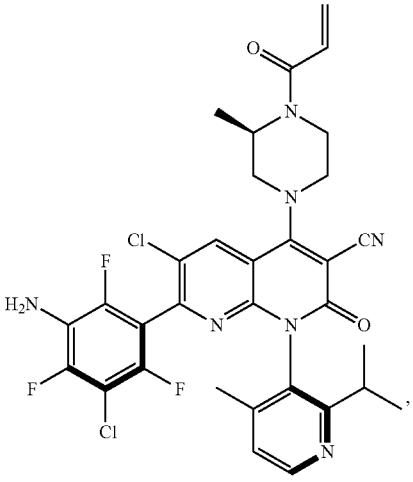

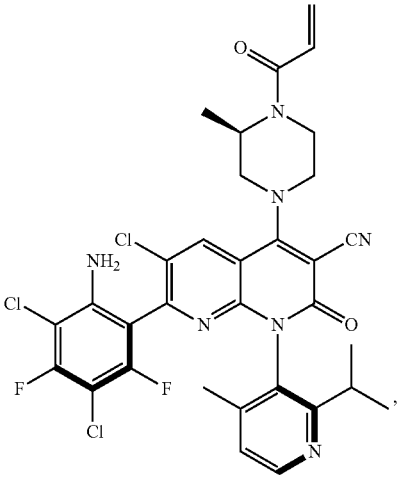

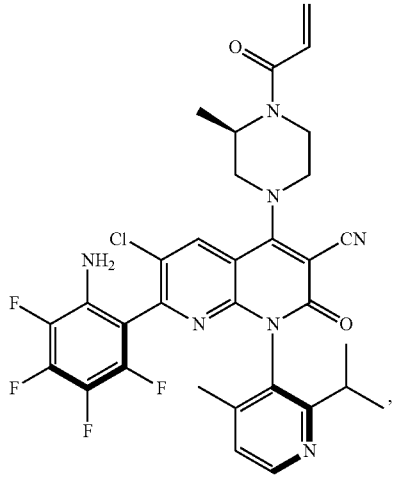

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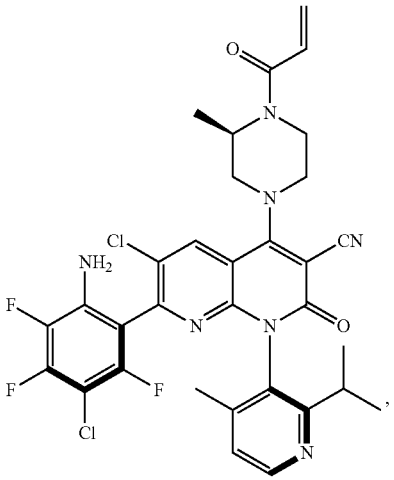

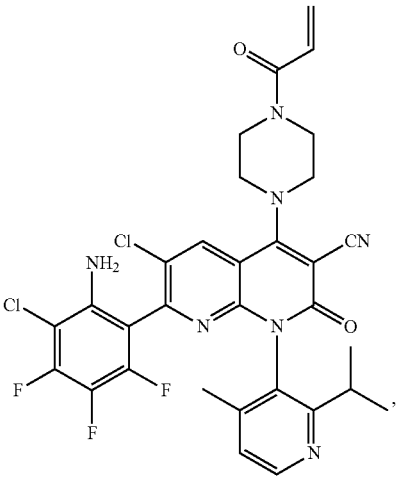

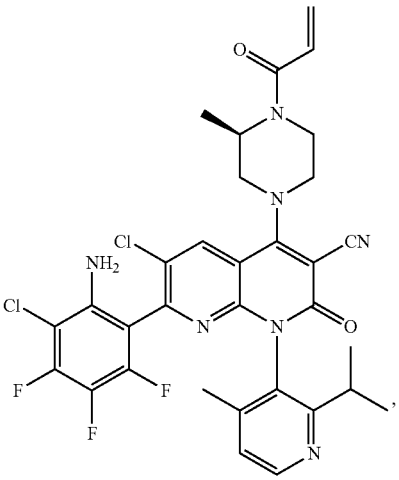

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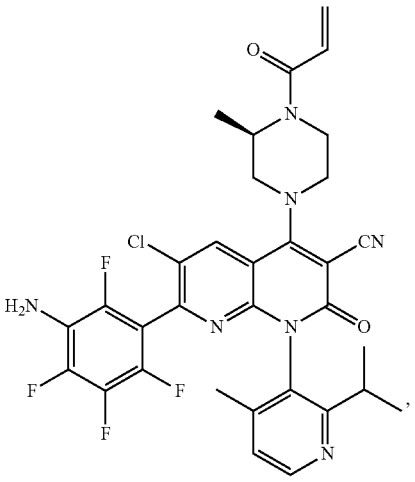

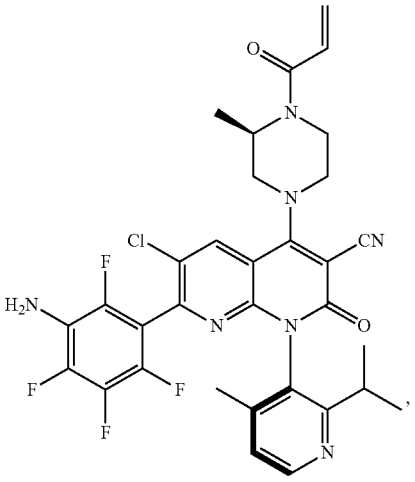

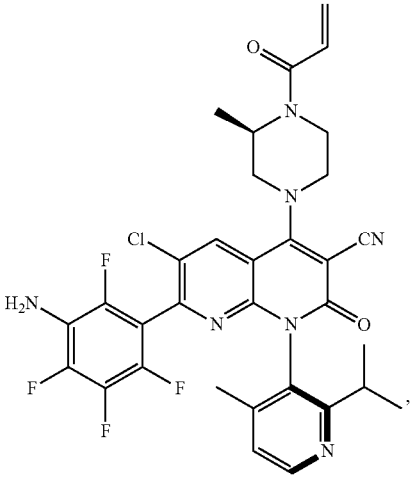

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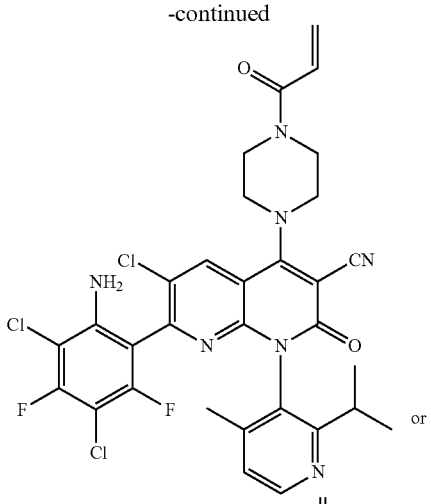

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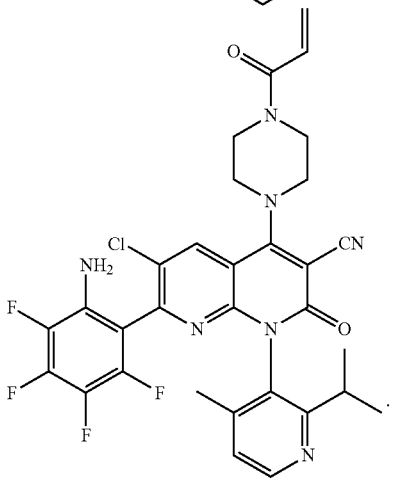
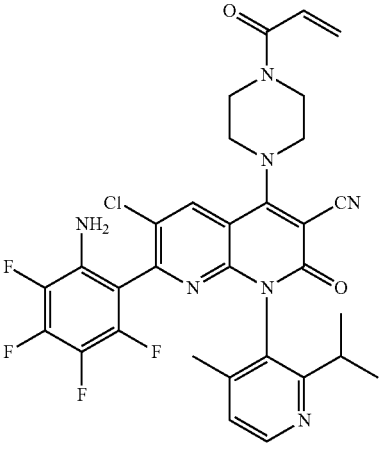


57. The compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, wherein:

the compound is selected from:



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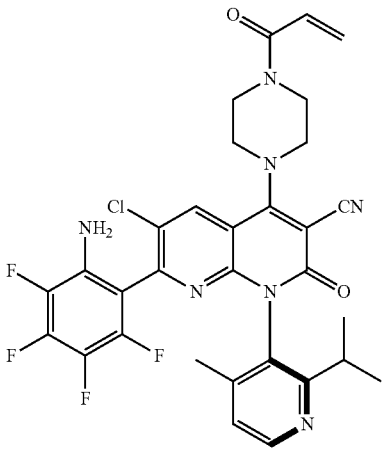

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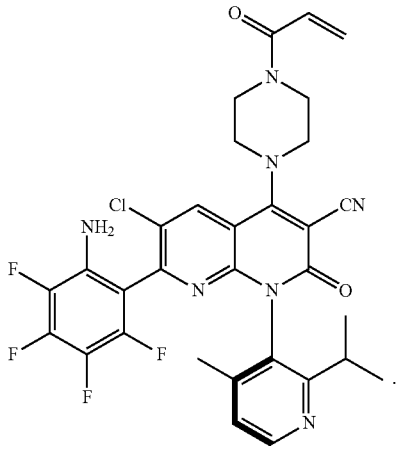
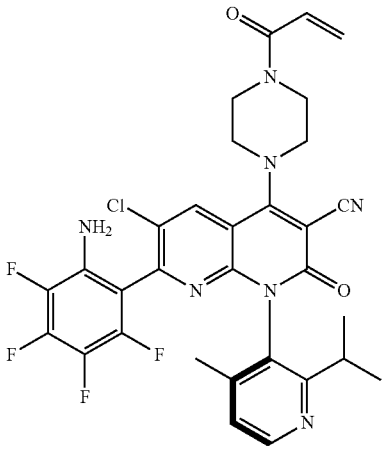


58. A pharmaceutical composition comprising the compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**, and at least one pharmaceutically acceptable excipient.

59. A method of treating a subject having a cancer related to KRAS G12C mutant protein, said method comprising administering to the subject a therapeutically effective amount of the compound of formula (I), a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof according to claim **50**.

60. The method according to claim **59**, wherein, the compound is selected from:

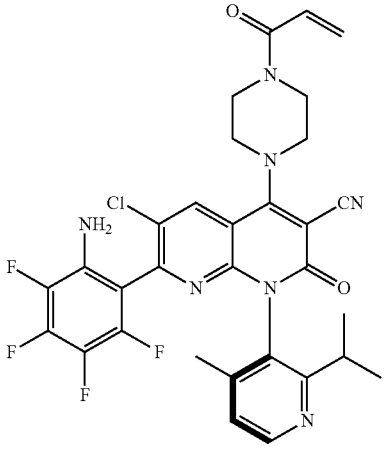


a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a pharmaceutically acceptable salt of the atropisomer thereof.

61. The method according to claim **60**, wherein the cancer is selected from blood cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer or lung cancer, wherein the blood cancer is selected from acute myeloid leukemia or acute lymphocytic leukemia; the lung cancer is selected from non-small cell lung cancer or small cell lung cancer.

62. A method of treating a subject having a cancer related to KRAS G12C mutant protein, said method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to claim **58**.

63. The method according to claim **62**, wherein said pharmaceutical composition comprising a compound having a structure selected from:



a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof or a phar-

maceutically acceptable salt of the atropisomer thereof, and at least one pharmaceutically acceptable excipient.

64. The method according to claim **63**, wherein the cancer is selected from blood cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer or lung cancer; wherein, the blood cancer is selected from acute myeloid leukemia or acute lymphocytic leukemia; and the lung cancer is selected from non-small cell lung cancer or small cell lung cancer.

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