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(54) **PTERIDINE DERIVATIVES AS MODULATORS OF ROR GAMMA**

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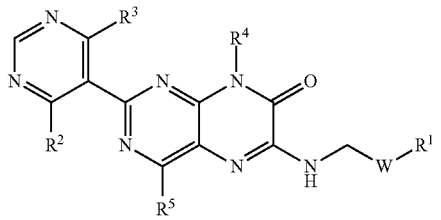
(57) **ABSTRACT**

The present invention encompasses compounds of formula (I) wherein the variables are defined herein which are suitable for the modulation of RORγ and the treatment of diseases related to the modulation of RORγ. The present invention also encompasses processes of making compounds of formula (I) and pharmaceutical preparations containing them.

(I)



PTERIDINE DERIVATIVES AS MODULATORS OF ROR GAMMA

BACKGROUND OF THE INVENTION

Technical Field

[0001] The present invention relates to novel compounds which modulate the activity of RORγ and their use as medicaments.

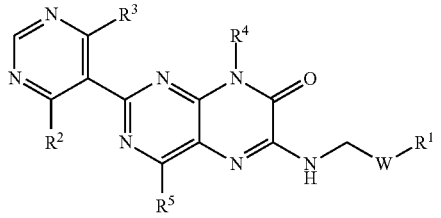
Background

[0002] RORγ (retinoic acid receptor related orphan receptor gamma) (also referred to as "RORγt") is a transcription factor belonging to the steroid hormone receptor superfamily (reviewed in Jetten 2006. Adv. Dev Biol. 16: 313-355.). RORγ has been identified as a transcriptional factor that is required for the differentiation of T cells and secretion of Interleukin 17 (IL-17) from a subset of T cells termed Th_{17} cells (Ivanov, Cell 2006, 126, 1121-1133). The rationale for the use of a RORγ targeted therapy for the treatment of chronic inflammatory diseases is based on the emerging evidence that Th_{17} cells and the cytokine IL-17 contribute to the initiation and progression of the pathogenesis of several autoimmune diseases including psoriasis, ankylosing spondylitis, rheumatoid arthritis, multiple sclerosis and Crohn's disease (reviewed in Miossec, Nature Drug Discovery 2012, 11, 763-776; see also Khan et al., Bioorganic & Medicinal Chemistry Letters 23 (2013), 532-536). The outcome of recent clinical trials with neutralizing antibodies to IL-17 and its receptor IL-17RA (Leonardi 2012, New England Journal of Medicine, 366, 1190-1199; Papp 2012, New England Journal of Medicine 366, 1181-1189) in psoriasis highlight the role of IL-17 in the pathogenesis of this disease. As such, attenuation of IL-17 secretion from activated Th_{17} T cells via inhibition of RORγ may offer similar therapeutic benefit.

SUMMARY OF THE INVENTION

[0003] The invention comprises a novel class of heteroaromatic compounds and methods for making and using the same, said compounds having the general structure of formula (I), wherein the substituent groups are as herein defined:

(I)



[0004] These compounds are useful for the treatment of autoimmune and allergic disorders in that they exhibit potent inhibitory activity against RORγ.

[0005] In a further aspect, a goal of the present invention is to provide compounds with metabolic stability properties consistent with acceptable pharmacokinetic properties. As is known in the art, compounds having poor metabolic stability may not readily achieve desirable therapeutic levels. The preferred compounds of the present invention would be expected to have metabolic stability properties consistent with being a suitable drug.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Conventions Used

[0006] Terms that are not specifically defined here have the meanings that would be apparent to a person skilled in the art, in light of the overall disclosure and the context as a whole.

[0007] As used herein, the following definitions apply, unless stated otherwise:

[0008] The use of the prefix C_{x-y}, wherein x and y each represent a natural number, indicates that the chain or ring structure or combination of chain and ring structure as a whole, specified and mentioned in direct association, may consist of a maximum of y and a minimum of x number of carbon atoms.

[0009] In general, for groups comprising two or more subgroups, unless otherwise indicated the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_{1-3}-alkyl" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached. However, if a bond is depicted just prior to the first named subgroup, then that first named subgroup is the radical attachment point, for example, the substituent "—$S(O)_nC_{1-6}$alkyl" means a C_{1-6}-alkyl-group which is bound to an $S(O)_n$ group, the latter of which is bound to the core or to the group to which the substituent is attached.

[0010] Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both straight-chain (unbranched) and branched form. If an alkyl is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case, on all the hydrogen-carrying carbon atoms.

[0011] For example, the term "C_{1-5}alkyl" includes for example H_3C—, H_3C—CH_2—, H_3C—CH_2—CH_2—, H_3C—$CH(CH_3)$—, H_3C—CH_2—CH_2—CH_2—, H_3C—CH_2—$CH(CH_3)$—, H_3C—$CH(CH_3)$—CH_2—, H_3C—$C(CH_3)_2$—, H_3C—CH_2—CH_2—CH_2—CH_2—, H_3C—CH_2—CH_2—$CH(CH_3)$—, H_3C—CH_2—$CH(CH_3)$—CH_2—, H_3C—$CH(CH_3)$—CH_2—CH_2—, H_3C—CH_2—$C(CH_3)_2$—, H_3C—$C(CH_3)_2$—CH_2—, H_3C—$CH(CH_3)$—$CH(CH_3)$— and H_3C—CH_2—$CH(CH_2CH_3)$—.

[0012] Further examples of alkyl are methyl (Me; —CH_3), ethyl (Et; —CH_2CH_3), 1-propyl (n-propyl; n-Pr; —$CH_2CH_2CH_3$), 2-propyl (i-Pr; iso-propyl; —$CH(CH_3)_2$), 1-butyl (n-butyl; n-Bu; —$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (iso-butyl; i-Bu; —$CH_2CH(CH_3)_2$), 2-butyl (sec-butyl; sec-Bu; —$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (tert-butyl; t-Bu; —$C(CH_3)_3$), 1-pentyl n-pentyl; —$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (—$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (—$CH(CH_2CH_3)_2$), 3-methyl-1-butyl (iso-pentyl; —$CH_2CH_2CH(CH_3)_2$), 2-methyl-2-butyl (—$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (—$CH(CH_3)CH(CH_3)_2$), 2,2-dimethyl-1-propyl(neo-pentyl; —$CH_2C(CH_3)_3$), 2-methyl-1-butyl (—$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (n-hexyl; —$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (—$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (—$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (—$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (—$CH(CH_3)CH(CH_3)$

CH_2CH_3), 4-methyl-2-pentyl (—$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (—$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (—$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (—$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (—$CH(CH_3)C(CH_3)_3$), 2,3-dimethyl-1-butyl (—$CH_2CH(CH_3)CH(CH_3)CH_3$), 2,2-dimethyl-1-butyl (—$CH_2C(CH_3)_2CH_2CH_3$), 3,3-dimethyl-1-butyl (—$CH_2CH_2C(CH_3)_3$), 2-methyl-1-pentyl (—$CH_2CH(CH_3)CH_2CH_2CH_3$), 3-methyl-1-pentyl (—$CH_2CH_2CH(CH_3)CH_2CH_3$), 1-heptyl (n-heptyl), 2-methyl-1-hexyl, 3-methyl-1-hexyl, 2,2-dimethyl-1-pentyl, 2,3-dimethyl-1-pentyl, 2,4-dimethyl-i-pentyl, 3,3-dimethyl-i-pentyl, 2,2,3-trimethyl-i-butyl, 3-ethyl-1-pentyl, 1-octyl (n-octyl), 1-nonyl (n-nonyl); 1-decyl (n-decyl) etc.

[0013] By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

[0014] The above definition for alkyl also applies if alkyl is a part of another (combined) group such as for example C_{x-y}alkylamino or C_{x-y}alkoxy.

[0015] Unlike alkyl, alkenyl, when used alone or in combination, consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C—C double bond and a carbon atom can only be part of one C—C double bond. If in an alkyl as hereinbefore defined having at least two carbon atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding alkenyl is formed. Alkenyl may optionally be present in the cis or trans or E or Z orientation with regard to the double bond(s).

[0016] Unlike alkyl, alkynyl, when used alone or in combination, consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C—C triple bond. If in an alkyl as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding alkynyl is formed.

[0017] Haloalkyl (haloalkenyl, haloalkynyl), when used alone or in combination, is derived from the previously defined alkyl (alkenyl, alkynyl) by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a haloalkyl (haloalkenyl, haloalkynyl) is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

[0018] Examples of haloalkyl (haloalkenyl, haloalkynyl) are —CF_3, —CHF_2, —CH_2F, —CF_2CF_3, —$CHFCF_3$, —CH_2CF_3, —CF_2CH_3, —$CHFCH_3$, —$CF_2CF_2CF_3$, —$CF_2CH_2CH_3$, —$CF{=}CF_2$, —$CCl{=}CH_2$, —$CBr{=}CH_2$, —$C{\equiv}C{-}CF_3$, —$CHFCH_2CH_3$, —$CHFCH_2CF_3$ etc.

[0019] Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

[0020] The term "cycloalkyl", when used alone or in combination, refers to a nonaromatic 3 to 12-membered (but preferably, 3 to 6-membered) monocyclic carbocyclic radical or a nonaromatic 6 to 10-membered fused bicyclic, bridged bicyclic, propellane or spirocyclic carbocyclic radical. The C_{3-12} cycloalkyl may be either saturated or partially unsaturated, and the carbocycle may be attached by any atom of the cycle which results in the creation of a stable structure. Non-limiting examples of 3 to 10-membered monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, and cyclohexanone. Non-limiting examples of 6 to 10-membered fused bicyclic carbocyclic radicals include bicyclo[1.1.1]pentane, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, and bicyclo[4.4.0]decanyl (decahydronaphthalenyl). Non-limiting examples of 6 to 10-membered bridged bicyclic carbocyclic radicals include bicyclo[2.2.2]heptanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.2.1]octanyl. Non-limiting examples of 6 to 10-membered propellane carbocyclic radicals include but are not limited to [1.1.1.]propellane, [3.3.3]propellane and [3.3.1]propellane. Non-limiting examples of 6 to 10-membered spirocyclic carbocyclic radicals include but are not limited to spiro[3,3]heptanyl, spiro[3,4]octanyl and spiro[4,4]heptanyl.

[0021] The term "heterocyclyl", when used alone or in combination, refers to a heterocyclic ring system that contains 2-10 carbon atoms and one to four heteroatom ring atoms chosen from NH, NR', oxygen and sulfur wherein R' is C_{1-6} alkyl. The term "heterocyclyl" includes stable nonaromatic 4-8 membered monocyclic heterocyclic radicals or a stable nonaromatic 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical. The heterocycle may be either completely saturated or partially unsaturated. In one embodiment the heterocycle is a C_{3-6} heterocycle, i.e., containing 3 to 6 ring carbon atoms. Non-limiting examples of nonaromatic monocyclic heterocyclic radicals include tetrahydrofuranyl, azetidinyl, pyrrolidinyl, pyranyl, tetrahydropyranyl, dioxanyl, thiomorpholinyl, 1,1-dioxo-1.lamda$_6$-thiomorpholinyl, morpholinyl, piperidinyl, piperazinyl, and azepinyl. Non-limiting examples of nonaromatic 6 to 11-membered fused bicyclic radicals include octahydroindolyl, octahydrobenzofuranyl, and octahydrobenzothiophenyl. Non-limiting examples of nonaromatic 6 to 11-membered bridged bicyclic radicals include 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[3.2.1]octanyl. Non-limiting examples of nonaromatic 6 to 11-membered spirocyclic heterocyclic radicals include 7-aza-spiro[3,3]heptanyl, 7-spiro[3,4]octanyl, and 7-aza-spiro[3,4]octanyl. Sulfur and nitrogen may optionally be present in all the possible oxidation stages (for example, sulfur: sulfoxide —SO—, sulfone —SO_2—; nitrogen: N-oxide).

[0022] The term "aryl", when used alone or in combination, refers to an aromatic hydrocarbon ring containing from six to fourteen carbon ring atoms (e.g., a C_{6-14} aryl, preferably C_6-10 aryl). The term C_{6-14} aryl includes monocyclic rings, fused rings and bicyclic rings where at least one of the rings is aromatic. Non-limiting examples of C_{6-14} aryls include phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, benzocycloheptanyl and benzocycloheptenyl.

[0023] As used herein, the term "heteroaryl", when used alone or in combination, refers to a heteroaromatic ring system that contains 2-10 carbon atoms and 1-4 heteroatom ring atoms selected from N, NH, NR', O and S wherein R' is C_{1-6} alkyl. The term "heteroaryl" includes aromatic 5 to 6-membered monocyclic heteroaryls and aromatic 7 to 11-membered heteroaryl bicyclic or fused rings where at least one of the rings is aromatic. Non-limiting examples of 5 to 6-membered monocyclic heteroaryl rings include furanyl, oxazolyl, isoxazolyl, oxadiazolyl, pyranyl, thiazolyl,

pyrazolyl, pyrrolyl, imidazolyl, tetrazolyl, triazolyl, thienyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, and purinyl. Non-limiting examples of 7 to 11-membered heteroaryl bicyclic or fused rings include benzimidazolyl, 1,3-dihydrobenzoimidazol-2-one, quinolinyl, dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzofuranyl, benzopyranyl, benzodioxolyl, benzoxazolyl, benzothiazolyl, pyrrolo[2,3-b] pyridinyl, and imidazo[4,5-b]pyridinyl. Sulfur and nitrogen may optionally be present in all the possible oxidation stages (for example, sulphur: sulfoxide —SO—, sulfone —SO_2—; nitrogen: N-oxide).

[0024] The compounds of the invention are only those which are contemplated to be chemically stable as will be appreciated by those skilled in the art. For example, a compound which would have a "dangling valency", or a carbanion are not compounds contemplated by the inventive methods disclosed herein.

[0025] Unless specifically indicated, throughout the specification and appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, etc.) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof, and their corresponding unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like.

[0026] Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

[0027] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (also see Pharmaceutical salts, Birge, S. M. et al., J. Pharm. Sci., (1977), 66, 1-19).

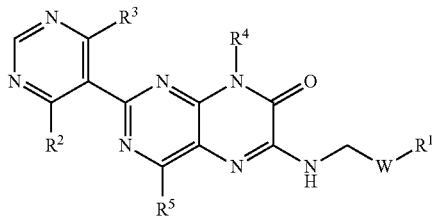
[0028] The pharmaceutically acceptable salts of the present invention can be synthesised from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

[0029] By a therapeutically effective amount for the purposes of this invention is meant a quantity of substance that is capable of obviating symptoms of illness or alleviating these symptoms, or which prolong the survival of a treated patient.

Embodiments of the Invention

[0030] A general embodiment of the invention is directed to a compound of formula (I) below:

(I)



[0031] wherein:

[0032] R^1 is selected from —$S(O)_nR^6$, —$S(O)_nNR^7R^8$, and —S(O)(NH)R^6;

[0033] wherein:

[0034] R^6 is:

[0035] C_{1-3} alkyl

[0036] R^7 and R^8 are each —H; and

[0037] n is 1 or 2;

[0038] R^2 and R^3 are independently selected from

[0039] C_{1-3}alkyl;

[0040] cyclopropyl; and

[0041] methoxy;

[0042] R^4 is C_{1-6}alkyl, optionally substituted with one or two groups independently selected from

[0043] C_{3-6}cycloalkyl;

[0044] halogen;

[0045] —CF_3; and

[0046] —CN;

[0047] R^5 is selected from

[0048] C_{1-3}alkyl, optionally substituted with 1 to 3 fluoro groups;

[0049] —CH_2OH;

[0050] —$CH_2OC(O)C_{1-3}$alkyl; and

[0051] —OC_{1-3}alkyl;

[0052] W is selected from
[0053] pyridinyl;
[0054] pyrimidinyl;
[0055] pyrizinyl;
[0056] phenyl; and
[0057] piperidinyl;
[0058] and the pharmaceutically acceptable salts thereof.
[0059] In another embodiment, there are provided compounds of the formula (I) as described according to the embodiment above and wherein
[0060] R^1 is selected from —$S(O)_{nR6}$, —$S(O)_nNR^7R^8$, and —$S(O)(NH)R^6$;
[0061] wherein:
[0062] R^6 is C_{1-3} alkyl;
[0063] R^7 and R^8 are each —H; and
[0064] n is 2;
[0065] R^2 and R^3 are independently selected from
[0066] methyl;
[0067] cyclopropyl; and
[0068] methoxy;
[0069] R^4 is C_4alkyl, optionally substituted with one or two groups independently selected from cyclopropyl;
[0070] —F;
[0071] —CF_3; and
[0072] —CN;
[0073] R^5 is selected from
[0074] —CH_3;
[0075] —CH_2F;
[0076] —CH_2OH;
[0077] —$CH_2OC(O)CH_3$; and
[0078] —OCH_3;
[0079] W is selected from
[0080] 2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, 2-pyrizinyl and phenyl;
[0081] and the pharmaceutically acceptable salts thereof.
[0082] In another embodiment, there are provided compounds of the formula (I) as described according to any of the embodiments above and wherein
[0083] R^1 is selected from —$S(O)_nR^6$, —$S(O)_nNR^7R^8$, and —$S(O)(NH)R^6$;
[0084] wherein:
[0085] R^6 is C_{1-2} alkyl;
[0086] R^7 and R^8 are each —H; and
[0087] n is 2;
[0088] R^2 and R^3 are independently selected from
[0089] methyl;
[0090] cyclopropyl; and
[0091] methoxy;
[0092] R^4 is C_4alkyl, optionally substituted with one or two groups independently selected from
[0093] cyclopropyl;
[0094] —F;
[0095] —CF_3; and
[0096] —CN;
[0097] R^5 is selected from
[0098] —CH_3;
[0099] —CH_2F;
[0100] —CH_2OH;
[0101] —$CH_2OC(O)CH_3$; and
[0102] —OCH_3;
[0103] W is selected from
[0104] 2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, 2-pyrizinyl and phenyl;
[0105] and the pharmaceutically acceptable salts thereof.
[0106] In another embodiment, there are provided compounds of the formula (I) as described according to any of the embodiments above and wherein
[0107] R^1 is selected from —$S(O)_nR^6$, —$S(O)_nNR^7R^8$, and —$S(O)(NH)R^6$;
[0108] wherein:
[0109] R^6 is C_{1-2} alkyl;
[0110] R^7 and R^8 are each —H; and
[0111] n is 2;
[0112] R^2 is methyl or methoxy;
[0113] R^3 is cyclopropyl;
[0114] R^4 is C_{1-4}alkyl, optionally substituted with a group selected from cyclopropyl and —CF_3;
[0115] R^5 is selected from
[0116] —CH_3;
[0117] —CH_2F; and
[0118] —CH_2OH;
[0119] W is selected from
[0120] 2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, and phenyl;
[0121] and the pharmaceutically acceptable salts thereof.
[0122] In another embodiment, there are provided compounds of the formula (I) as described according to any of the embodiments above and wherein
[0123] R^2 is methyl or methoxy;
[0124] R^3 is cyclopropyl;
[0125] R^4 is C_{1-4}alkyl, optionally substituted with a group selected from cyclopropyl and —CF_3;
[0126] R^5 is —CH_3;
[0127] W is selected from
[0128] 2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, and phenyl;
[0129] and the pharmaceutically acceptable salts thereof.
[0130] In another embodiment, there are provided compounds of the formula (I) as described according to any of the embodiments above and wherein
[0131] W is selected from 2-pyridinyl and, 3-pyridinyl;
[0132] and the pharmaceutically acceptable salts thereof.
[0133] In another aspect of the invention, there is provided a compound of the general formula (I) according to any of the embodiments above, or a pharmaceutically acceptable salt thereof for use in a therapeutic method as described hereinbefore and hereinafter.
[0134] Table 1 shows representative compounds of the invention which can be made by the methods described in the general synthetic schemes, the examples, and known methods in the art.

TABLE 1

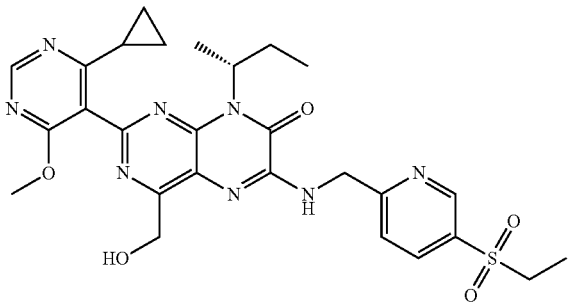
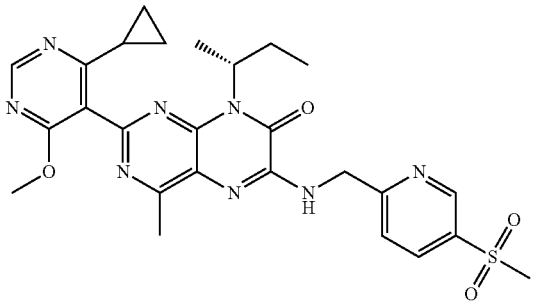
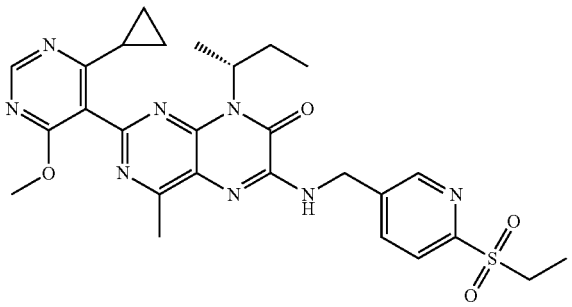
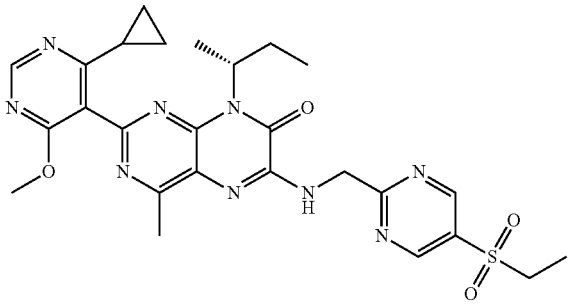
Example	Structure	RT	m/z [M + H]+	HPLC Method
1		0.96	581.5	A
2		0.99	551.4	A
3		1.03	565.5	A
4		1.03	566.4	A

TABLE 1-continued

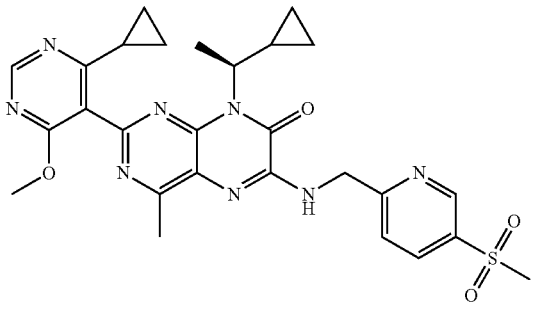
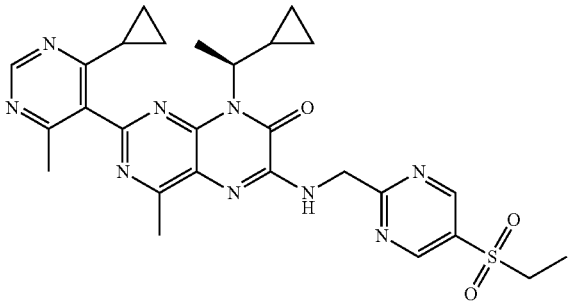
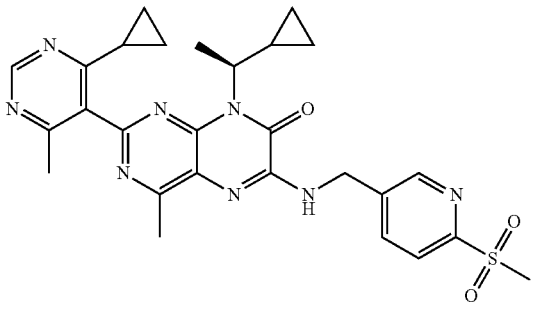
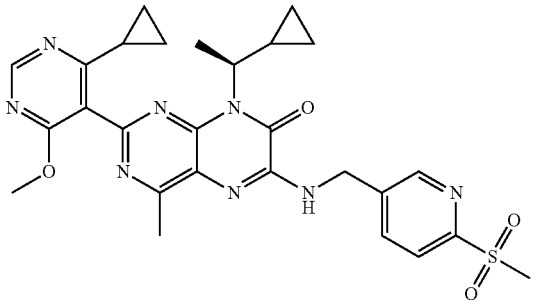
Example	Structure	RT	m/z [M + H]+	HPLC Method
5		1.01	563.4	A
6		1.00	562.3	A
7		0.96	547.4	A
8		1.01	563.5	A

TABLE 1-continued

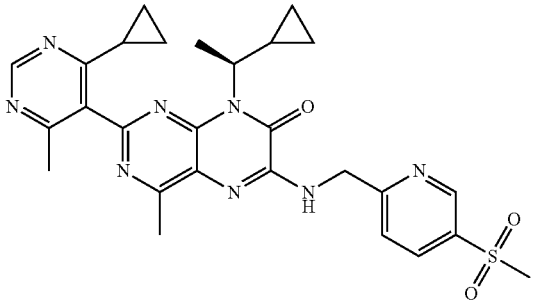
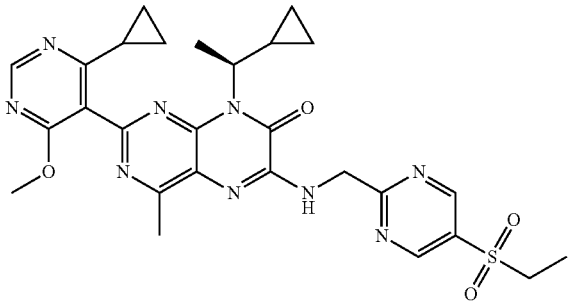
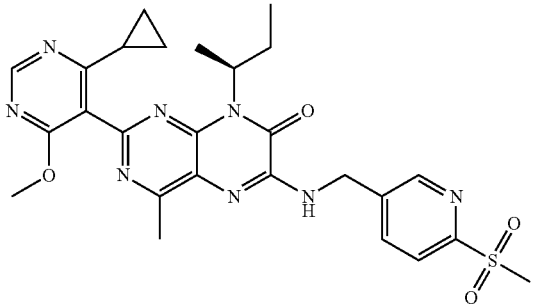
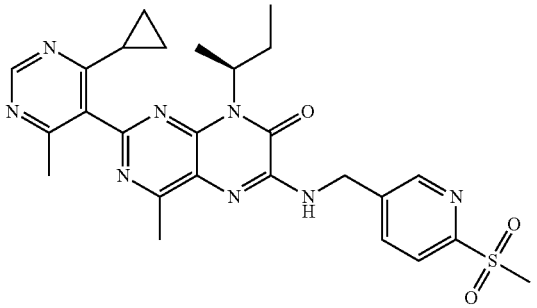
Example	Structure	RT	m/z [M + H]+	HPLC Method
9		0.95	547.4	A
10		1.05	578.4	A
11		0.99	551.4	A
12		0.94	535.5	A

TABLE 1-continued

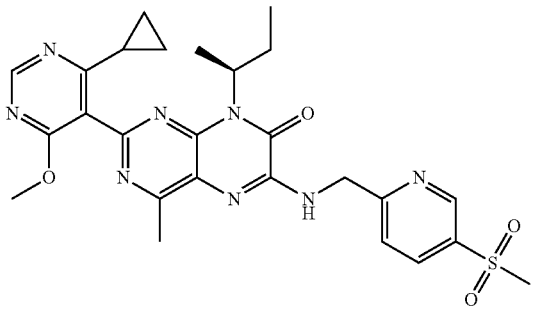
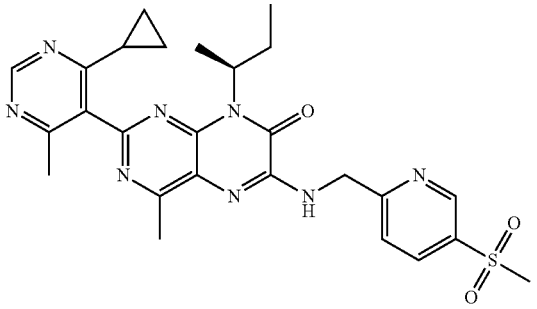
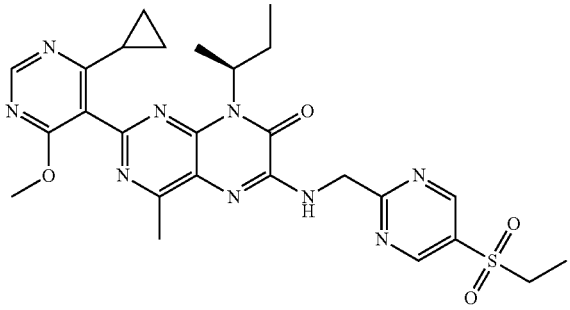
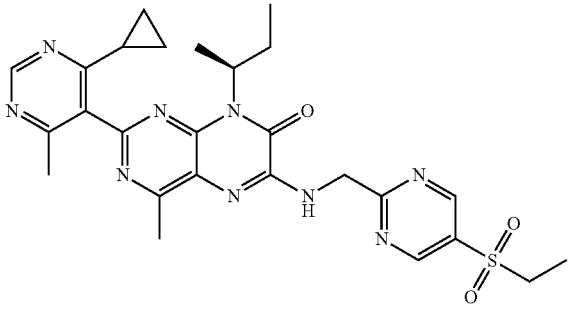
Example	Structure	RT	m/z [M + H]+	HPLC Method
13		1.00	551.6	A
14		0.95	535.7	A
15		1.04	566.7	A
16		0.99	550.3	A

TABLE 1-continued

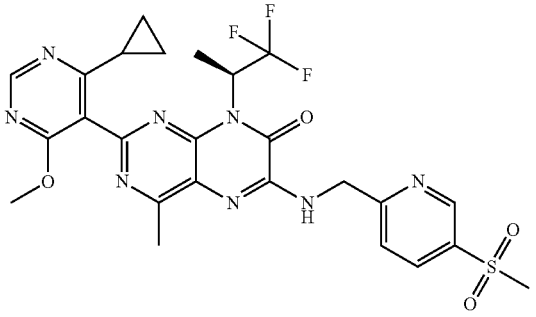
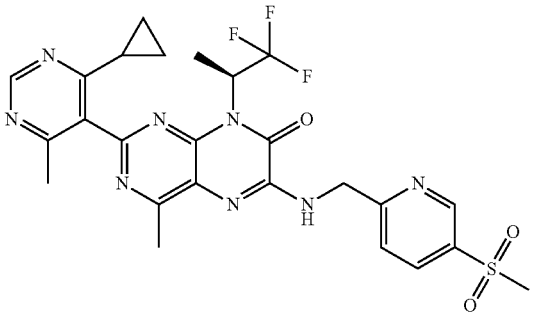
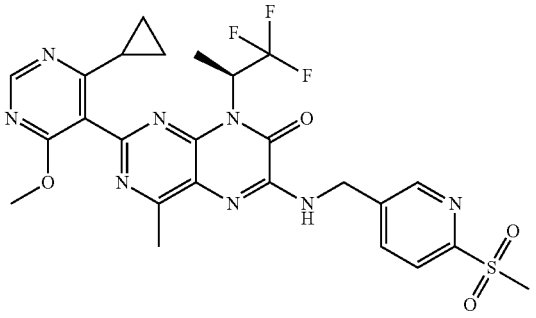
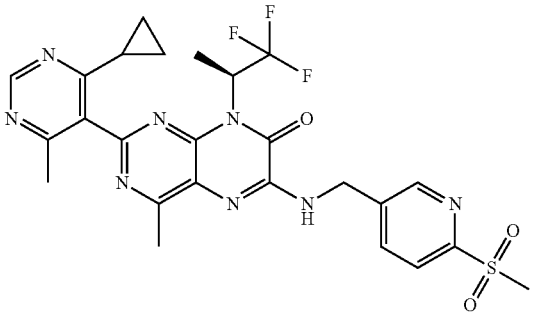
Example	Structure	RT	m/z [M + H]+	HPLC Method
17		1.01	591.3	A
18		0.94	575.4	A
19		1.01	591.5	A
20		0.96	575.4	A

TABLE 1-continued

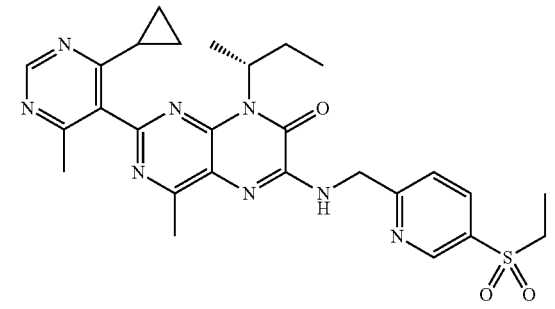
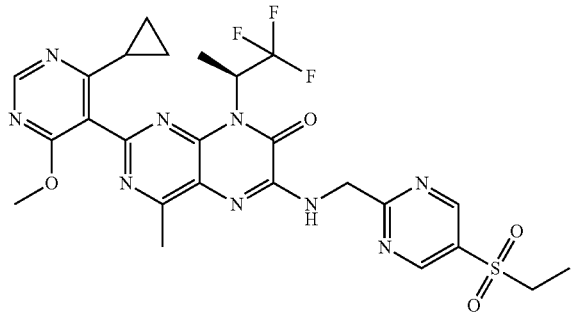
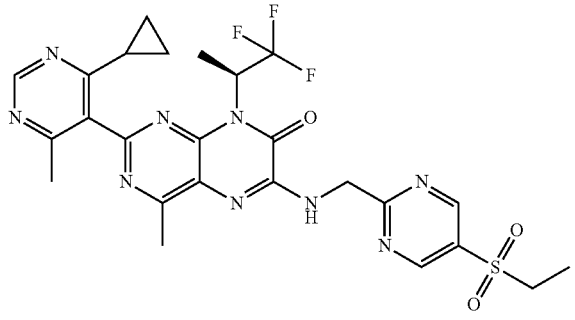
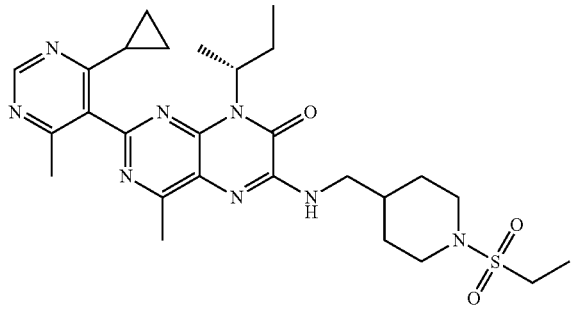
Example	Structure	RT	m/z [M + H]+	HPLC Method
21		1.02	565.4	A
22		1.00	606.4	A
23		0.95	590.4	A
24		1.20	555.3	A

TABLE 1-continued

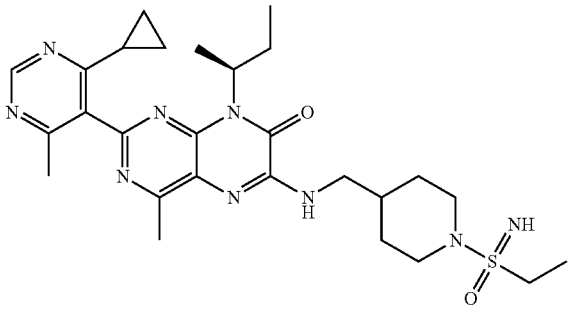
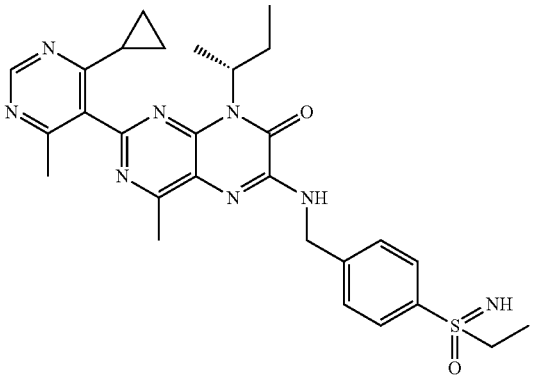
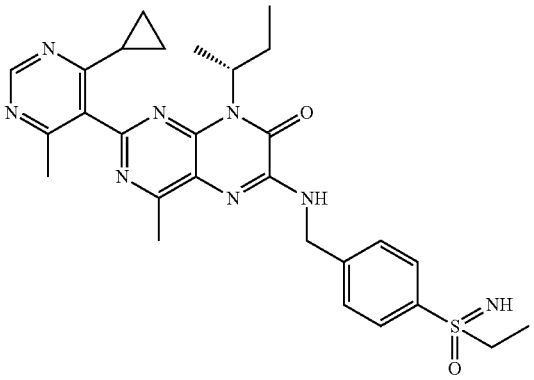
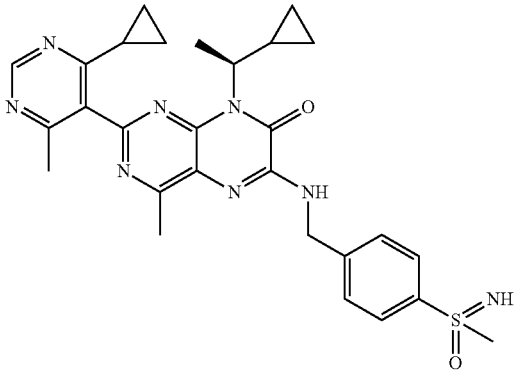
Example	Structure	RT	m/z [M + H]+	HPLC Method
25		1.04	545.3	A
26a		1.04	547.3	A
26b		1.04	547.2	A
27a		0.91	545.4	A

TABLE 1-continued

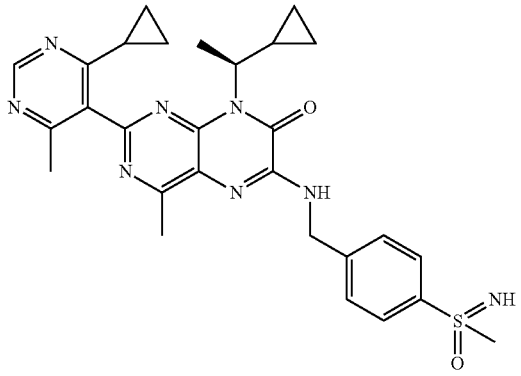
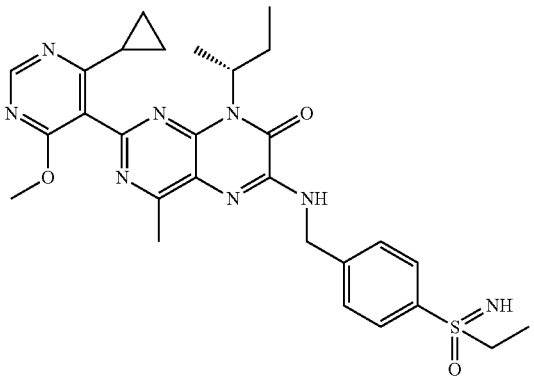
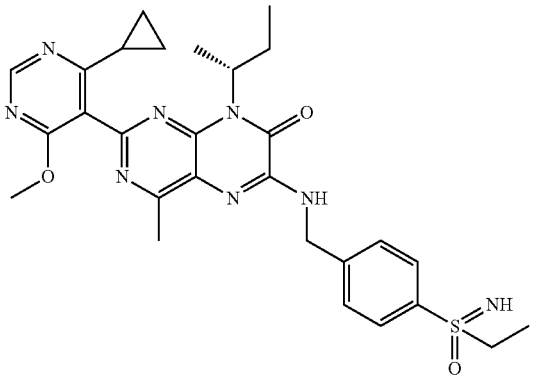
Example	Structure	RT	m/z [M + H]+	HPLC Method
27b		0.91	545.4	A
29a		1.09	563.3	A
29b		1.09	563.3	A

TABLE 1-continued

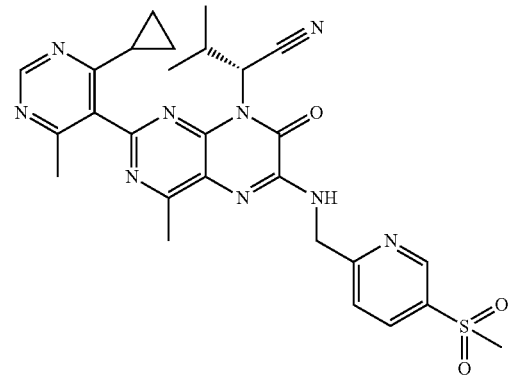
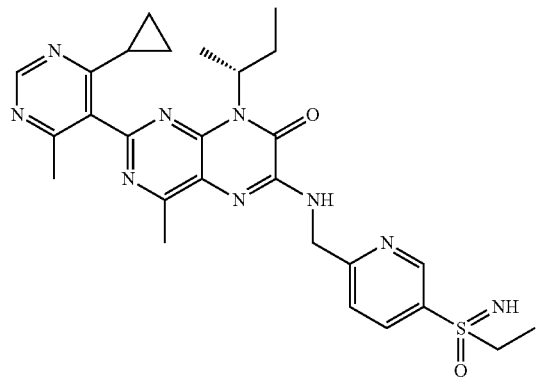
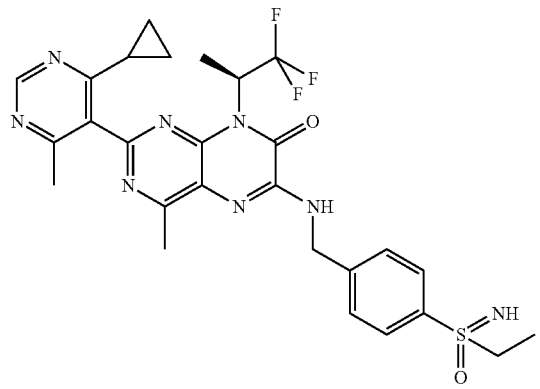
Example	Structure	RT	m/z [M + H]+	HPLC Method
31		1.00	560.2	A
33		1.04	547.2	A
34a		0.90	587.2	A

TABLE 1-continued

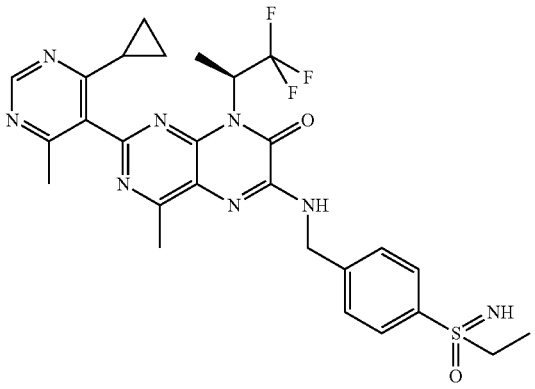
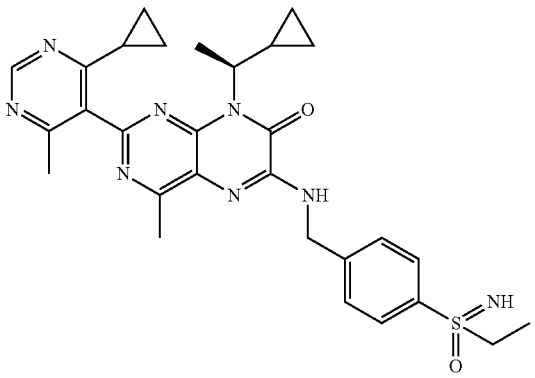
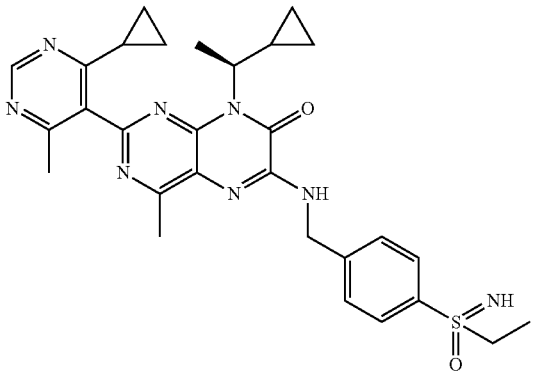
Example	Structure	RT	m/z [M + H]+	HPLC Method
34b		0.90	587.2	A
36a		0.95	559.4	A
36b		0.95	559.4	A

TABLE 1-continued

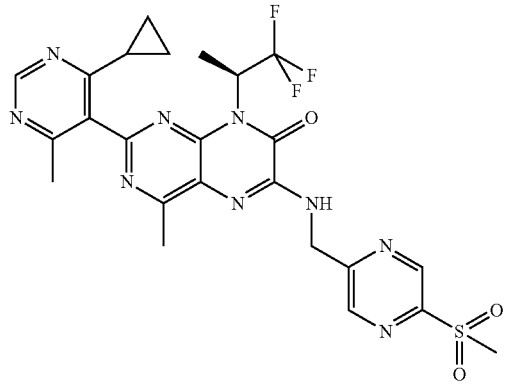
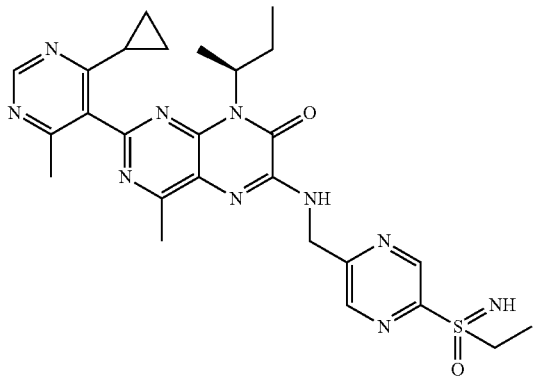
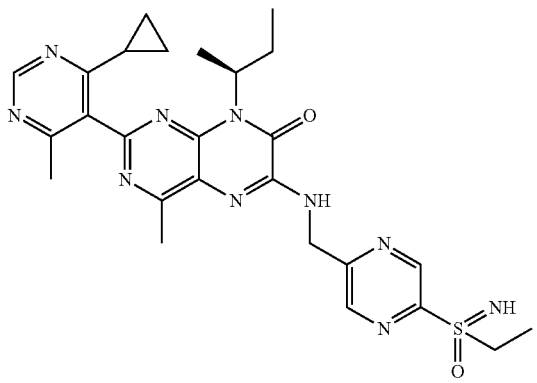
Example	Structure	RT	m/z [M + H]+	HPLC Method
37		1.07	576.2	A
38a		0.95	547.3	A
38b		0.93	547.3	A

TABLE 1-continued

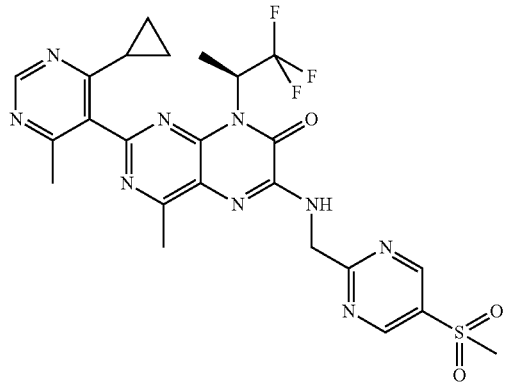
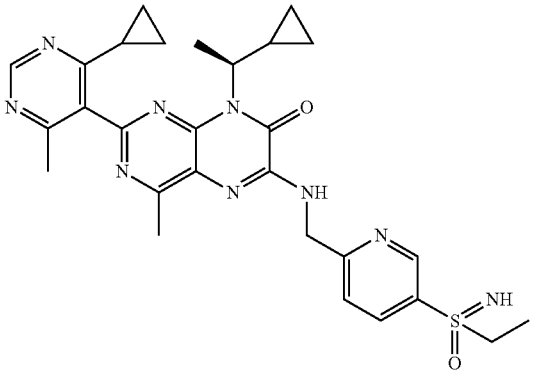
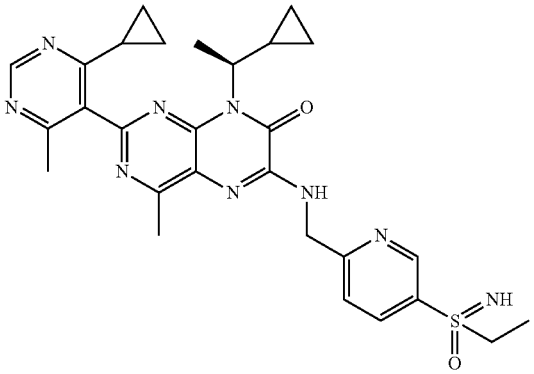
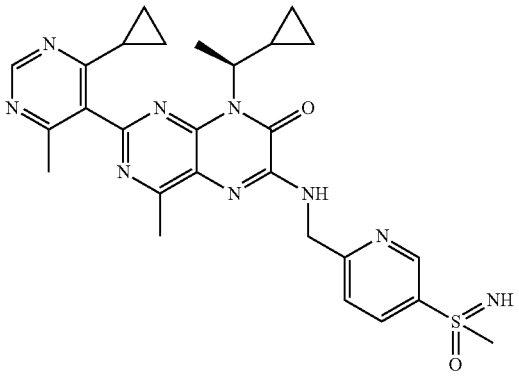
Example	Structure	RT	m/z [M + H]+	HPLC Method
41		1.07	574.2	A
42a		0.87	560.4	A
42b		0.87	560.4	A
43a		0.82	546.4	A

TABLE 1-continued

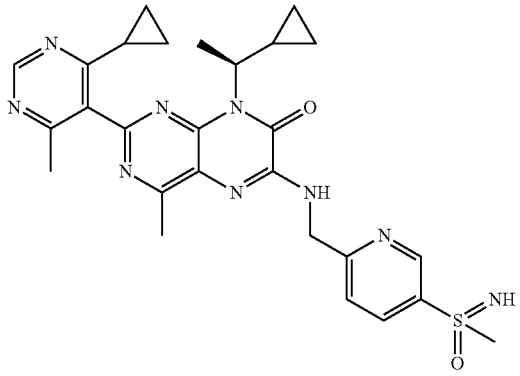
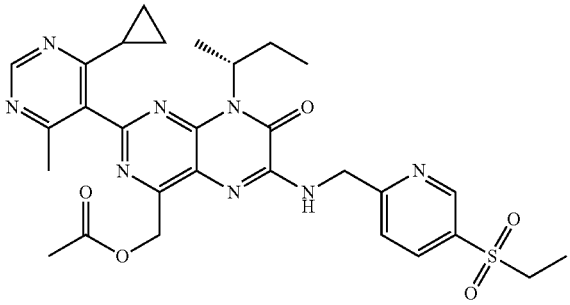
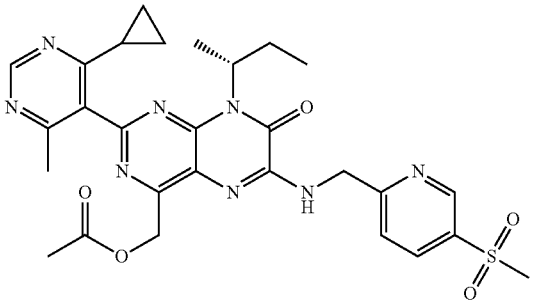
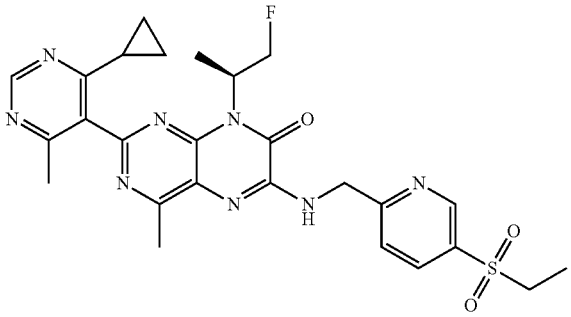
Example	Structure	RT	m/z [M + H]+	HPLC Method
43b		0.83	546.4	A
46		1.03	607.7	A
47		0.99	593.1	A
48		0.86	553.1	A

TABLE 1-continued

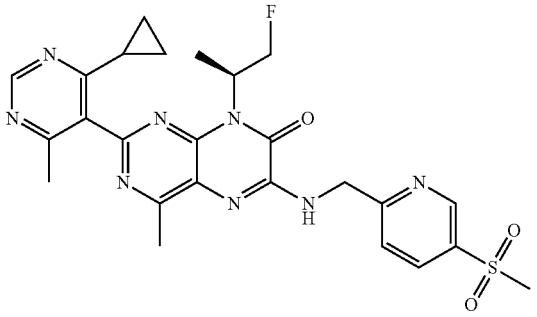
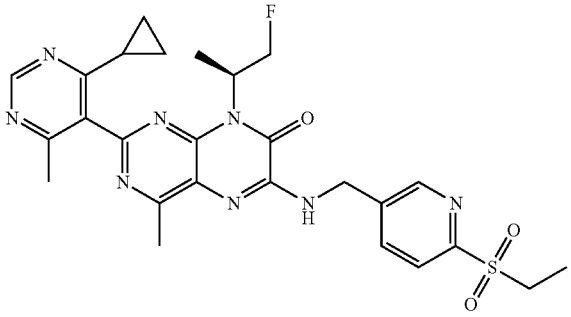
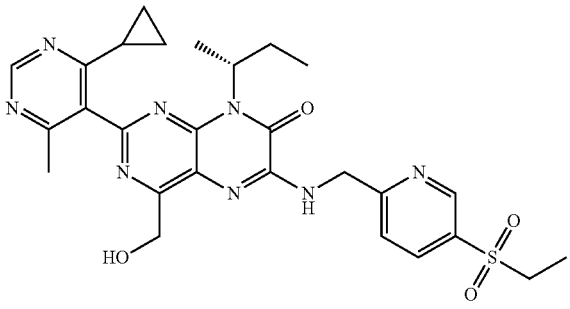
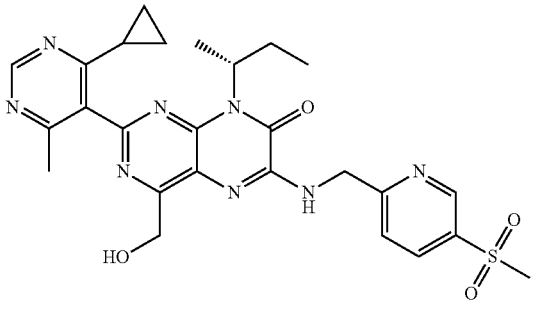
Example	Structure	RT	m/z [M + H]+	HPLC Method
49		0.81	539.1	A
50		0.86	553.1	A
51		0.87	565.2	A
52		0.83	551.2	A

TABLE 1-continued

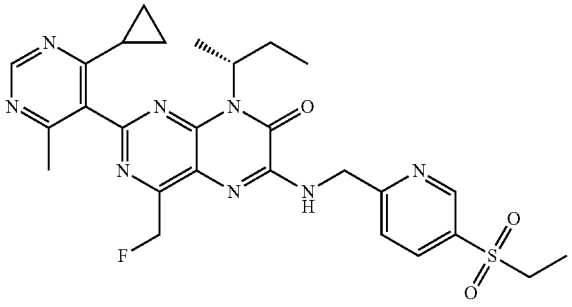
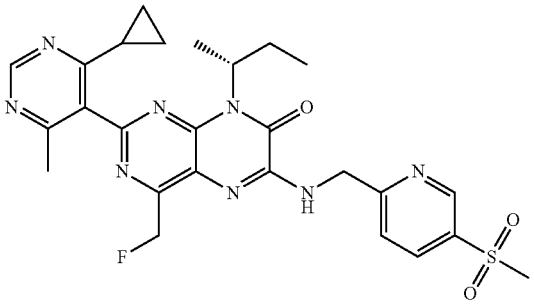
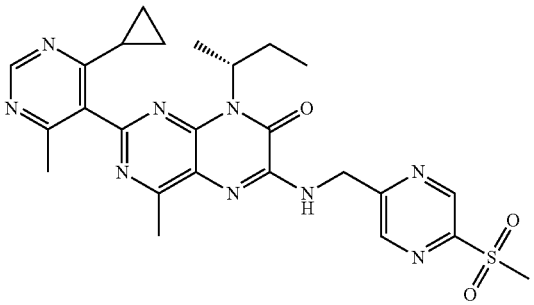
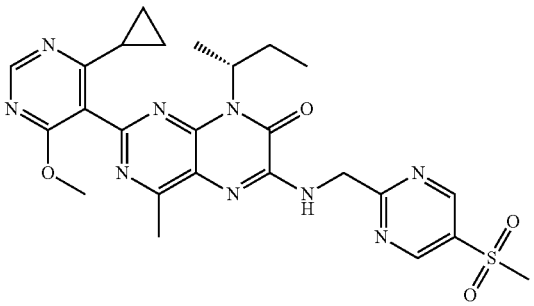
Example	Structure	RT	m/z [M + H]+	HPLC Method
53		0.96	567.2	A
54		0.91	553.2	A
55		0.96	536.0	A
56		1.02	552.0	A

TABLE 1-continued

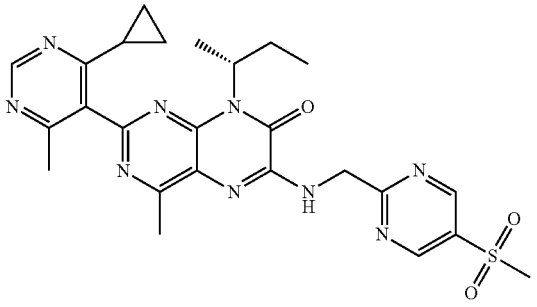
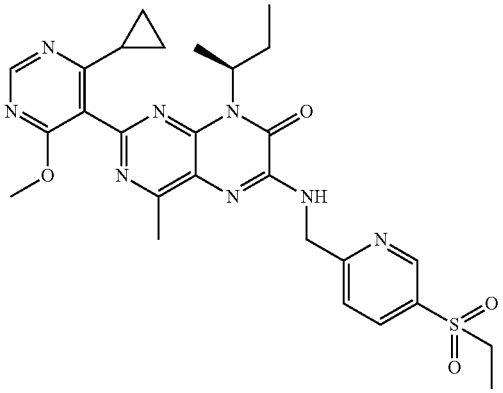
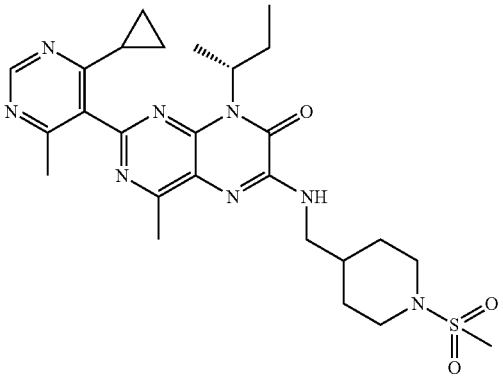
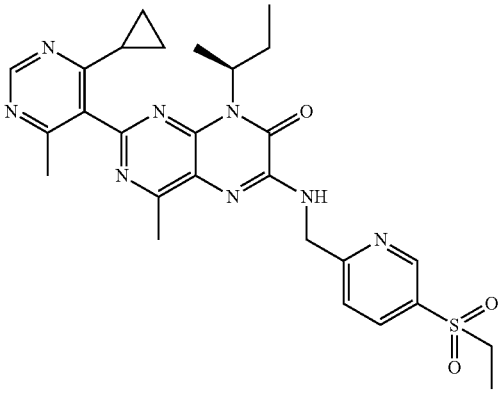
Example	Structure	RT	m/z [M + H]+	HPLC Method
57		0.96	534.2	A
58		1.08	564.9	A
59		1.15	541.3	A
60		1.03	549.0	A

TABLE 1-continued

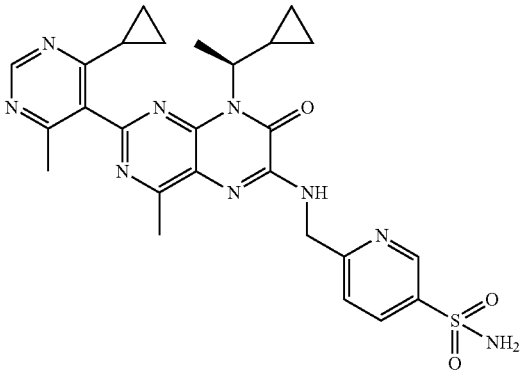
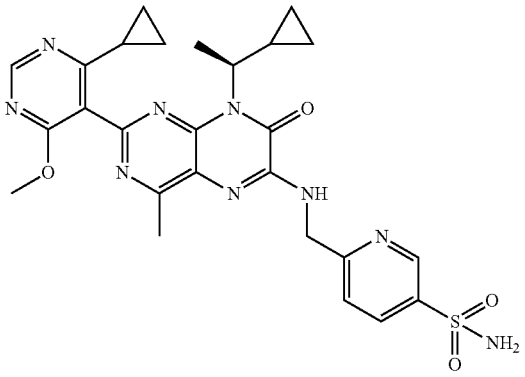
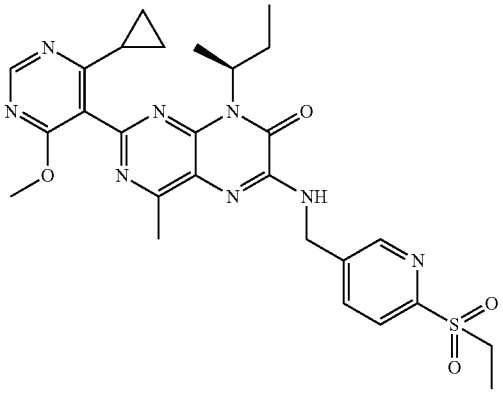
Example	Structure	RT	m/z [M + H]+	HPLC Method
61		0.88	548.2	A
62		0.94	565.2	A
63		1.07	563.2	A

TABLE 1-continued

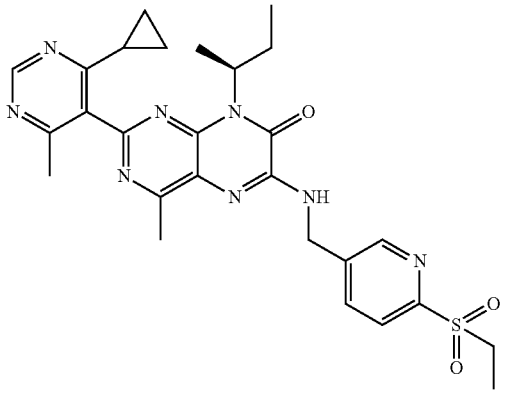
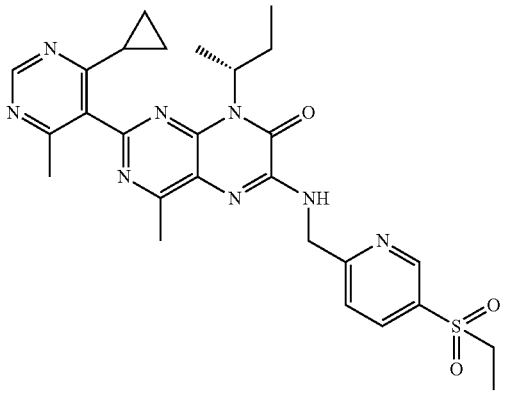
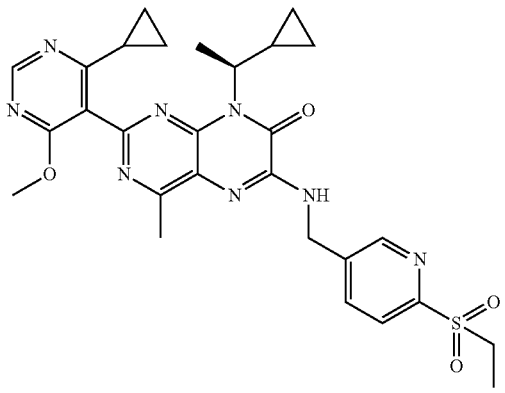
Example	Structure	RT	m/z [M + H]+	HPLC Method
64		1.02	550.5	A
65		1.01	549.3	A
66		1.09	577.0	A

TABLE 1-continued

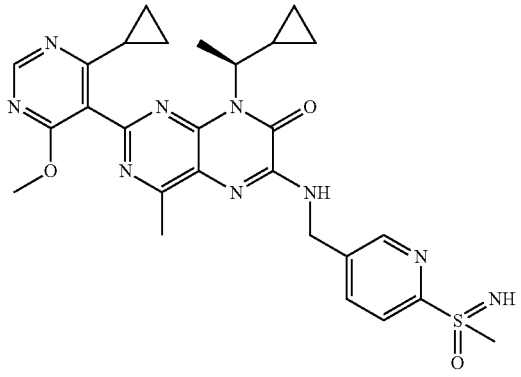
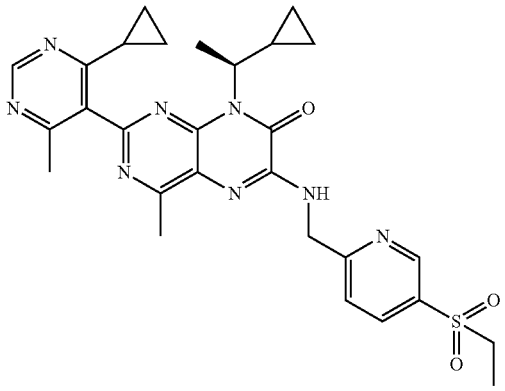
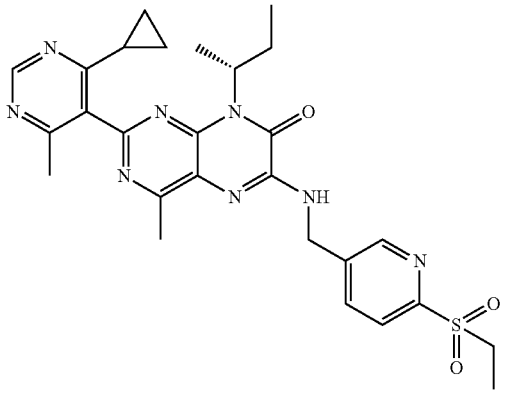
Example	Structure	RT	m/z [M + H]+	HPLC Method
67		0.95	561.3	A
68		1.04	562.2	A
69		1.02	547.3	A

TABLE 1-continued

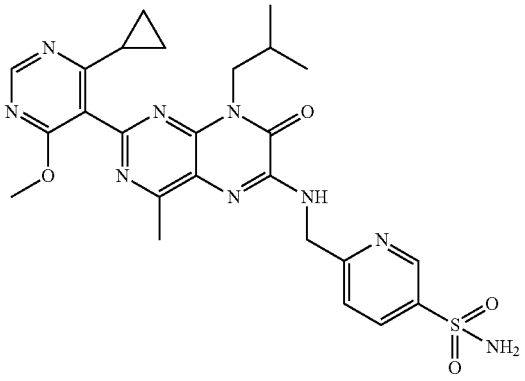
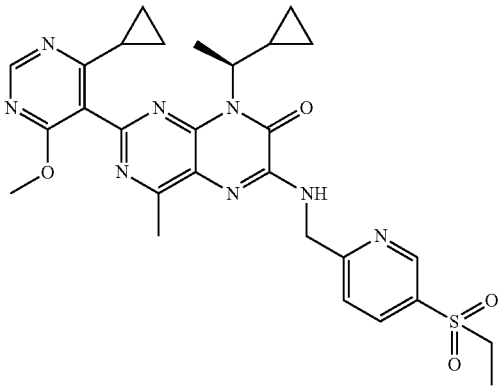
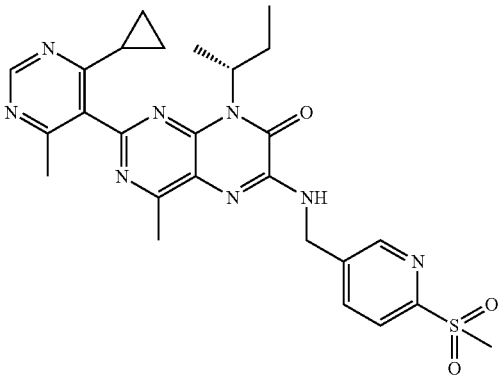
Example	Structure	RT	m/z [M + H]+	HPLC Method
70		0.92	552.5	A
71		1.09	578.4	A
72		0.98	533.2	A

TABLE 1-continued

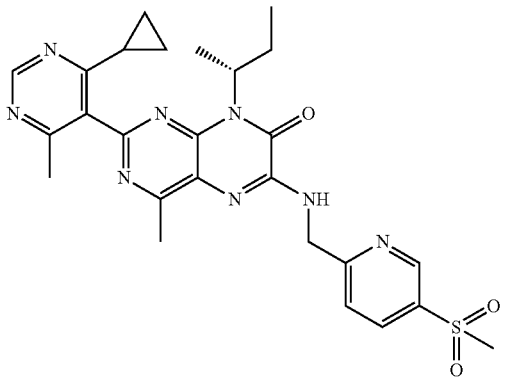
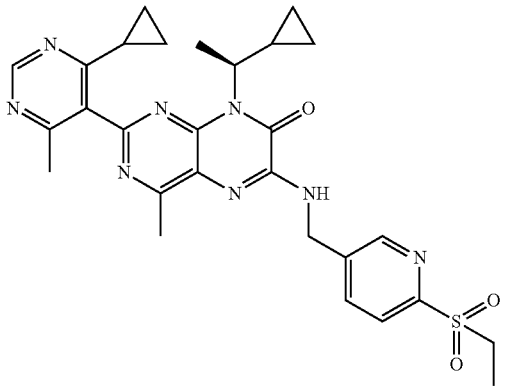
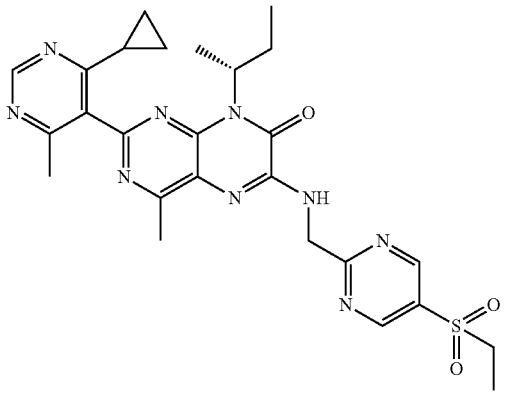
Example	Structure	RT	m/z [M + H]+	HPLC Method
73		0.98	535.3	A
74		1.04	562.2	A
75		1.02	549.2	A

TABLE 1-continued

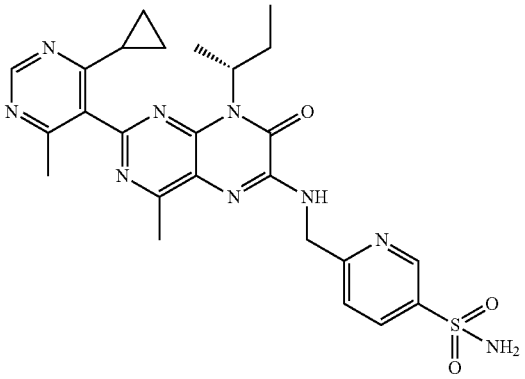
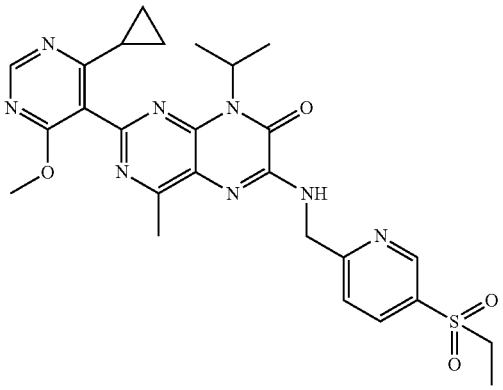
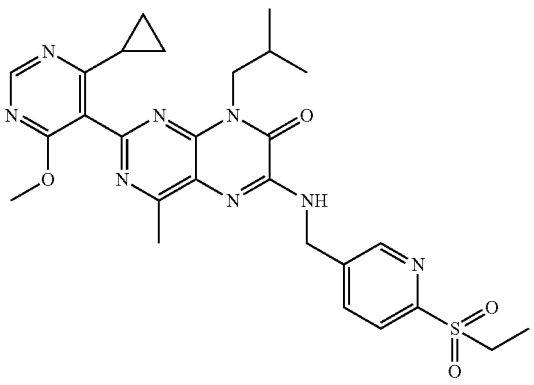
Example	Structure	RT	m/z [M + H]+	HPLC Method
76		0.87	536.1	A
77		1.01	551.3	A
78		1.01	565.1	A

TABLE 1-continued

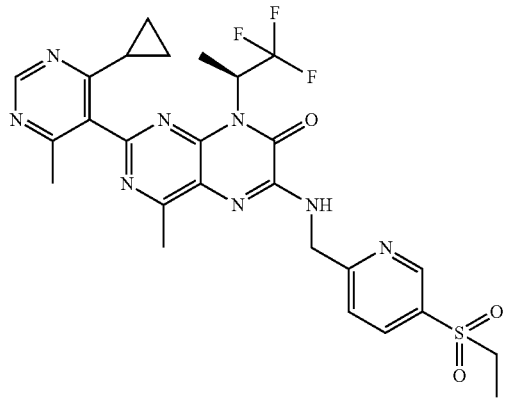
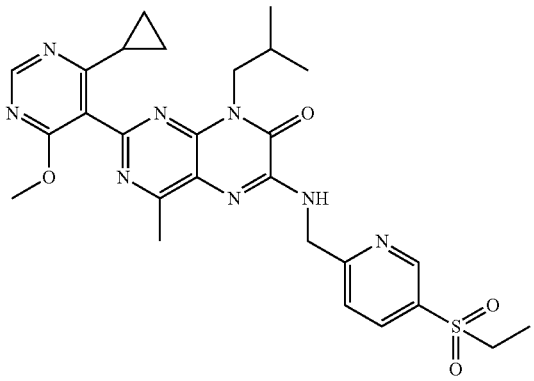
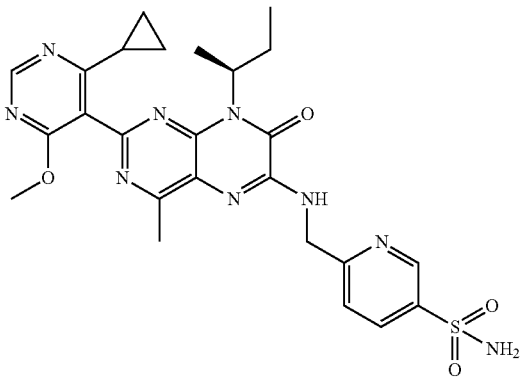
Example	Structure	RT	m/z [M + H]+	HPLC Method
79		1.01	589.2	A
80		1.06	565.3	A
81		0.93	552.2	A

TABLE 1-continued

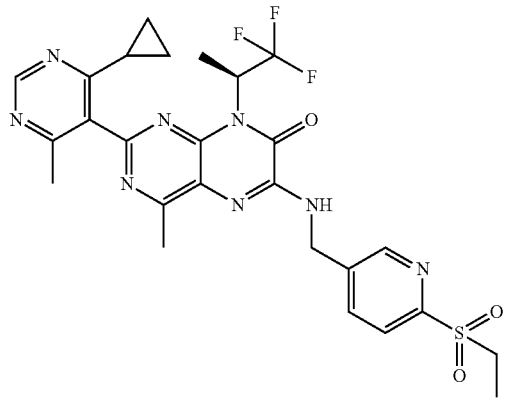
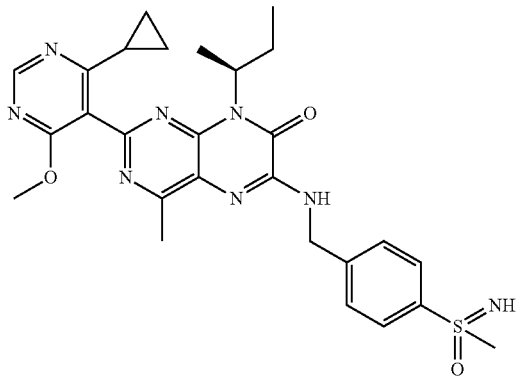
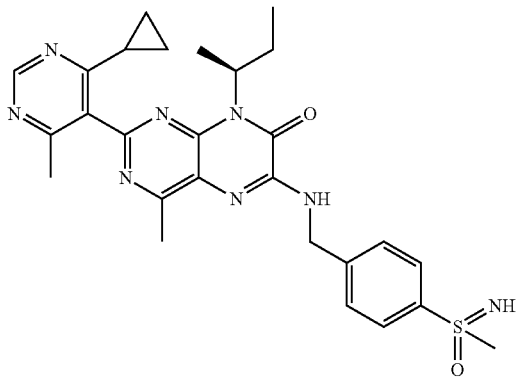
Example	Structure	RT	m/z [M + H]+	HPLC Method
82		1.01	589.1	A
83		0.94	549.2	A
84		0.87	533.2	A

TABLE 1-continued

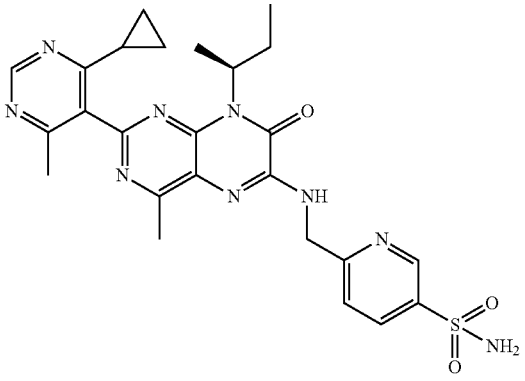
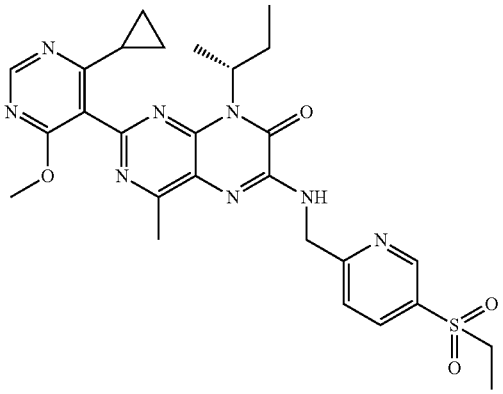
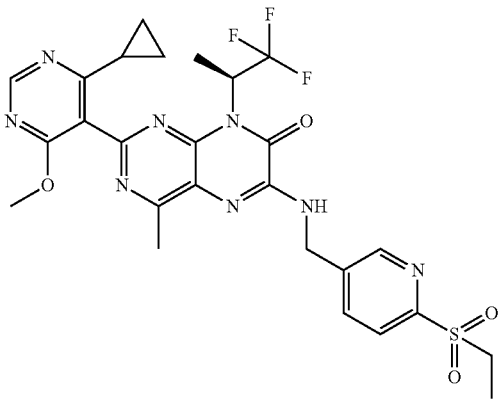
Example	Structure	RT	m/z [M + H]+	HPLC Method
85		0.91	536.2	A
86		1.12	566.3	A
87		1.03	603.2	A

TABLE 1-continued

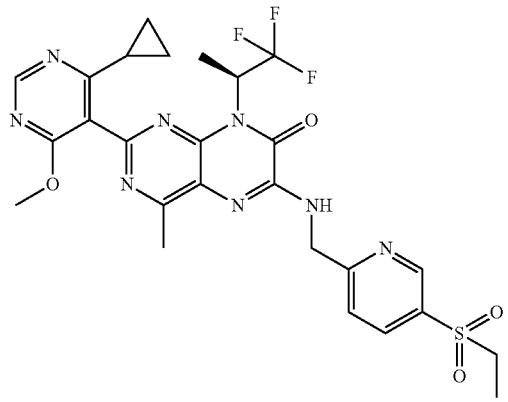
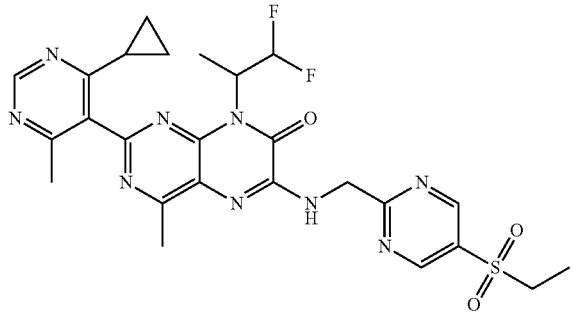
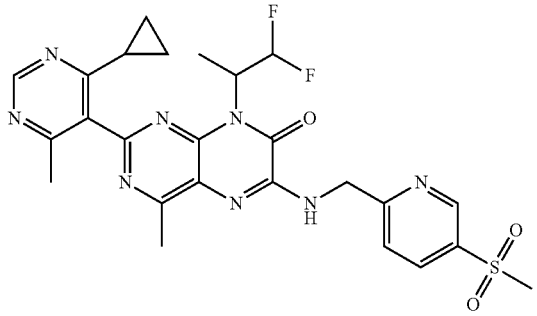
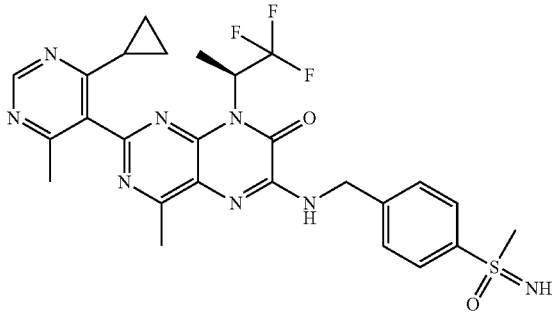
Example	Structure	RT	m/z [M + H]+	HPLC Method
88		1.03	605.1	A
89		0.93	572.1	A
90		0.89	557.3	A
91a		0.91	573.2	A

TABLE 1-continued

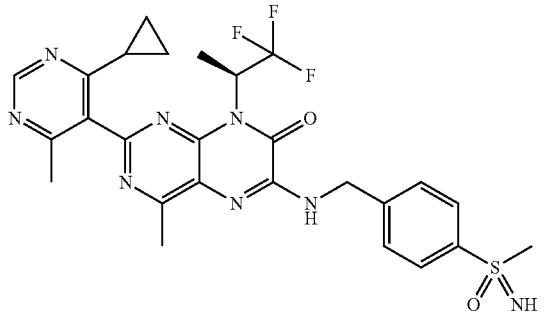
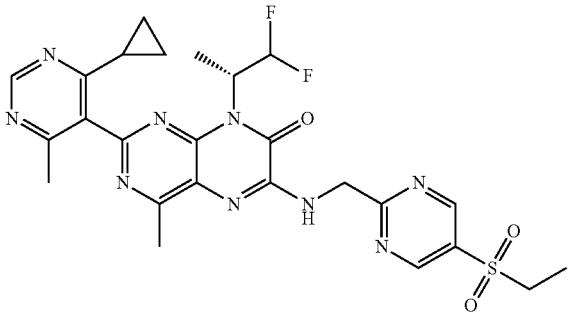
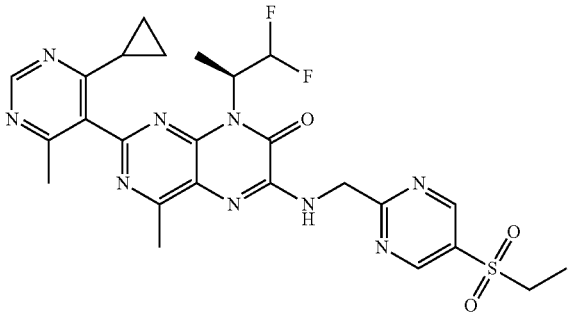
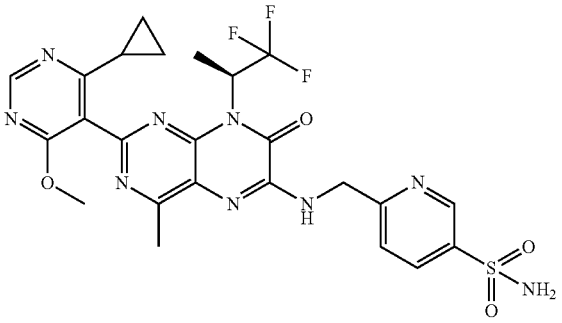
Example	Structure	RT	m/z [M + H]+	HPLC Method
91b		0.91	573.2	A
93		0.94	572.2	A
94		0.94	572.3	A
95		0.92	592.3	A

TABLE 1-continued

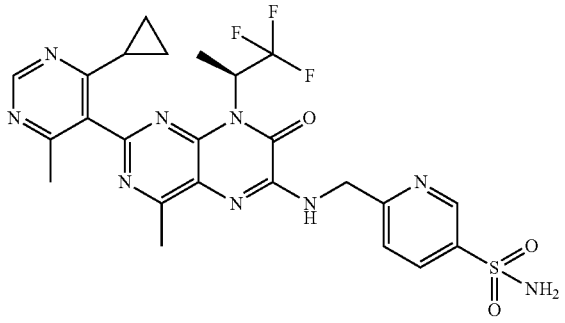
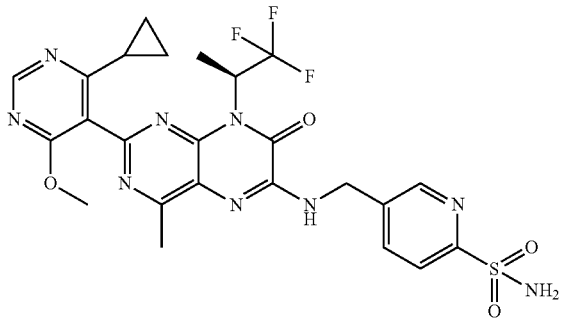
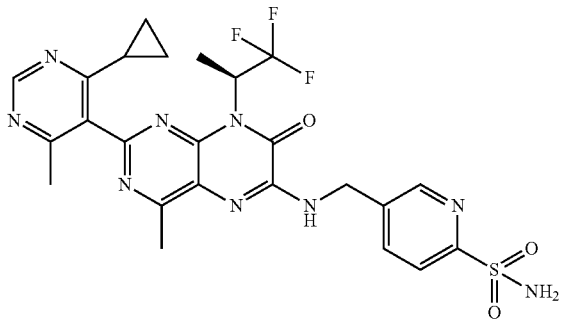
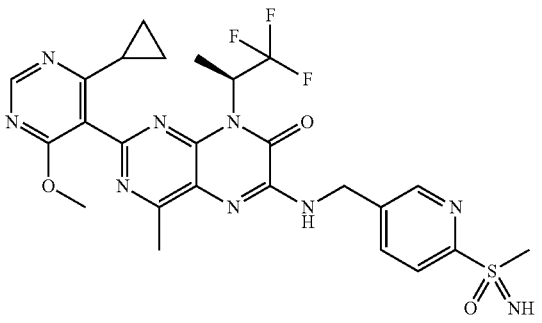
Example	Structure	RT	m/z [M + H]+	HPLC Method
96		0.86	576.3	A
97		0.90	592.2	A
98		0.85	576.3	A
99a		0.92	589.2	A

TABLE 1-continued

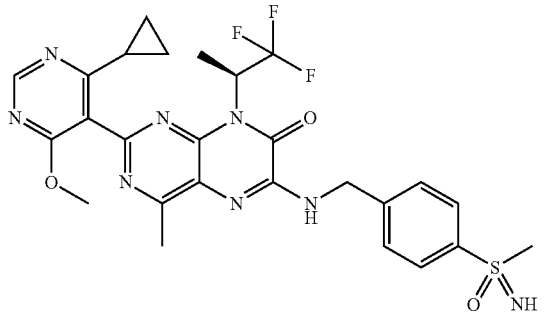
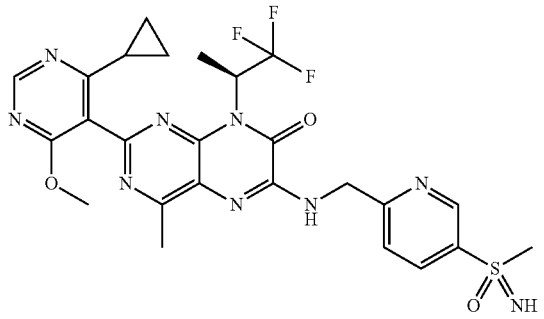
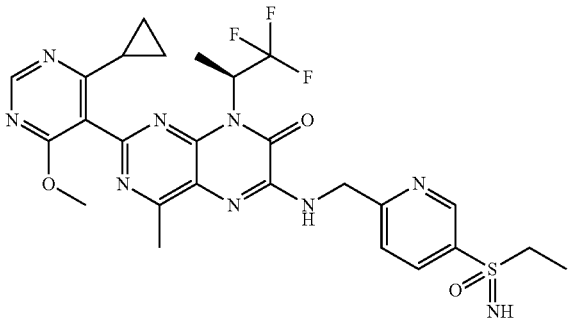
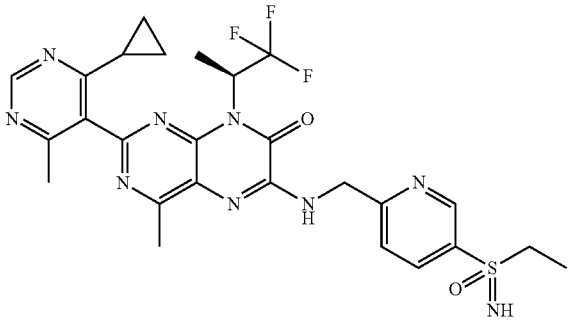
Example	Structure	RT	m/z [M + H]+	HPLC Method
99b		0.92	589.2	A
101a		0.95	604.2	A
101b		0.95	604.3	A
102a		0.89	588.3	A

TABLE 1-continued

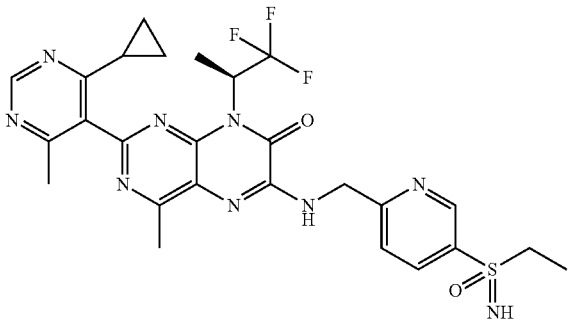
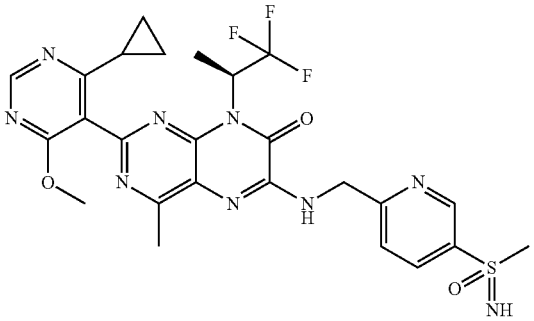
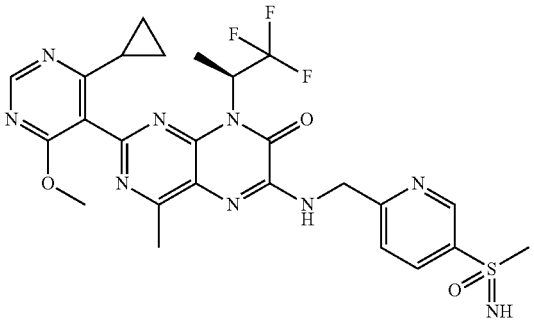
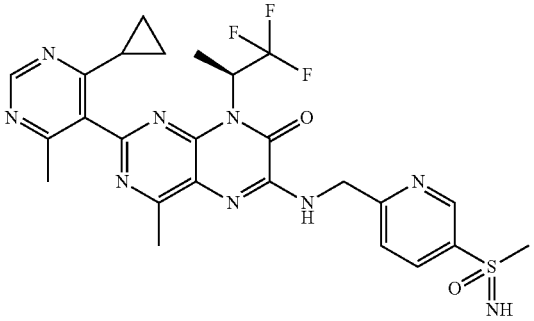
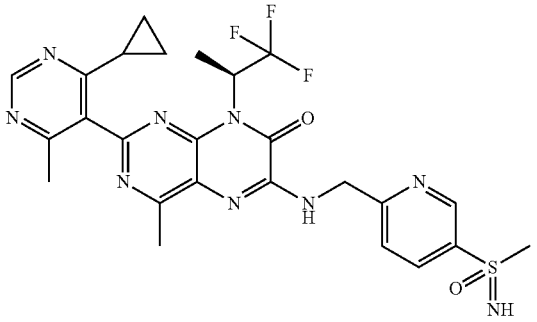
Example	Structure	RT	m/z [M + H]+	HPLC Method
102b		0.89	588.2	A
105a		0.90	590.3	A
105b		0.90	590.3	A
106a		0.84	574.2	A

TABLE 1-continued

Example	Structure	RT	m/z [M + H]+	HPLC Method
106b		0.84	574.2	A

[0135] In one embodiment, the invention relates to a compound selected from the group consisting of compounds 1-106b depicted in Table 1 above and the pharmaceutically acceptable salts thereof.

[0136] The present invention further relates to a pharmaceutically acceptable salt of a compound of the formula (I) with inorganic or organic acids or bases.

[0137] In another aspect, the invention relates to compounds of formula (I) or the pharmaceutically acceptable salts thereof as medicaments.

[0138] In another aspect, the invention relates to compounds of formula (I) or the pharmaceutically acceptable salts thereof for use in a method for treatment of a patient.

[0139] In another aspect, the invention relates to compounds of formula (I) or the pharmaceutically acceptable salts thereof for use in the treatment of autoimmune diseases and allergic disorders.

[0140] In another aspect, the invention relates to the use of compounds of formula (I) or the pharmaceutically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of autoimmune diseases and allergic disorders.

[0141] In another aspect, the invention relates to a method for the treatment of autoimmune diseases and allergic disorders comprising administering a therapeutically effective amount of a compound of formula (I) or one of the pharmaceutically acceptable salts thereof to a patient.

[0142] In another aspect, the invention relates to a pharmaceutical composition containing as active substance one or more compounds of formula (I) or the pharmaceutically acceptable salts thereof optionally in combination with conventional excipients and/or carriers.

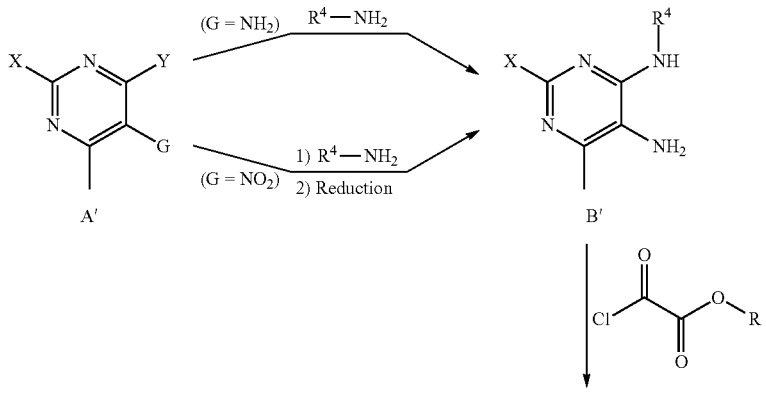
[0143] The compounds of formula (I) may be made using the general synthetic methods described below, which also constitute part of the invention.

General Synthetic Methods

[0144] The compounds according to the invention may be prepared by the methods of synthesis and synthetic examples below, methods known to those of ordinary skill in the art and methods reported in the chemical literature. In the methods of synthesis and examples described hereinafter, the substituents R^1, R^2, R^3, R^4, R^5, and W shall have the meanings defined hereinbefore in the detailed description of the compounds of formula I. The methods that are described here are intended as an illustration and for the enablement of the instant invention without restricting the scope of its subject matter, the claimed compounds, and the examples. Where the preparation of starting compounds is not described, they are commercially obtainable, may be prepared analogously to compounds or methods described herein, or are described in the chemical literature. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art.

[0145] Compounds of formula (I) having R^5 being methyl may be prepared from intermediate A' according to Scheme I. The preparations of intermediates having other R^5 that are found in the embodiments are illustrated in Methods 16-19 in the Synthetic Examples section, below.

Scheme 1



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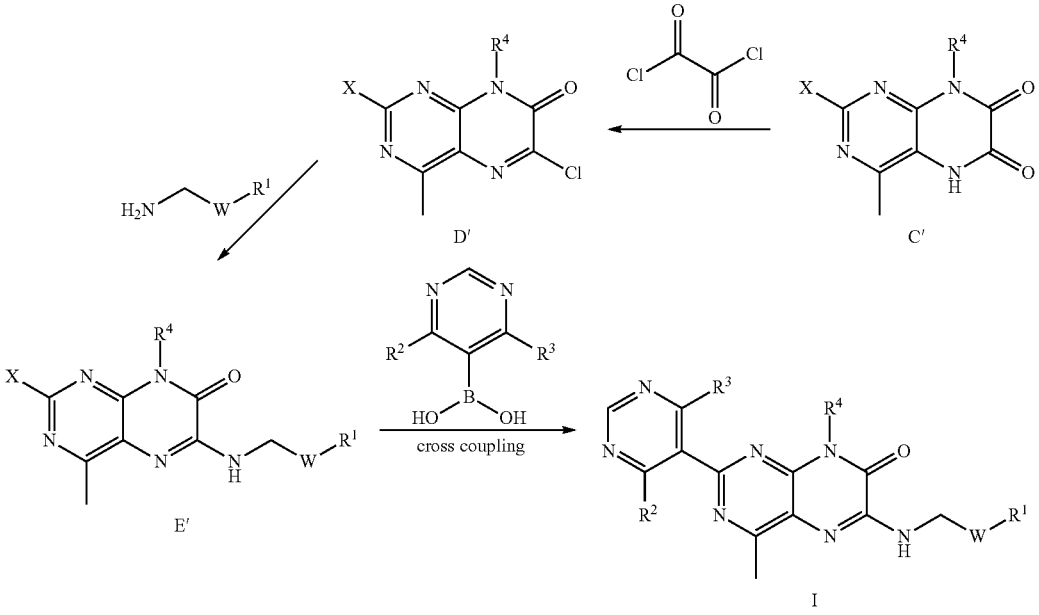


[0146] As illustrated in Scheme I, a suitable pyrimidine of formula A', wherein G is NH_2, X is a suitable group for palladium-mediated cross coupling reactions (e.g., I, Br, Cl, or OSO_2CF_3), and Y is a suitable leaving group (e.g., Cl), may be reacted with a suitable amine or amine salt (e.g., hydrochloride salt) of formula R^4NH_2 such as isopropyl amine in the presence of a suitable base (e.g., i-Pr_2EtN, or Et_3N) in a suitable solvent (e.g., n-butanol) and under a suitable reaction conditions such as an appropriate temperature (e.g., about 120° C.) to provide a compound of formula B'. Alternatively, the said pyrimidine of formula A' wherein G is a suitable synthetic precursor for NH_2 (e.g., a nitro group) may be reacted with a suitable amine or amine salt (e.g., hydrochloride salt) of formula R^4NH_2 such as 1-methyl cyclopropylamine in the presence of a suitable reagent and solvent (e.g., i-Pr_2EtN and THF, respectively), and under a suitable reaction conditions such as an appropriate temperature (e.g., about −78° C. to about 25° C.) to afford an intermediate, which may be converted to a compound of formula B' upon further reaction with suitable reagents (e.g., a NO_2 group that may be reduced with a suitable reagent such as $SnCl_2$). The selection of a suitable amine of formula R^4NH_2 and pyrimidine of formula A' for the aforementioned reaction by a person skilled in the art may be based on criteria such as steric and electronic nature of the amine and the pyrimidine. A diaminopyrimidine of formula B' may be reacted with a suitable reagent such as chloro-oxo-acetic acid ethyl ester in a suitable solvent (e.g., acetone) and in the presence of a suitable base (e.g., K_2CO_3) to furnish a compound of formula C'. A dicarbonyl compound of formula C' may be reacted with a suitable dehydrochlorinating reagent such as oxalyl chloride in the presence of a suitable additive (e.g., a catalytic amount of DMF) in a suitable solvent (e.g., CH_2Cl_2), and under a suitable reaction conditions such as an appropriate temperature (e.g., about ambient temperature) to provide a compound of formula D'. A chloro-pteridinone of formula D' may be reacted with a suitable amine or amine salt of formula R^1—W—CH_2—NH_2 such as 4-ethanesulfonyl benzyl amine in the presence of a suitable base (e.g., Et_3N) in a suitable solvent (e.g., THF) and under a suitable reaction conditions such as an appropriate temperature (e.g., about ambient temperature) to yields a compound of formula E'. Intermediate E' may be heated with a suitable cross-coupling pyrimidine partner (e.g., a boronic acid) and a suitable base (e.g., K_3PO_4), in a suitable solvent (e.g., 1,4-dioxane), in the presence of a suitable cross-coupling catalyst (e.g., Pd(dppf)Cl_2), under suitable reaction conditions such as a suitable atmosphere (e.g., argon) and at a suitable temperature (e.g., about 100° C.) to provide a compound of formula (I).

Synthetic Examples

[0147] Non-limiting examples demonstrating the preparation of the compounds of the invention are provided below. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Intermediates and products may be purified by chromatography on silica gel, recrystallization and/or reverse phase HPLC (RP-HPLC). Discrete enantiomers may be obtained by resolution of racemic products using chiral HPLC. RP-HPLC purification methods used anywhere from 0-100% acetonitrile in water containing 0.1% formic acid or 0.1% TFA and used one of the following columns:

[0148] a) Waters Sunfire OBD C18 5 μM 30×150 mm column

[0149] b) Waters XBridge OBD C18 5 μM 30×150 mm column

[0150] c) Waters ODB C8 5 μM 19×150 mm column

[0151] d) Waters Atlantis ODB C18 5 μM 19×50 mm column

[0152] e) Waters Atlantis T3 OBD 5 μM 30×100 mm column

[0153] f) Phenomenex Gemini Axia C18 5 μM 30×100 mm column

UPLC/MS Methods:

[0154] Analytical UPLC/MS Analysis Method A:

[0155] Column: Waters CSH 2.1×50 mm C18 1.7 um column

[0156] Gradient:

Time (min)	0.05% Formic Acid in Water	0.05% Formic Acid in ACN	Flow (mL/min)
0	90	10	0.8
1.19	0	100	0.8
1.77	0	100	0.8

LIST OF ABBREVIATIONS USED IN SYNTHETIC EXAMPLES

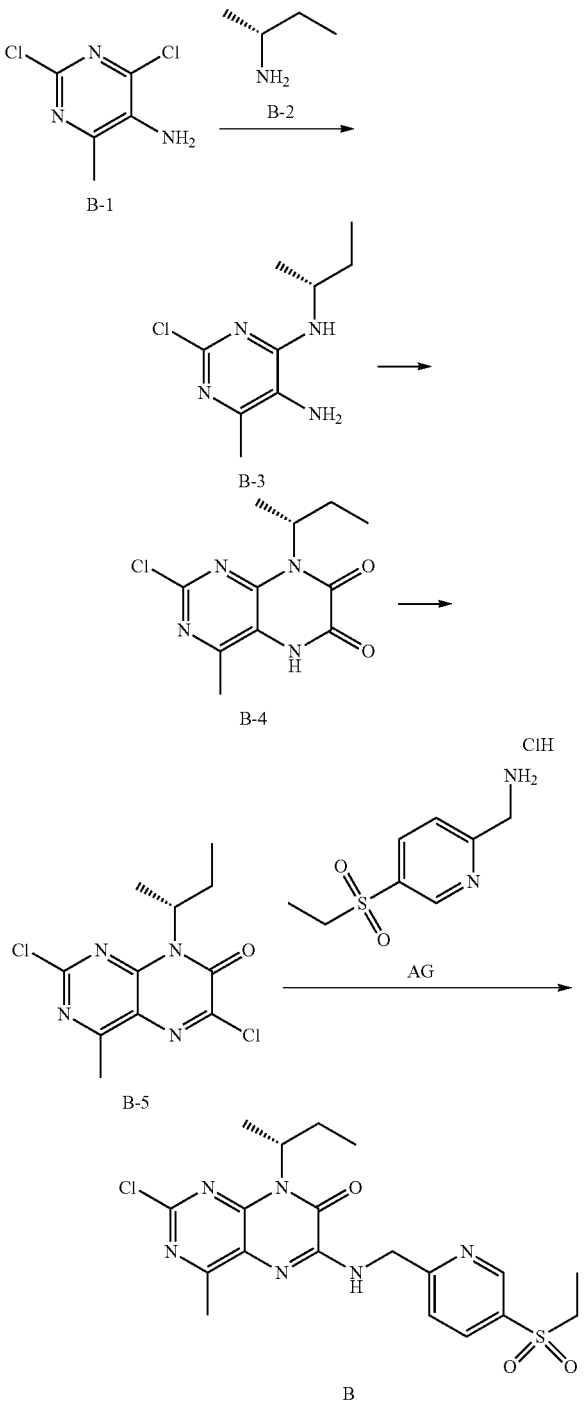
[0157]

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
aq	Aqueous
Bu	Butyl
Boc_2O	Di-tert-butyl dicarbonate
DCM	Dichloromethane
DIEA	N,N-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
dppf	1.1'-bis(diphenylphosphino)ferrocene
ES+	Electron spray positive ionization
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
h	hour(s)
HPLC	High performance liquid chromatography
i	Iso
LC	Liquid chromatography
Me	Methyl
MeOH	Methanol
min	Minutes
MS	Mass spectrometry
NMP	N-Methylpyrrolidinone
Pd/C	Palladium on carbon
Ph	Phenyl
PPh3	Triphenylphosphine
Pr	Propyl
RaNi	Raney Nickel
RT	Retention time (HPLC)
rt	Ambient temperature
SFC	Supercritical Fluid Chromatography
t	Tertiary
tert	Tertiary
Tf	Triflate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
UPLC	Ultra Performance Liquid Chromatography

Method 1:

Synthesis of Intermediate B

[0158]



[0159] To a stirred suspension of B-1 (5.00 g, 28 mmol) in n-butanol (25 mL) is added B-2 (2.05 g, 28 mmol) followed by DIEA (9.93 mL, 56.2 mmol). The mixture is stirred for 15 h at 120° C. The reaction is cooled to rt and quenched by

the addition of saturated aqueous NH_4Cl solution. The reaction is then diluted with EtOAc. The organic layer is separated and washed with water, followed by brine. The organic layer is dried (Na_2SO_4), decanted and concentrated. The resulting residue is purified by SiO_2 flash chromatography to yield B-3.

[0160] To a stirred suspension of B-3 (1.7 g, 8 mmol) in acetone (30 mL) is added ethyl chlorooxoacetate (0.97 mL, 8.7 mmol) followed by K_2CO_3 (3.39 g, 24.5 mmol). The mixture is stirred at rt for 18 h and the solid precipitate is isolated to yield B-4.

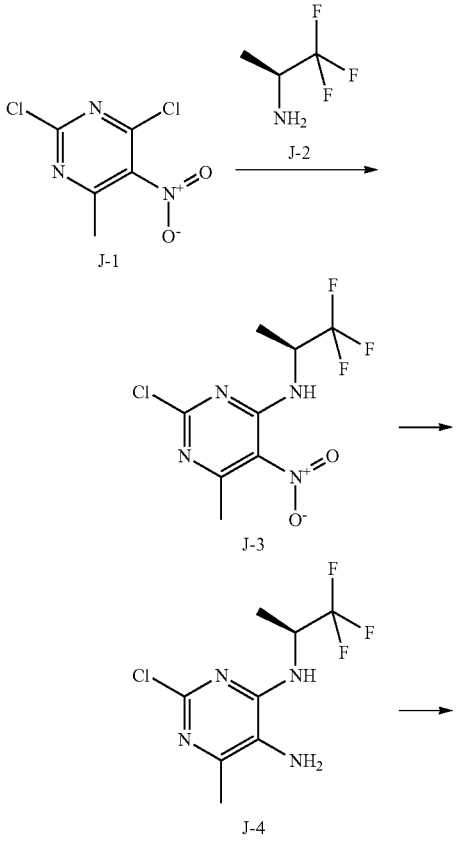
[0161] To a stirred suspension of B-4 (1.0 g, 3.72 mmol) in CH_2Cl_2 (20 mL) is added oxalyl chloride (0.64 mL) followed by 10 drops of DMF. The mixture is stirred for 5 h at rt. The mixture is then concentrated at reduced pressure to yield B-5.

[0162] To a stirred suspension of B-5 (400 mg, 1.0 mmol) in DMF (4 mL) is added DIEA (450 mg, 2.5 mmol) (or TEA), followed by AG (330 mg, 1.0 mmol). The reaction is allowed to stir for 6 h at rt. The reaction is quenched by the addition of cold water and the precipitate is filtered to yield intermediate B. MS (ES+): m/z 451.1 $[M+H]^+$.

Method 2:

Synthesis of Intermediate J

[0163]



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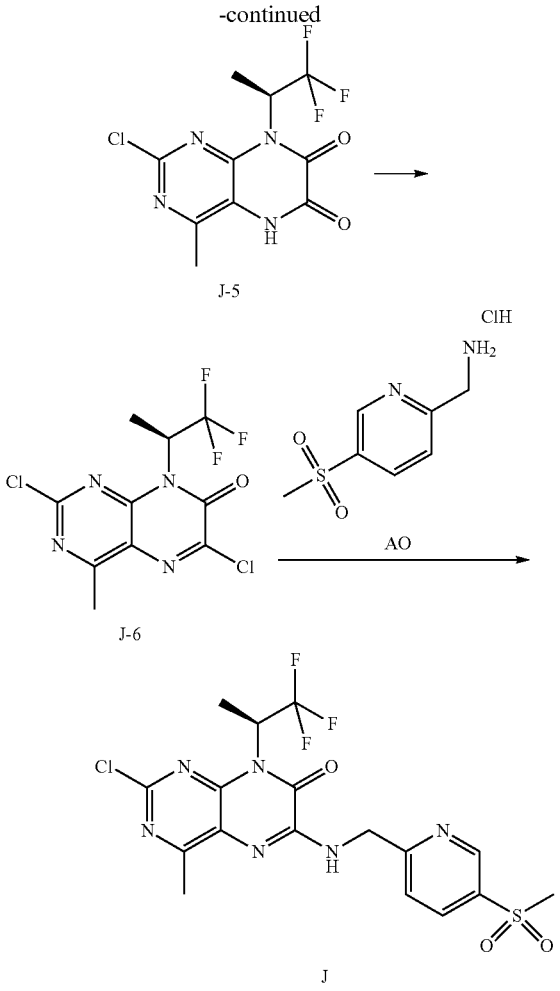


[0164] To a stirred suspension of J-1 (10.0 g, 48.0 mmol) and J-2 (8.94 g, 48.0 mmol) in DCM (150 mL) at 5° C. is added triethylamine (14.6 g, 144 mmol). The reaction is stirred at that temperature for 5 h. The solution is poured into water (200 mL), extracted with DCM (3×250 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resulting residue is purified by SiO_2 flash chromatography to yield J-3.

[0165] To a solution of J-3 (20.0 g, 48 mmol) in EtOH (180 mL) at 5° C. is added a solution of NH_4Cl (2.56 g, 48 mmol) in water (80 mL) and Fe (8.00 g, 143 mmol). The mixture is heated to 50° C. for 3 h. The reaction mixture is then poured into water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The crude product is purified by SiO_2 flash chromatography to yield J-4.

[0166] As an alternative procedure for the reduction of nitropyrimidine to the corresponding amino pyrimidine the following general procedure is utilized for analogous intermediates: To a solution of the nitropyrimidine in EtOH is added catalytic RaNi. The reaction vessel is evacuated and purged with N_2(g), then evacuated and filled with H_2(g). The reaction is maintained under H_2(g) atmosphere for 15 h. The vessel is evacuated and purged with N_2(g).

[0167] The reaction is filtered through a pad of diatomaceous earth to remove the Ni catalyst and the filtrate is concentrated. The resulting residue is purified by SiO_2 flash chromatography to afford the corresponding aminopyrimidine.

[0168] To a stirred solution of J-4 (6.05 g, 21.1 mmol) in DCM (100 mL) at 8° C. is added ethyl chlorooxoacetate (2.41 mL, 21.1 mmol). The reaction is stirred at 5-10° C. for 2 h. The reaction is then filtered, washed with DCM and redissolved in EtOH (100 mL). Triethylamine (5.94 mL, 42.3 mmol) is added and the mixture is heated to 90° C. for 1 h. The mixture is then cooled to rt and the pH of is adjusted to 5 with acetic acid. The reaction is then concentrated in vacuo and the residue is dissolved in DCM, washed with water, brine and concentrated. The residue is triturated in EtOAc/Heptanes to yield J-5.

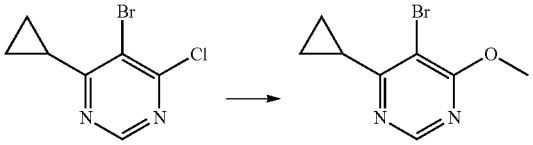
[0169] To a solution of J-5 (1.00 g, 3.24 mmol) in CH_2Cl_2 (50 mL) is added oxalyl chloride (0.55 mL, 6.48 mmol) followed by 10 drops of DMF. The reaction is allowed to stir at rt for 18 h. The volatiles are removed in vacuo. The crude is redissolved in DCM and reconcentrated. The resulting residue yields J-6.

[0170] To a stirred solution of J-6 (550 mg, 1.68 mmol) in DMF (10 mL) is added AO (374 mg, 1.68 mmol) followed by DIEA (0.75 mL, 4.20 mmol). The reaction is stirred at rt and monitored by LC-MS until complete (~1 h). The reaction mixture is quenched with enough cold water to precipitate a solid. The mixture is stirred for 15 min and the solid is filtered to yield intermediate J. MS (ES+): m/z 477.2 $[M+H]^+$.

Method 3:

Synthesis of Intermediate AB

[0171]

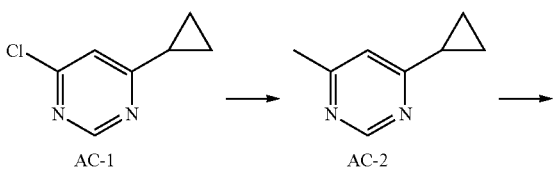


[0172] To a solution of AB-1 (300 mg, 1.29 mmol) in anhydrous MeOH (15 mL) is added NaOMe (208 mg, 3.86 mmol). The mixture is stirred at rt for 1 h. The solution is filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield intermediate AB. MS (ES+): m/z 230.8 $[M+H]^+$.

Method 4:

Synthesis of Intermediate AC

[0173]



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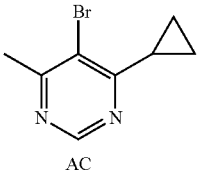


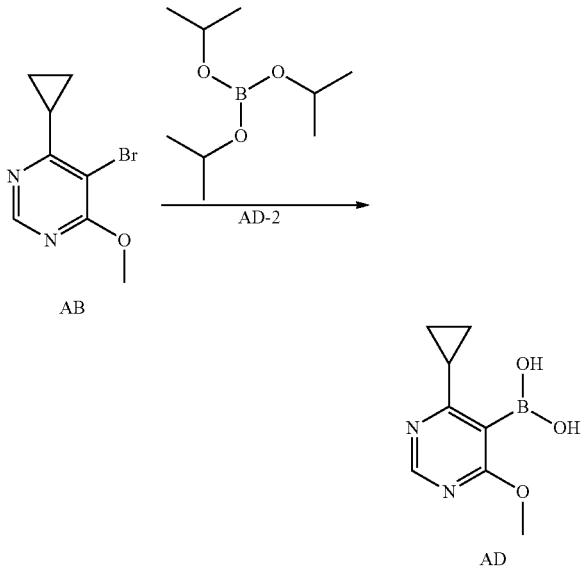
[0174] To a solution of AC-1 (320 mg, 2.07 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (520 mg, 4.14 mmol), and aq Na_2CO_3 (2M, 3.1 mL, 6.21 mmol) in dioxane (10 mL) is added dichloropalladium 4-di-tert-butylphosphanyl-N,N-dimethyl-aniline (73 mg, 0.10 mmol). The mixture is heated to 130° C. for 40 min in a microwave reactor. The mixture is diluted with MeOH (5 mL), filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield AC-2.

[0175] To a solution of AC-2 (363 mg, 2.71 mmol) in EtOH (10 mL) at −10° C. is added Br_2 (432 mg, 2.71 mmol). The reaction mixture is stirred at rt for 18 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield intermediate AC. MS (ES+): m/z 214.3 $[M+H]^+$.

Method 5:

A. Synthesis of Intermediate AD

[0176]



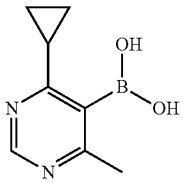
[0177] To a solution of AB (6.00 g, 26.2 mmol) and AD-2 (7.86 mL, 34.1 mmol) in toluene (60 mL) and THF (18 mL) at −78° C. is added n-butyl lithium (12.6 mL, 31.4 mmol), dropwise, over 30 min. The solution is the stirred at −78° C. for 30 min and is then slowly warmed to −20° C. The solution is then quenched with 1 N HCl (40 mL). The layers are then separated and the aqueous layer is adjusted to pH ~8 with 2M NaOH. A white solid begins to precipitate and the mixture is cooled in the refrigerator for 1 h. The solids are filtered to yield intermediate AD. The aqueous layer is

extracted with MeTHF and concentrated to give additional intermediate AD. MS (ES+): m/z 195.1 $[M+H]^+$.

B. Synthesis of Intermediate AE

[0178]

AE

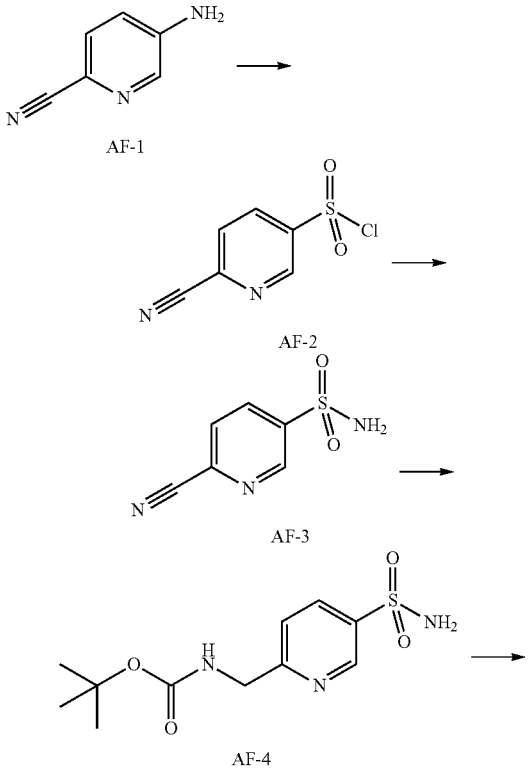


[0179] To a solution of AC (see Method 4) (20 g, 93.86 mmol) in toluene (200 mL) and THF (50 mL) under Ar is added triisopropyl borate (28.2 mL, 122.02 mmol) and the resulting mixture is cooled to −74° C. n-BuLi (2.7 M in hexanes, 56.7 mL, 150.18 mmol) is added dropwise through additional funnel over 1 hour. After the addition, the reaction mixture is stirred at −74° C. for 5 min then quenched with 1N HCl aqueous solution (85 mL, 255.31 mmol). The mixture is slowly warmed up to room temperature then the layers are separated. To the stirring aqueous solution is added $NaHCO_3$ solid (10 g, 119.03 mmol). The product is collected by filtration.

Method 6:

Synthesis of Intermediate AF

[0180]



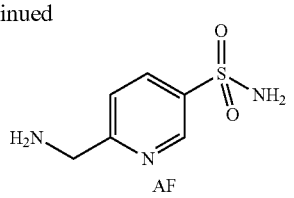
AF-1

AF-2

AF-3

AF-4

-continued



AF

[0181] AF-1 (20.0 g, 168 mmol) is added to conc. HCl (200 mL) at 0° C. followed by dropwise addition of aq $NaNO_2$ (25.5 g in 25 mL H_2O) maintaining an internal temperature of <5° C. The solution is allowed to stir at 0° C. for 15 min and then is slowly added to a mixture of SO_2 (108 g) and CuCl (84 mg) in AcOH (200 mL, >5 eq) at 5° C. The solution is stirred 90 min at 5° C. The reaction mixture is extracted with DCM (2×500 mL), dried (Na_2SO_4), and the organic solution of AF-2 used directly in the next step.

[0182] To a solution of AF-2 (20.0 g, 99 mmol) in DCM (200 mL) is added a solution of ammonia in MeOH (100 mL) at 0° C. and stirred at rt for 30 min. The mixture is concentrated to dryness and the resulting residue is purified by SiO_2 flash chromatography to yield AF-3.

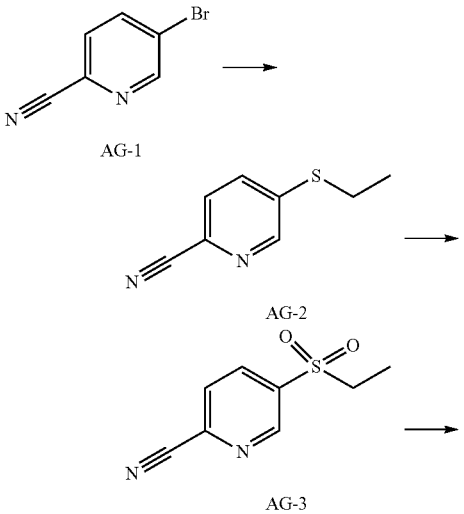
[0183] To a solution of AF-3 (15.0 g, 82 mmol) in MeOH (200 mL) is added RaNi (10.0 g), TEA (34.4 mL) and Boc_2O (17.8 g). The mixture is stirred at rt under H_2 (50 psi) for 12 h. The vessel is purged with N_2, filtered and the filtrate concentrated. The residue is purified by SiO_2 flash chromatography to yield AF-4.

[0184] A solution of AF-4 (30.0 g, 105 mmol) in HCl in MeOH (500 mL) is stirred at rt for 12 h. The mixture is concentrated and recrystallized to yield intermediate AF. MS (ES+): m/z 188.1 $[M+H]^+$.

Method 7:

Synthesis of Intermediate AG

[0185]

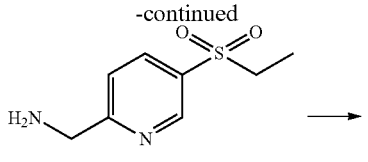


AG-1

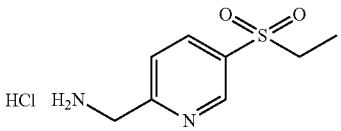
AG-2

AG-3

-continued



AG-4



AG

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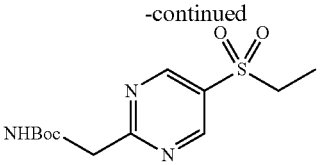
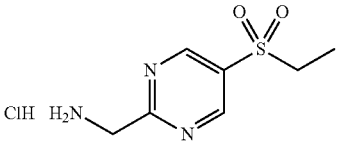


AH-4



AH

[0186] A mixture of AG-1 (8.0 g, 43.96 mmol), K_2CO_3 (7.88 g, 57.1 mmol) and sodium ethanethiolate (4.06 g, 48.3 mmol) in NMP (60.0 mL) under N_2 is stirred at rt for 18 h. The reaction mixture is poured into H_2O and filtered. The solids are washed with H_2O and dried under vacuum to yield AG-2.

[0187] To a suspension of AG-2 (6.0 g, 36.6 mmol) in AcOH (2.63 g, 43.8 mmol) is added a solution of $KMnO_4$ (5.78 g, 36.6 mmol) in H_2O (20.0 mL) dropwise. The reaction mixture is stirred at rt for 15 h. The mixture is diluted with water and extracted with EtOAc. The organic layer is dried (Na_2SO_4), decanted and concentrated. The resulting residue is purified by SiO_2 flash chromatography to yield AG-3.

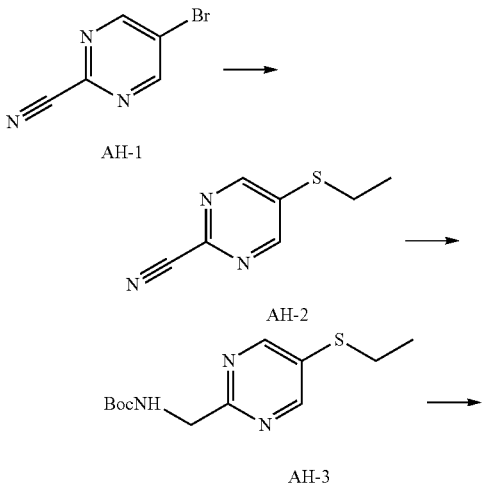
[0188] A solution of AG-3 (3.3 g, 16.8 mmol) and Pd/C (500 mg, 10% on carbon catalyst) in MeOH (30 mL) is stirred at rt under H_2 (50 psi) for 8 h. The vessel is purged with N_2, filtered and the filtrate concentrated to yield AG-4.

[0189] To a stirred solution of AG-4 (2.5 g, 12.5 mmol) in EtOAc (30 mL) is added HCl in EtOAc (2N, 20.0 mL). The solution is stirred at rt for 5 h and then filtered to yield intermediate AG. MS (ES+): m/z 201.2 $[M+H]^+$.

Method 8:

Synthesis of Intermediate AH

[0190]



AH-1

AH-2

AH-3

[0191] A mixture of AH-1 (113 g, 0.62 mol), K_2CO_3 (171 g, 1.24 mol) and sodium ethanethiolate (67 g, 0.80 mol) in DMF (2 L) is stirred at rt under N_2 for 18 h. The mixture is diluted with H_2O and extracted with EtOAc. The organic layers are dried (Na_2SO_4), decanted and concentrated. The resulting residue is purified by SiO_2 flash chromatography to yield AH-2.

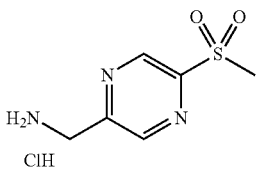
[0192] A solution of AH-2 (20.0 g, 0.12 mol), RaNi (40 g), Boc_2O (31.7 g, 0.14 mol) and TEA (24.5 g, 0.24 mol) in THF (600 mL) is stirred at rt under H_2 (50 psi) for 12 h. The mixture is filtered and the filtrate concentrated under reduced pressure. The resulting residue is purified by SiO_2 flash chromatography to yield AH-3.

[0193] To a suspension of AH-3 (65 g, 0.24 mol) in AcOH (200 mL) at −10° C. is added dropwise a solution of $KMnO_4$ (45.8 g, 0.29 mL) in water (500 mL). Following complete addition, the reaction mixture is stirred at rt for 30 min. The mixture is diluted with H_2O and basified by addition of aqueous Na_2CO_3 to ~pH 8 and extracted with EtOAc. The combined organic layers are dried (Na_2SO_4), decanted, and concentrated. The resulting residue is purified by crystallization to yield AH-4.

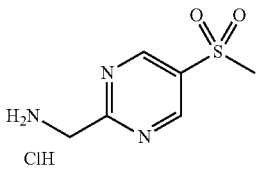
[0194] To a stirred solution of compound AH-4 (46.5 g, 0.15 mol) in MeOH (300 mL) is added 4M HCl in MeOH (300 mL) at rt and stirred for 15 h. The mixture is concentrated under reduced pressure. The resulting residue is purified by crystallization to yield intermediate AH. MS (ES+): m/z 202.1 $[M+H]^+$.

[0195] Intermediate AI and Intermediate AJ are synthesized in a fashion analogous to Intermediate AH.

AI



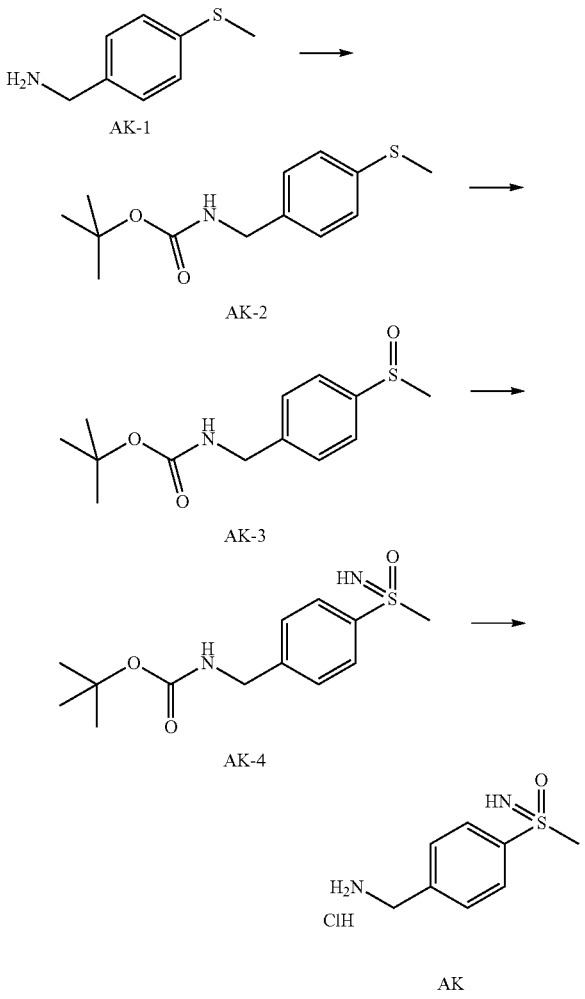
AJ



Method 9:

Synthesis of Intermediate AK

[0196]



[0197] To a solution of AK-1 (2.00 g, 13.1 mmol) in THF (25 mL) is added Boc_2O (3.45 mL, 15.0 mmol) and TEA (3.64 mL, 26.1 mmol). The reaction mixture is stirred at rt for 18 h and then diluted with H_2O and extracted with EtOAc. The organic layers are concentrated to yield AK-2.

[0198] To solution of AK-2 (3.3 g, 13.1 mmol) in AcOH (10 mL) is slowly added H_2O_2 (1.37 mL, 13.7 mmol). The reaction mixture is stirred at rt for 3 h and is then quenched with saturated Na_2SO_3 solution and neutralized with 1N NaOH. The mixture is extracted with EtOAc and concentrated to yield AK-3.

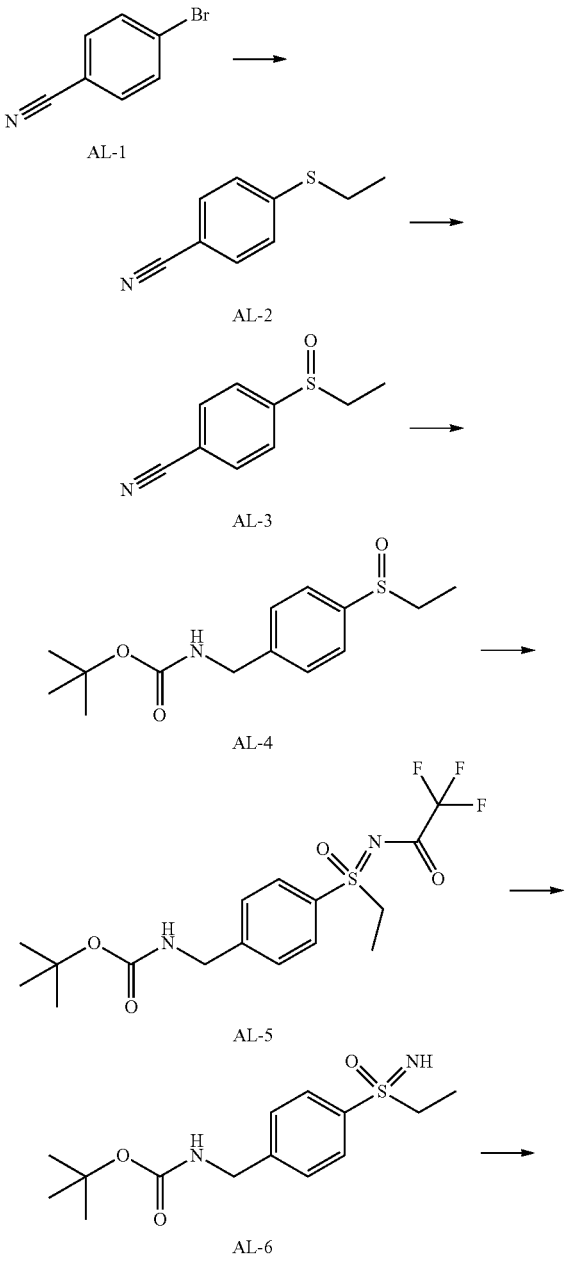
[0199] A mixture of AK-3 (1.0 g, 3.7 mmol), MgO (600 mg, 14.9 mmol), trifluoroacetamide (839 mg, 7.4 mmol), and Rh(II) acetate dimer (115 mg, 0.26 mmol) in DCM (10 mL) is added (diacetoxyiodo)benzene (1.79 g, 5.6 mmol). The mixture is stirred at rt for 18 h and then concentrated under reduced pressure. The resulting residue is dissolved in MeOH, filtered through a pad of diatomaceous earth and, K_2CO_3 (2.55 g, 18.6 mmol) is added to the filtrate. The mixture is stirred at rt for 18 h and is concentrated under reduced pressure. The resulting residue is purified by SiO_2 flash chromatography to yield AK-4.

[0200] To a stirred solution of compound AK-4 (585 mg, 2.1 mmol) in DCM (2 mL) is added HCl in dioxane (4N, 2 mL). The reaction mixture is stirred at rt for 15 h and then concentrated under reduced pressure to yield intermediate AK. MS (ES+): m/z 185.0 $[M+H]^+$.

Method 10:

Synthesis of Intermediate AL

[0201]



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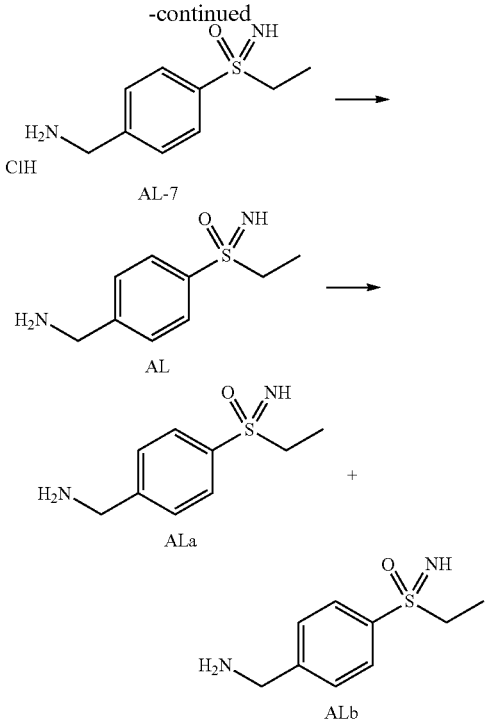


[0202] To a mixture of ethanethiol (49.2 g, 0.79 mol) in ACN (2 L) is added NaOtBu (126.5 g, 1.32 mol) at 0° C. under N_2. The mixture is stirred at 0° C. for 0.5 h. Then AL-1 (40 g, 0.66 mol) is added into the mixture. The reaction mixture is warmed to 50° C. and stirred for 11.5 h. The reaction is quenched by ice-water (500 mL) slowly and then extracted with EtOAc (IL×2). The combined organic phase is washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue is purified by column chromatography (Petroleum Ether:EtOAc=40:1 to 10:1) to yield AL-2.

[0203] A mixture of AL-2 (22 g, 0.135 mol) and H_2O_2 (15.4 mL) in ACN (220 mL) is stirred at 70° C. for 36 h. The mixture is quenched by H_2O (200 mL), extracted with EtOAc (300 mL×2). The organic layer is dried with anhydrous Na_2SO_4, filterated and concentrated. The residue is purified by silica gel chromatography (Petroleum ether: EtOAc=20:1 to 5:1) to afford AL-3.

[0204] A mixture of compound AL-3 (10.4 g, 0.058 mol), Boc_2O (13.9 g; 1.1 eq.; 0.064 mol), TEA (19.5 mL; 2.5 eq.) and RaNi (10 g) in MeOH (150 mL) is stirred at 40° C. under H_2 (50 psi) for 12 h. The mixture is filtrated through celite. The filtrate is concentrated. The residue is purified by silica gel chromatography (Petroleum ether:EtOAc=20:1 to 1:1) to afford AL-4.

[0205] A mixture of compound AL-4 (15 g, 0.053 mol), 2,2,2-Trifluoro-acetamide (6.6 g, 0.058 mol), MgO (4.3 g, 0.106 mol), $PhI(OAc)_2$ (17.1 g, 0.053 mol) and Rh catalyst (1.5 g) in DCM (150 mL) is stirred at 20° C. for 12 h. The mixture is filtrated. The filtrate is concentrated to yield crude AL-5. The crude product is used directly in the next step.

[0206] A mixture of compound AL-5 (20 g, 0.030 mol) and K_2CO_3 (8.4 g, 0.061 mol) in MeOH (200 mL) is stirred at 20° C. for 12 h. The mixture is filtrated. The filtrate is concentrated. The residue is purified by silica gel chromatography (Petroleum ether:EtOAc=3:1 to 1:1) to afford AL-6.

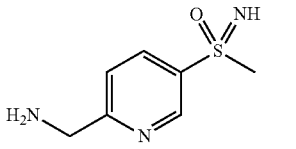
[0207] A solution of compound AL-6 (18 g, 0.030 mol) in HCl-MeOH (200 mL) is stirred at 20° C. for 3 h. The reaction mixture is concentrated. The residue is washed with DCM (50 mL×2) to afford AL-7.

[0208] To a mixture of compound AL-7 (13 g) in MeOH (300 mL) is added ion exchange resin until pH≥8. Then the mixture is stirred at room temperature for 1 h. The mixture is filtrated. The filtrate is concentrated to yield AL.

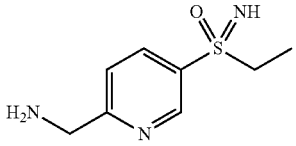
[0209] AL-8 is separated by SFC to give ALa and ALb.

[0210] Intermediate AM and Intermediate AN (as the HCl salt. MS (ES+): m/z 202.1 $[M+H]^+$) are synthesized in a fashion analogous to intermediate AL, with the exception of the SFC separation is carried out at the Boc stage (after step 5).

AM



AN



SFC Conditions for Separation of Sulfoximine Enantiomers

[0211] Racemic sulfoximine intermediates AK. AL, AM and AN were separated by SFC using one of the following conditions A, B, C or D:

A. Separation of AK

[0212] Instrument: Thar SFC80 preparative SFC

Column: Chiralpak AD-H 250*30 mm i.d. 5u

[0213] Mobile phase: A for C_{02} and B for MeOH (0.1% NH3H2O)

Gradient: B %=35%

[0214] Flow rate: 62 g/min

Wavelength: 220 nm

[0215] Column temperature: 40° C.
System back pressure: 100 bar

B. Separation of AN

[0216] Instrument: Thar SFC80 preparative SFC

Column: Chiralpak AD-H 250*30 mm i.d. 5u

[0217] Mobile phase: A for CO_2 and B for EtOH (0.1% NH_3H_2O)

Gradient: B %=40%

[0218] Flow rate: 65 g/min

Wavelength: 220 nm

[0219] Column temperature: 40° C.
System back pressure: 100 bar

C. Separation of AL

[0220] Instrument: Thar SFC80 preparative SFC

Column: Chiralpak AD-H 250*30 mm i.d. 5u

[0221] Mobile phase: A for CO_2 and B for MeOH (0.1% NH_3H_2O)

Gradient: B %=40%

[0222] Flow rate: 65 g/min

Wavelength: 220 nm

[0223] Column temperature: 40° C.
System back pressure: 100 bar

D. Separation of AM

[0224] Instrument: Thar SFC80 preparative SFC

Column: Chiralpak AD-H 250*30 mm i.d. 5u

[0225] Mobile phase: A for CO_2 and B for MeOH (0.1% NH_3H_2O)

Gradient: B %=35%

[0226] Flow rate: 60 g/min

Wavelength: 220 nm

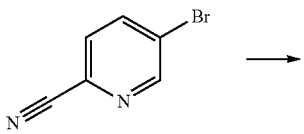
[0227] Column temperature: 40° C.
System back pressure: 100 bar

[0228] Chiral sulfoximine final compounds and intermediates derived from the first eluting enantiomer of AK, AL, AM or AN are labeled in the tables with an A or a. Those derived from the second eluting enantiomer are labeled with a B or b, for example, 26a and 26b.

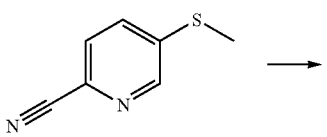
Method 11:

Synthesis of Intermediate AO

[0229]



AG-1



AO-2

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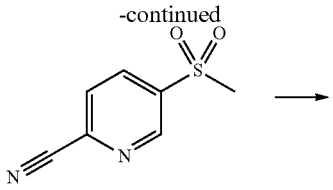
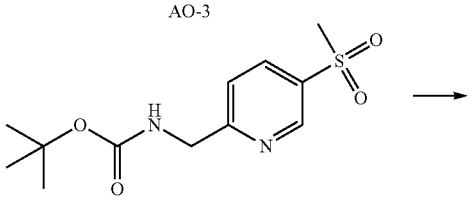
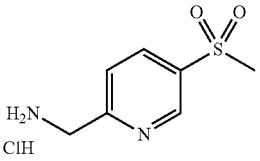


AO-3



AO-4



AO

[0230] To a solution of AG-1 (82.0 g, 448 mmol) in ACN (1.0 L) is added sodium t-butoxide (64.5 g). The mixture is cooled to 0° C. and sodium methanethiolate (172.5 g, 20% in H_2O) is added dropwise. The reaction mixture is then allowed to stir at rt for 16 h. Water (800 mL) is added and the mixture is extracted with DCM. The combined organic phases are washed with brine, dried (Na_2SO_4) and concentrated. The residue is purified by SiO_2 flash chromatography to yield AO-2.

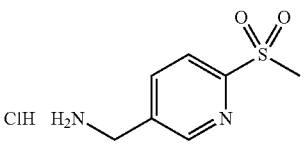
[0231] To a suspension of AO-2 (51.5 g, 343 mmol) in AcOH (500 mL) is added a solution of $KMnO_4$ (59.7 g, 36.6 mmol) in H_2O (500.0 mL) dropwise at 5° C. The reaction mixture is then stirred at rt for 1 h. The mixture is extracted with EtOAc, washed with aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated. The resulting residue is purified by recrystallization to yield AO-3.

[0232] To a solution of AO-3 (15.0 g, 82 mmol) in MeOH (200 mL) is added RaNi (10.0 g), TEA (34.4 mL) and Boc_2O (17.8 g). The mixture is stirred at rt under H_2 (50 psi) for 12 h. The vessel is purged with N_2, filtered and the filtrate concentrated. The residue is purified by SiO_2 flash chromatography to yield AO-4.

[0233] A solution of AO-4 (30.0 g, 105 mmol) in HCl in MeOH (500 mL) is stirred at rt for 12 h. The mixture is concentrated and recrystallized to yield intermediate AO. MS (ES+): m/z 187 $[M+H]^+$.

[0234] Intermediate AP and Intermediate AQ (as the HCl salt. MS (ES+): m/z 202.1 $[M+H]^+$) are synthesized in a fashion analogous to intermediate AO.

AP



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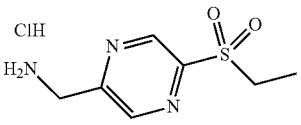
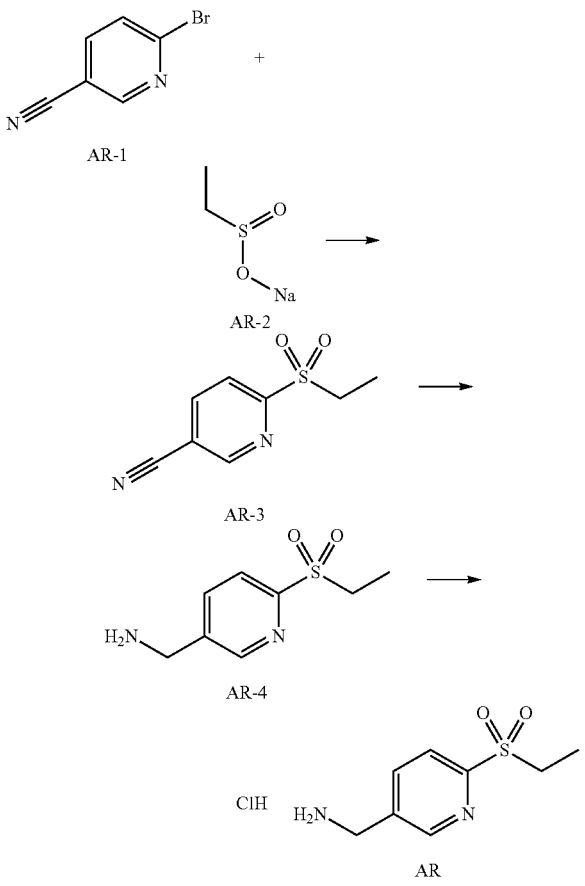
AQ



Method 12:

Synthesis of Intermediate AR

[0235]



[0236] To a mixture of AR-1 (10.0 g, 55 mmol), N,N-dimethyl-ethane-1,2-diamine (0.96 g, 11 mmol) and Copper (II) trifluoromethanesulfonate (1.98, 5 mmol) in DMSO (100 mL) is added AR-2 (8.27 g, 98 mmol) at rt. The mixture is then heated to 120° C. for 30 min, quenched with H_2O and extracted with EtOAc. The organic layer is dried, concentrated and purified by SiO_2 flash chromatography to yield AR-3.

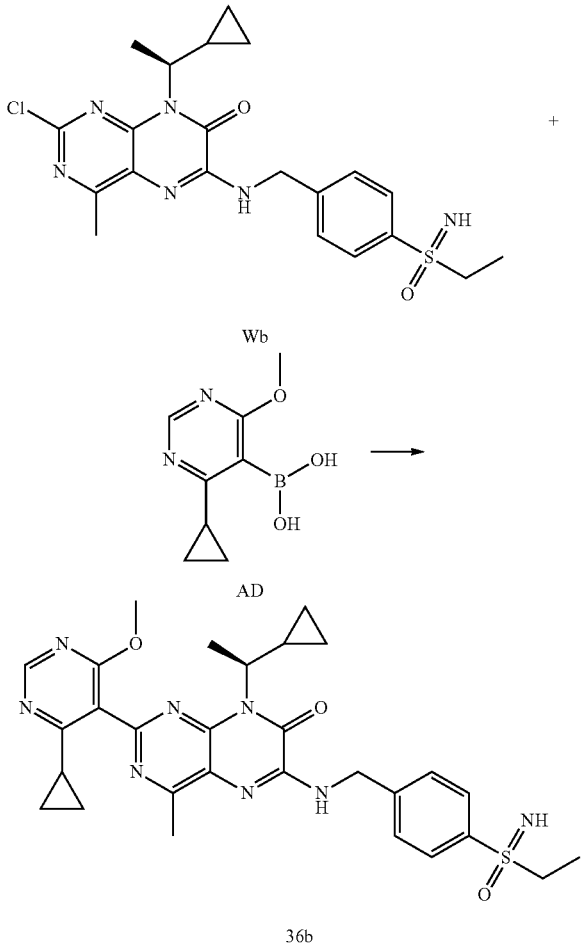
[0237] A mixture of AR-3 (32.3 g, 165 mmol) and Pd (3.50 g, 33 mmol) in NH_4OH (30 mL)/EtOH (200 mL) is stirred at rt under H_2 (15 psi) for 15 h. The mixture is filtered, concentrated and purified by SiO_2 flash chromatography to yield AR-4.

[0238] To a stirred solution of AR-4 (17.5 g, 87 mmol) in EtOH (100 mL) is added HCl in EtOH (100 mL). The solution is stirred at rt for 3 h and then concentrated and recrystallized to yield intermediate AR. MS (ES+): m/z 201 $[M+H]^+$.

Method 13:

Synthesis of Example 36b

[0239]

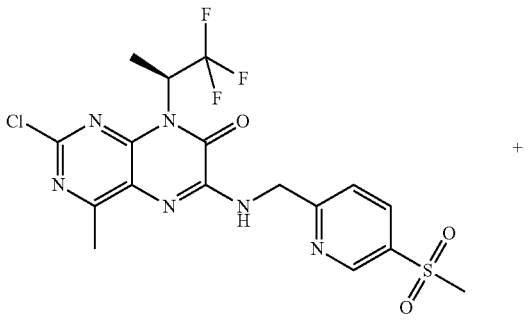


[0240] A mixture of Wb (130 mg, 0.29 mmol), intermediate AD (94 mg, 0.41 mmol), K_3PO_4 (123 mg, 0.58 mmol), and $Pd(dppf)Cl_2$ (36 mg, 0.05 mmol) in 1,4-dioxane (2 mL) is purged with argon, and then H_2O (0.5 mL) is added. The mixture is stirred at 100° C. for 18 h. After cooling to rt, the mixture is diluted with water (2 mL) and extracted with EtOAc (2×5 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resulting residue is purified by SiO_2 flash chromatography followed by reverse phase HPLC to yield Example 36b. MS (ES+): m/z 561.2 [M+H]+.

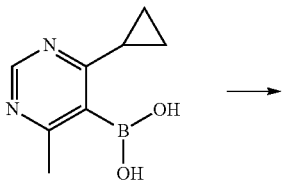
Method 14:

Synthesis of Example 18

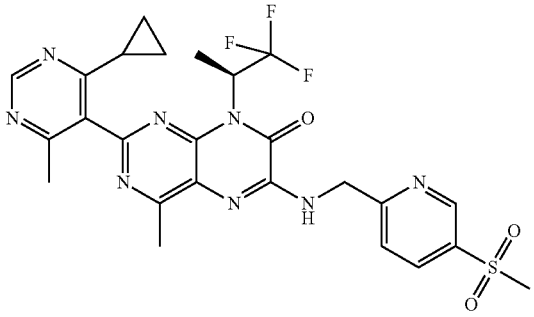
[0241]



J



AE



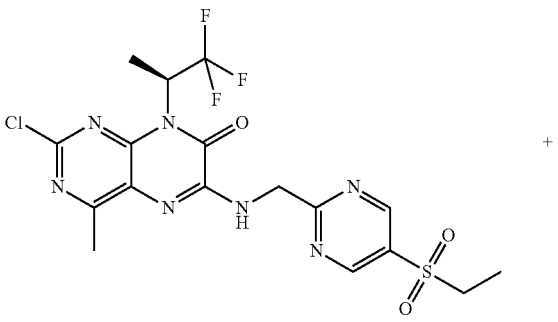
18

[0242] A mixture of J (5.0 g, 10.5 mmol), intermediate AE (3.0 g, 16.8 mmol), K_3PO_4 (5.6 g, 23.0 mmol), and Pd(dppf)Cl_2 (1.7 g, 2.1 mmol) in 1,4-dioxane (150 mL) and water (25 mL) is purged with argon. The mixture is stirred at 120° C. for 3 h. After cooling to rt, the aqueous layer is separated and the organic layer is concentrated. The residue is the dissolved in DCM and loaded onto KP—NH silica and eluted with DCM (500 mL). The organic phase is again concentrated and the residue is purified by purified by SiO_2 flash chromatography to yield Example 18. MS (ES+): m/z 575.4 $[M+H]^+$.

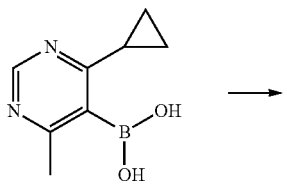
Method 15:

Synthesis of Example 23

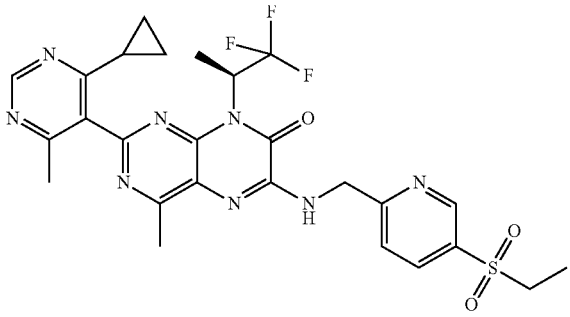
[0243]



L



AE



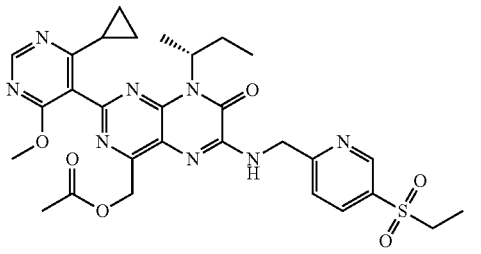
23

[0244] A mixture of L (1.7 g, 3.45 mmol), intermediate AE (1.23 g, 6.91 mmol), K_3PO_4 (1.47 g, 6.91 mmol), and Pd(dppf)Cl_2 (423 mg, 0.52 mmol) in 1,4-dioxane (40 mL) and water (10 mL) is purged with argon. The mixture is stirred at 120° C. for 3 h. After cooling to rt, the aqueous layer is separated and the organic layer is concentrated. The residue is the dissolved in DCM and loaded onto KP—NH silica and eluted with DCM (300 mL). The organic phase is again concentrated and the residue is purified by purified by SiO_2 flash chromatography to yield Example 23. MS (ES+): m/z 590.4 $[M+H]^+$.

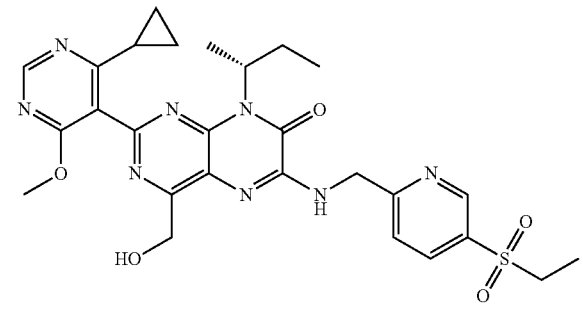
Method 16:

Synthesis of Example 1

[0245]



46



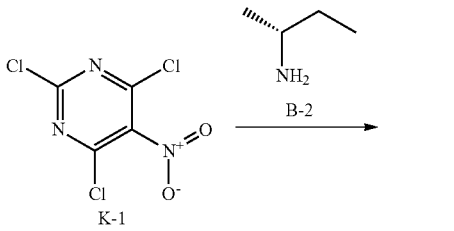
1

[0246] To a solution of 46 (30 mg, 0.48 mmol) in MeOH (1 mL) is added 4 M HCl in dioxane (0.5 mL, 2.00 mmol). The reaction is stirred at rt for 2 h. The mixture is concentrated and is purified by reverse phase HPLC (41-61% ACN/H2O) to give 1. MS (ES+): m/z 581.5 $[M+H]^+$. Example 51 and 52 synthesized in an analogous fashion to Example 1.

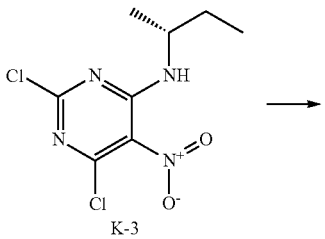
Method 17:

Synthesis of Intermediate K

[0247]

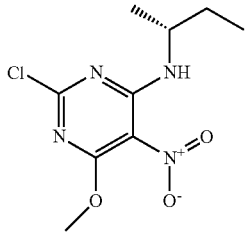


K-1



K-3

-continued



K-4

[0248] To a stirred suspension of K-1 (1.00 g, 4.38 mmol) and DIEA (1.83 mL, 10.51 mmol) in DCM (15 mL) at 0° C. is slowly added K-2 (1.00 g, 9.30 mmol) and the reaction is allowed to slowly warm to 25° C. and stirred for 4 h. The volatiles are removed under reduced pressure and the resulting residue is purified by SiO_2 flash chromatography to yield K-3.

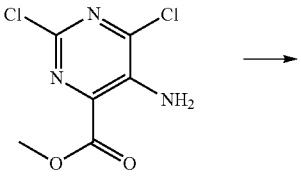
[0249] To a solution of K-3 (1.00 g, 3.77 mmol) in THF (20 mL) at 0° C. is added a solution of sodium methoxide in MeOH (8.29 mL, 4.15 mmol). The reaction mixture is allowed to warm to rt and stir overnight. The volatiles are removed under reduced pressure and the resulting residue is purified by SiO_2 flash chromatography to yield K-4.

[0250] The remainder of the synthesis is analogous to Method 2.

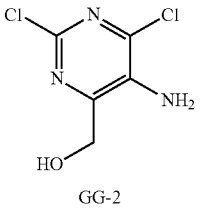
Method 18:

Synthesis of Intermediate GG

[0251]



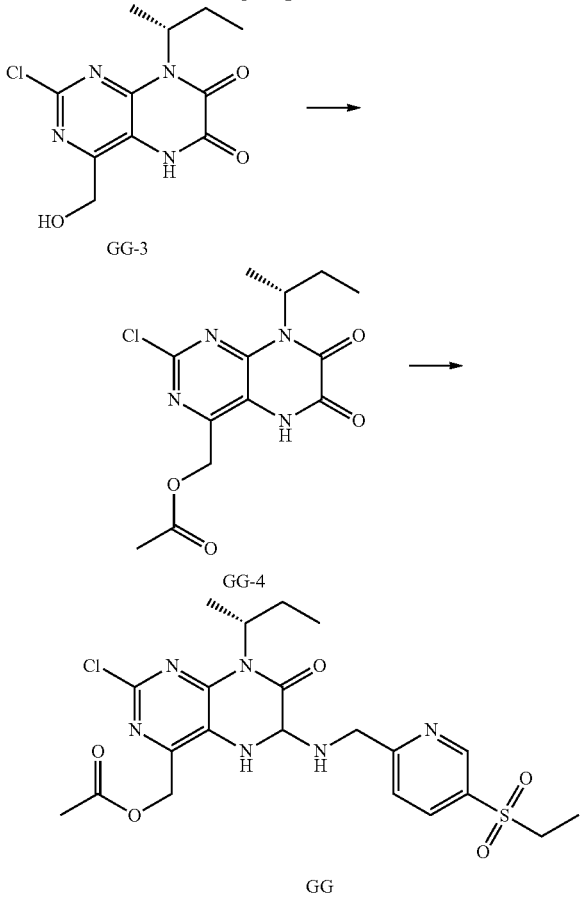
GG-1



GG-2

[0252] To a stirred suspension of GG-1 (1.20 g, 5.08 mmol) in EtOH (10 mL) at 0° C. is slowly added sodium borohyride (211 mg, 5.59 mmol) and the reaction is allowed to warm to 25° C. and stir for 1 h. The reaction is quenched with water (10 mL) and extracted with EtOAc (40 mL). The volatiles are removed under reduced pressure and the resulting residue is purified by SiO_2 flash chromatography to yield GG-2.

[0253] The next steps are analogous to Method 1 with the addition of the following step.



GG-3

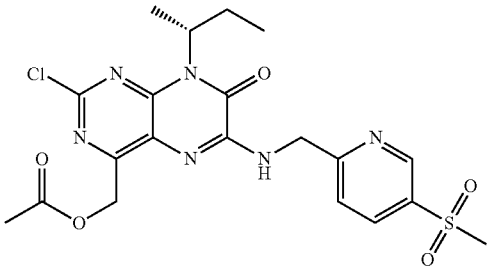
GG-4

GG

[0254] To a slurry of GG-3 (1.48 g, 5.20 mmol) and DMAP (140 mg, 1.14 mmol) is added acetic anhydride (4 mL) and Et3N (2.26 mL, 16.1 mmol). The suspension is allowed to stir at rt for 20 min. The reaction is diluted with water (25 mL) and extracted with EtOAc (40 mL). The volatiles are removed under reduced pressure and the resulting residue is purified by SiO_2 flash chromatography to yield GG4. GG-4 is converted to intermediate GG as in Method 1

[0255] Intermediate HH is prepared in an analogous fashion to Intermediate GG.

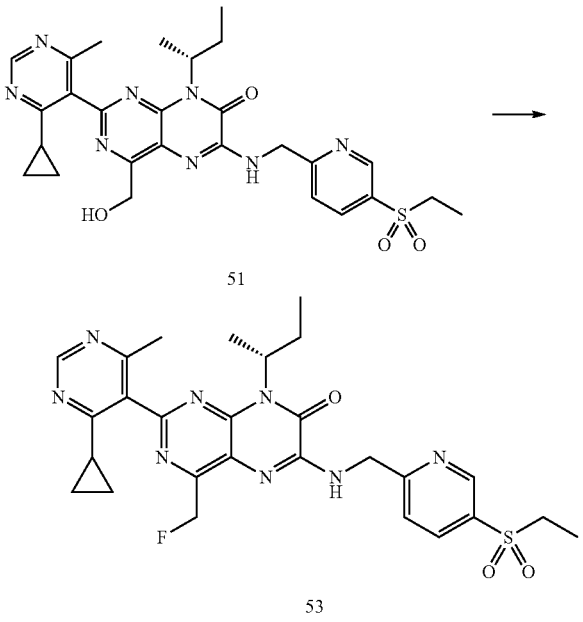
HH



Method 19:

Synthesis of Example 53

[0256]



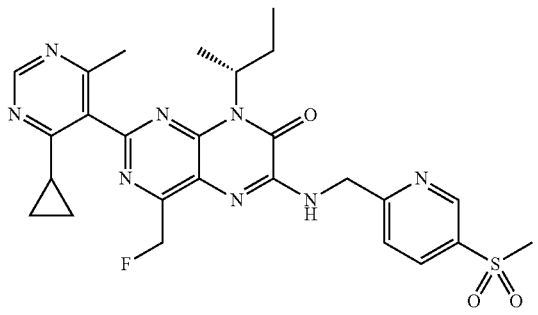
51

53

[0257] To a stirring solution of DAST, 1M in DCM (0.14 mL, 0.14 mmol) in DCM (5 mL) @-78 C is added dropwise over 1 min 51 (27 mg, 0.048 mmol) as a solution in DCM (2 mL). The reaction is stirred at −78 C for 10 min then rt for 1 h. The reaction is quenched with sat. $NaHCO_3$ (8 mL) with vigorous stirring for 15 min. The mixture is extracted with DCM (2×8 mL) and the organics dried (Na_2SO_4) and concentrated. The crude is purified by silica gel chromatography (MeOH/DCM) and product fractions are concentrated to a solid. Trituration in EtOAc/heptane yields product 53. LCMS (ESI+) m/z=567.2.

[0258] Example 54 is synthesized from intermediate 52 in an analogous manner as Example 53. LCMS (ESI+) m/z=553.2.

54



[0259] Table 2 summarizes the synthetic method used to prepare intermediates A-QQQb and the m/z found for each intermediate.

TABLE 2

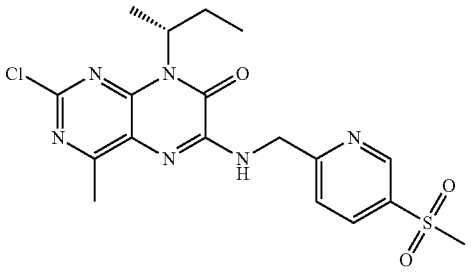
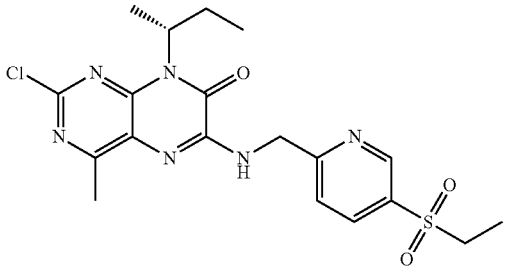
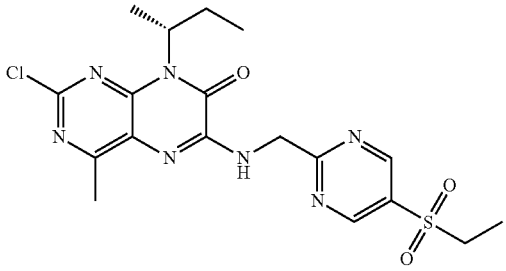
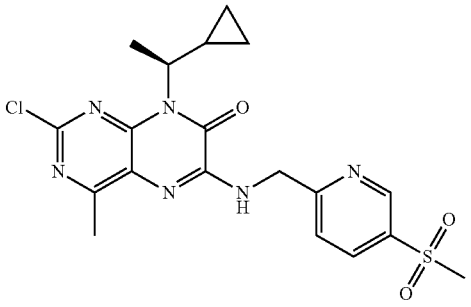
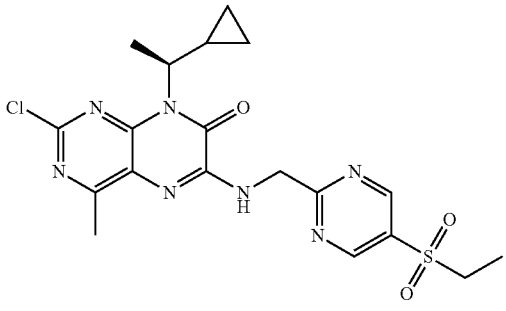
Intermediate	Structure	Synthetic Method	m/z [M + H]+
A		1	437.3
B		1	451.3
C		1	452.2
D		2	449.2
E		2	464.3

TABLE 2-continued

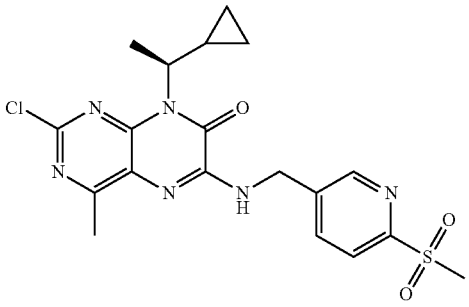
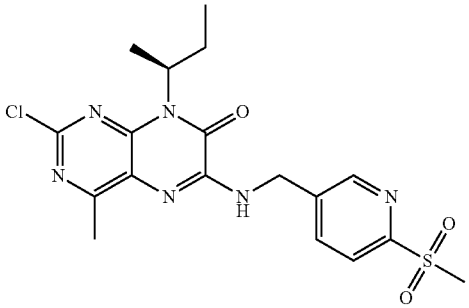
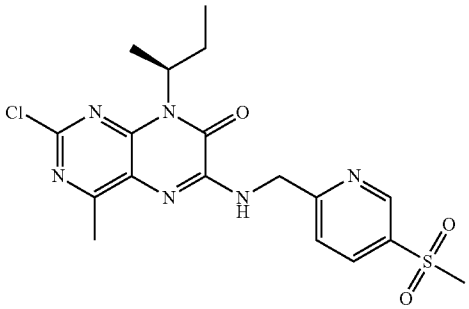
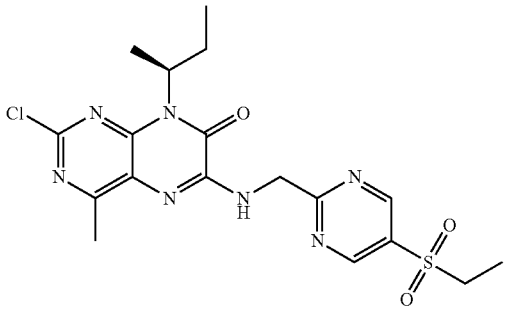
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
F		2	449.2
G		2	437.3
H		2	437.3
I		2	452.3

TABLE 2-continued

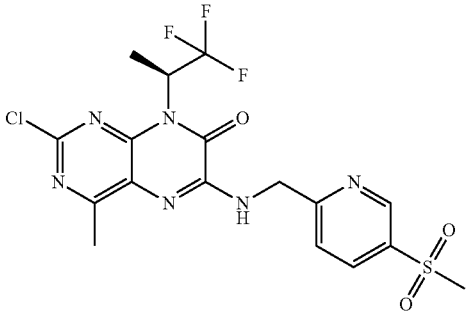
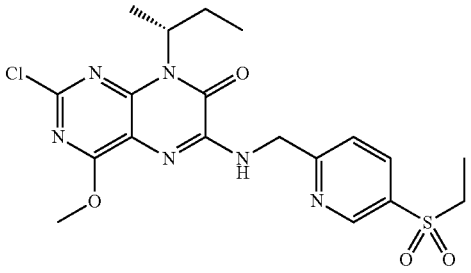
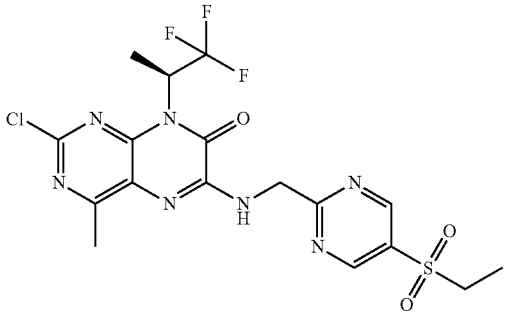
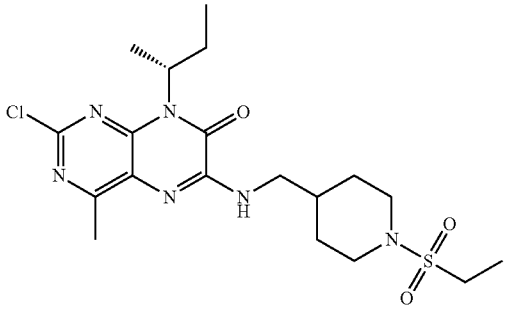
Intermediate	Structure	Synthetic Method	m/z [M + H]+
J		2	477.2
K		17	467.3
L		2	492.2
M		1	457.1

TABLE 2-continued

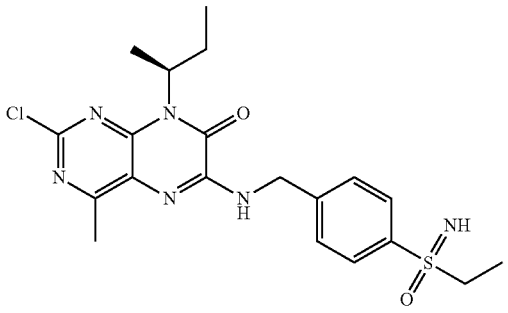
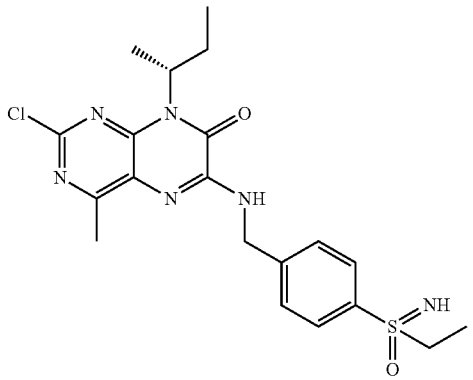
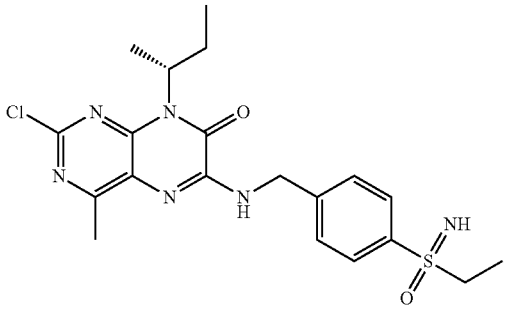
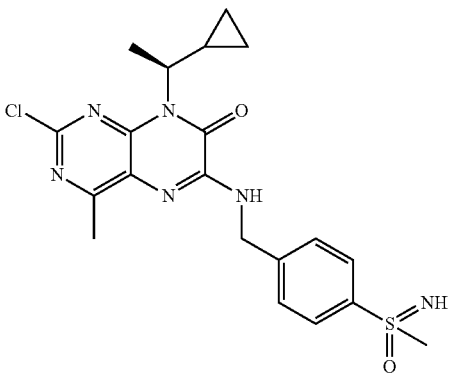
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
N		2	449.1
Oa		1	449.1
Ob		1	449.1
Pa		2	447.2

TABLE 2-continued

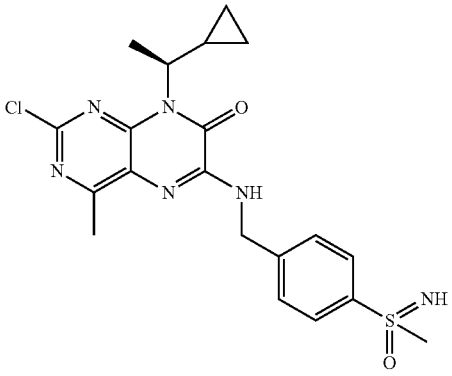
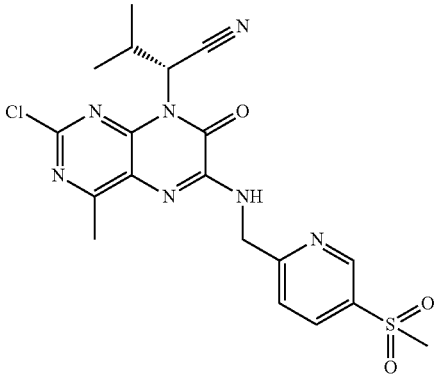
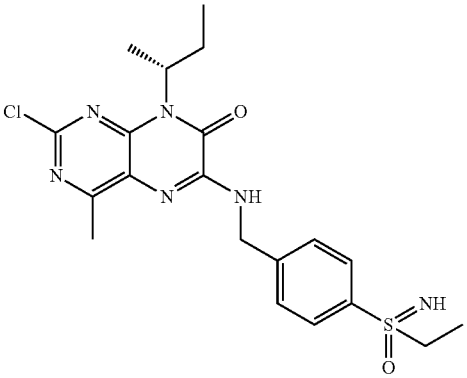
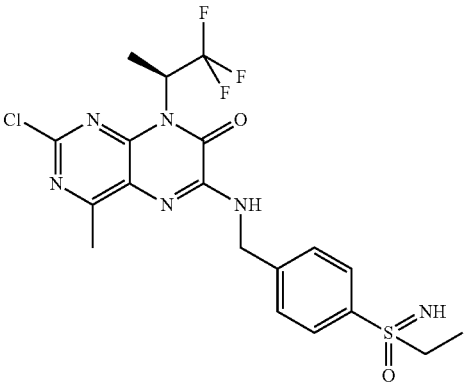
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
Pb		2	435.1
R		2	462.3
T		1	449.1
Ua		2	489.2

TABLE 2-continued

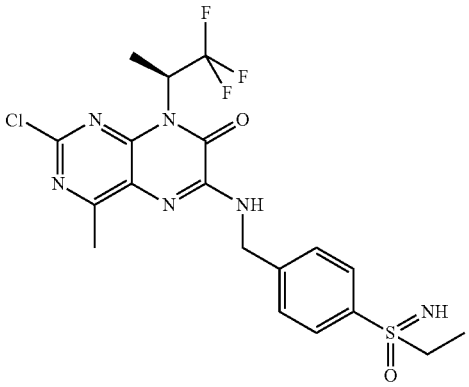
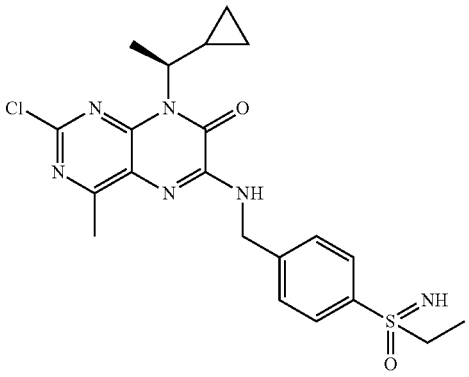
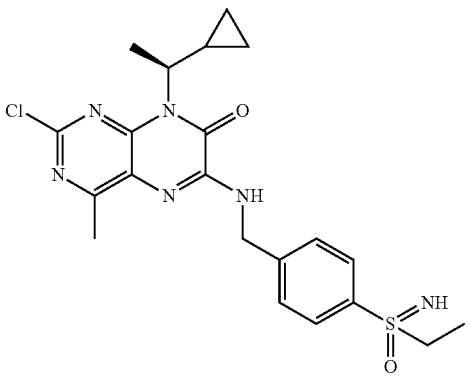
Intermediate	Structure	Synthetic Method	m/z [M + H]+
Ub		2	489.3
Wa		2	461.1
Wb		2	461.1

TABLE 2-continued

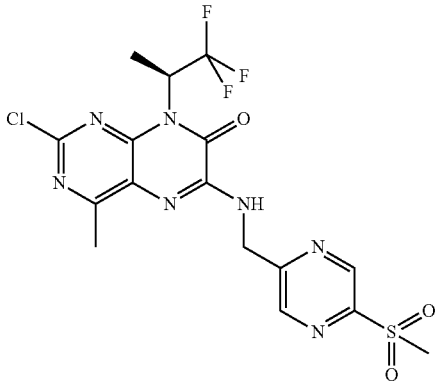
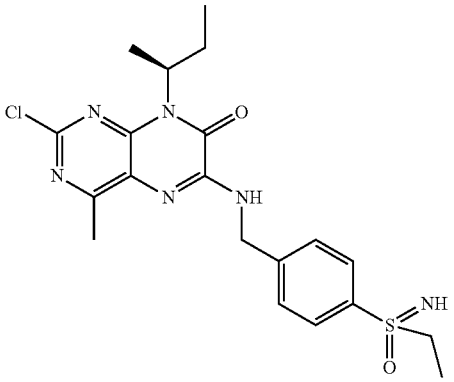
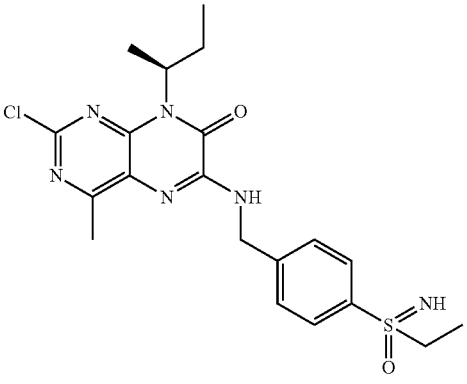
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
X		2	478.1
Ya		2	449.1
Yb		2	449.1

TABLE 2-continued

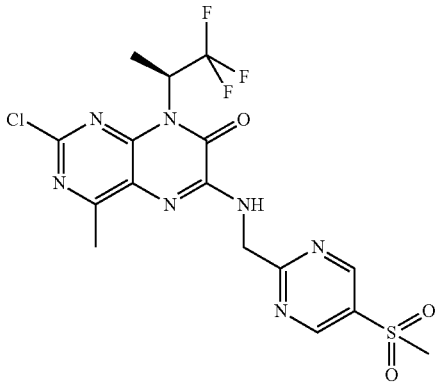
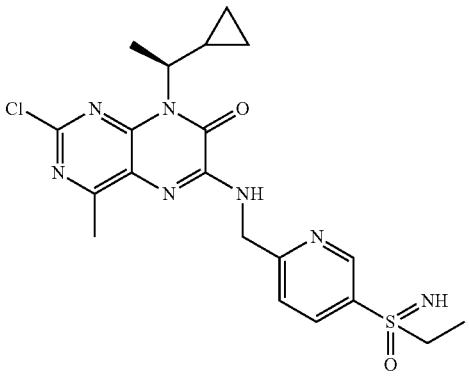
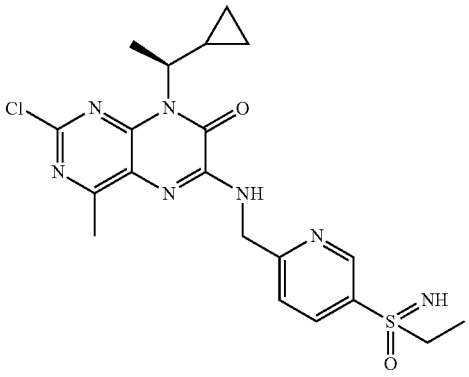
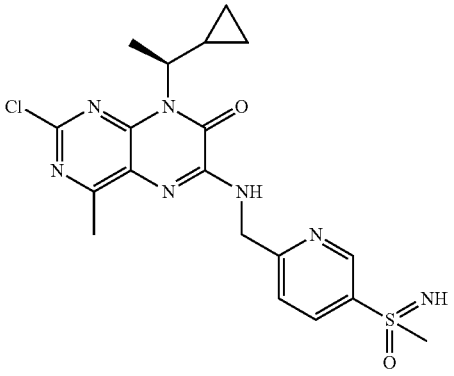
Intermediate	Structure	Synthetic Method	m/z [M + H]+
BB		2	478.1
CCa		2	462.3
CCb		2	462.3
DDa		2	448.2

TABLE 2-continued

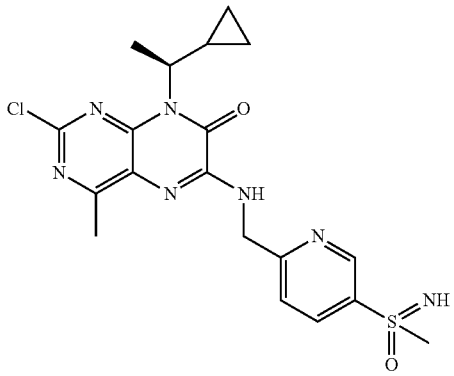
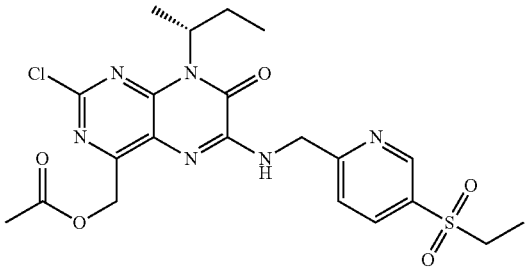
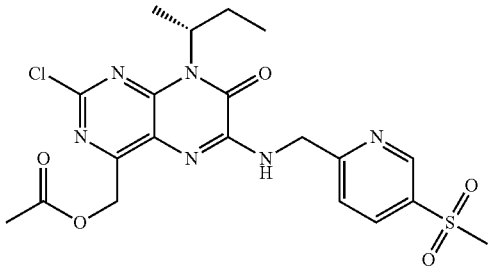
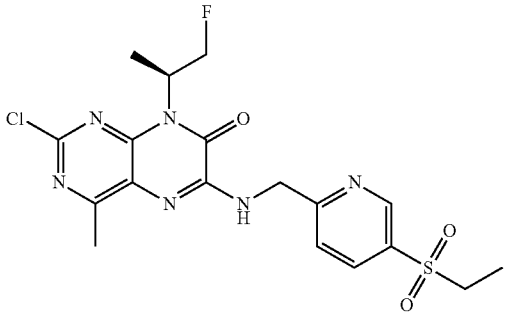
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
DDb		2	448.2
GG		18	509.2
HH		18	495.3
II		2	455.5

TABLE 2-continued

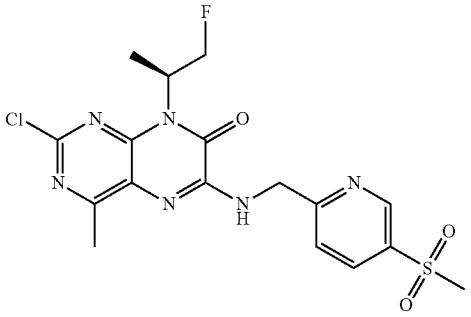
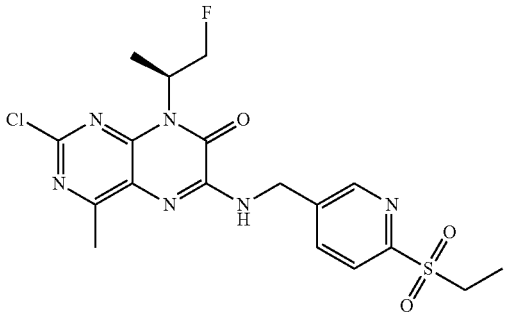
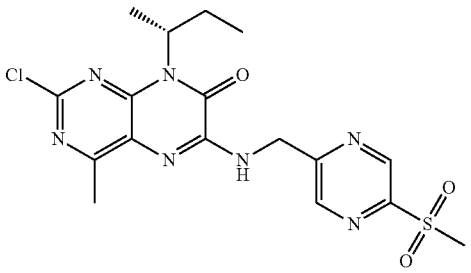
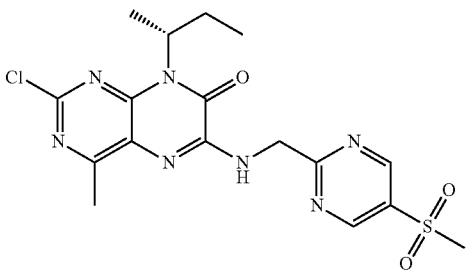
Intermediate	Structure	Synthetic Method	m/z [M + H]+
JJ		2	441.6
KK		2	455.6
LL		1	438.1
MM		1	438.1

TABLE 2-continued

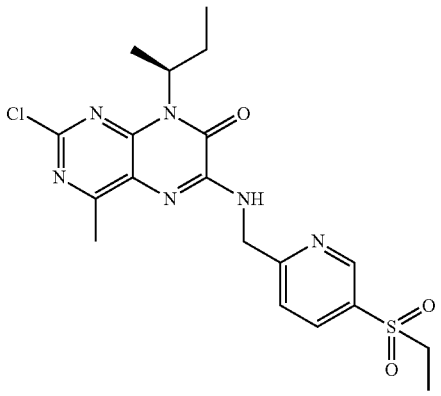
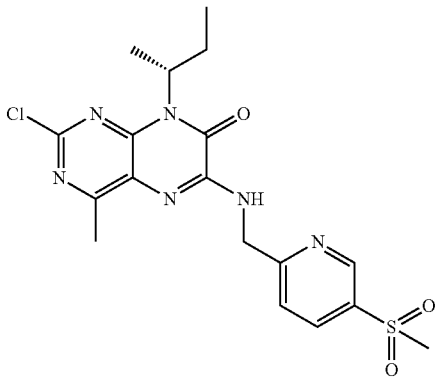
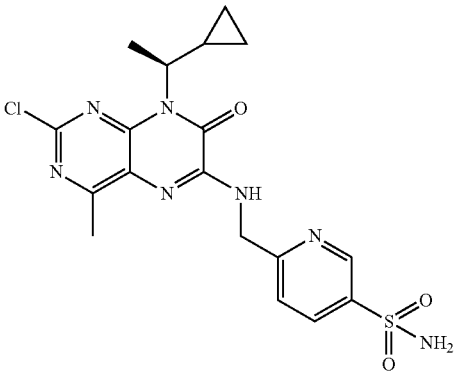
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
NN		2	451.1
OO		1	443.1
PP		2	450.2

TABLE 2-continued

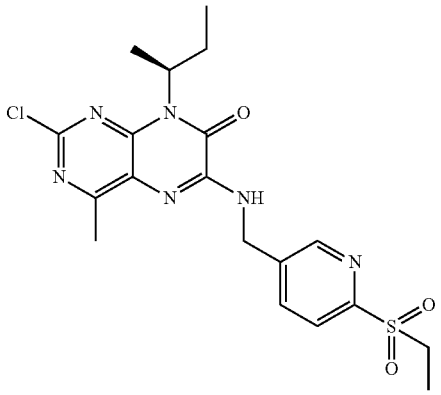
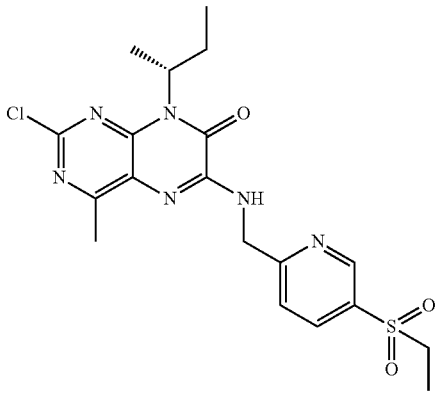
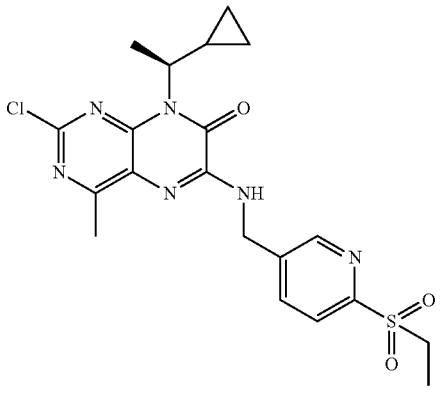
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
QQ		2	451.1
RR		1	451.1
SS		2	463.1

TABLE 2-continued

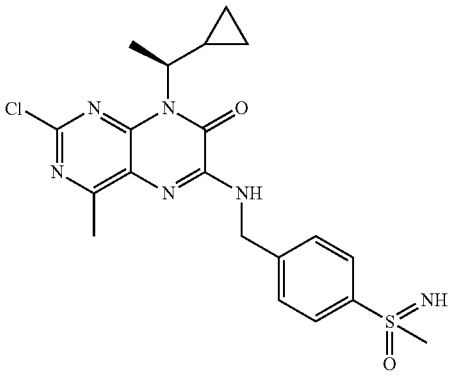
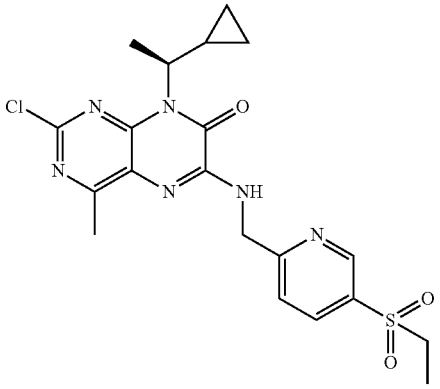
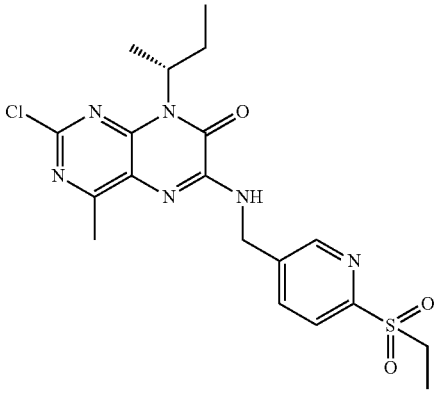
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
TT		2	447.2
UU		2	463.1
VV		1	451.2

TABLE 2-continued

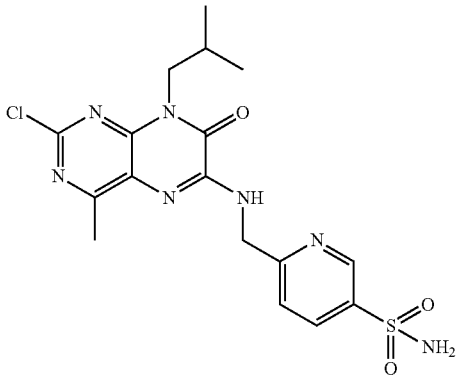
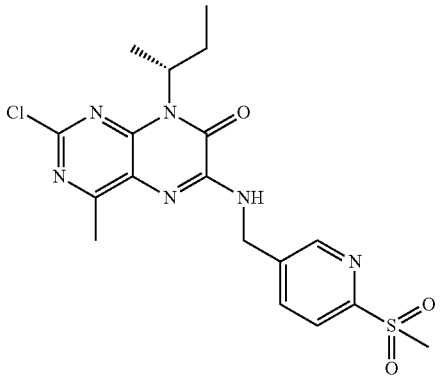
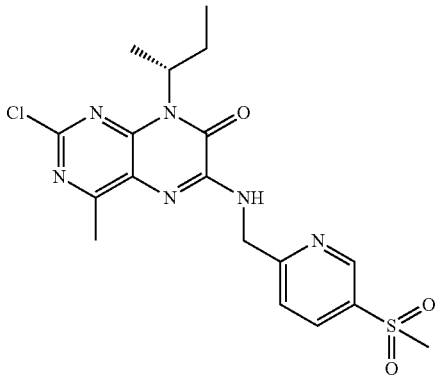
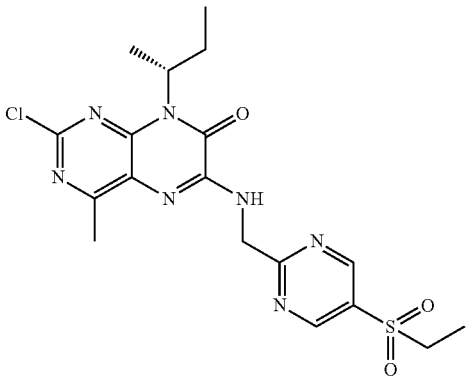
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
WW		1	437.2
XX		1	437.1
YY		1	437.1
ZZ		1	452.2

TABLE 2-continued

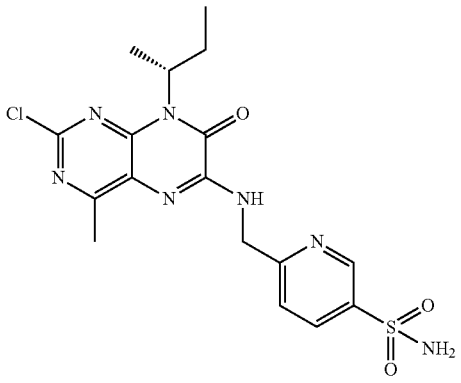
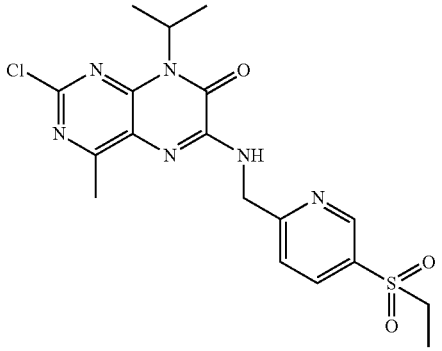
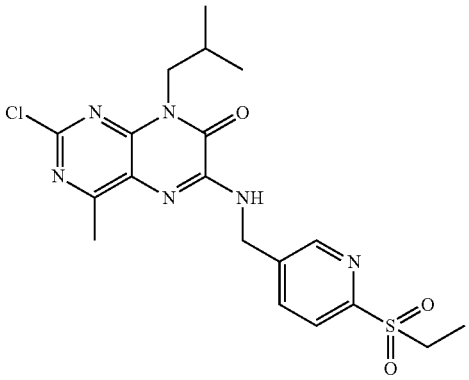
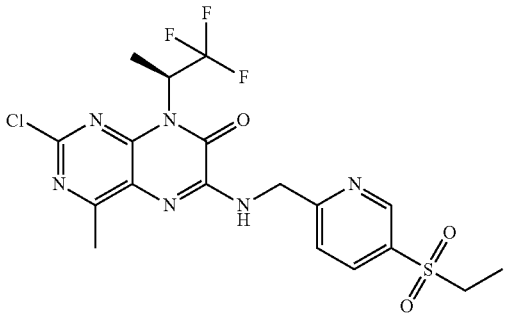
Intermediate	Structure	Synthetic Method	m/z [M + H]+
AAA		1	438.1
BBB		2	437.2
CCC		1	451.2
DDD		2	491.1

TABLE 2-continued

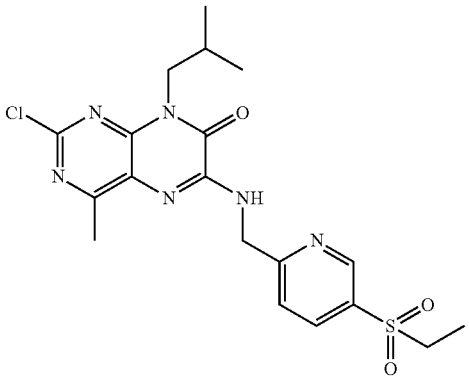
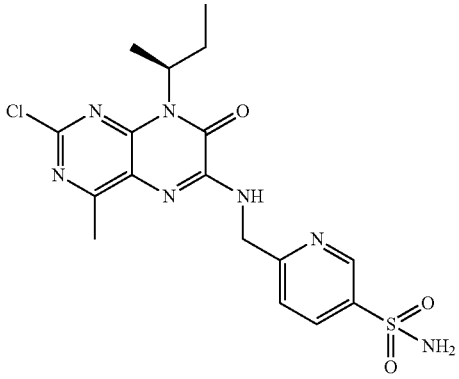
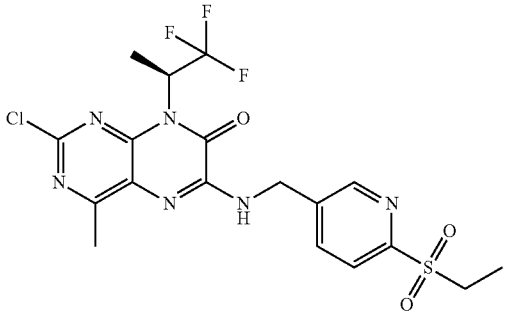
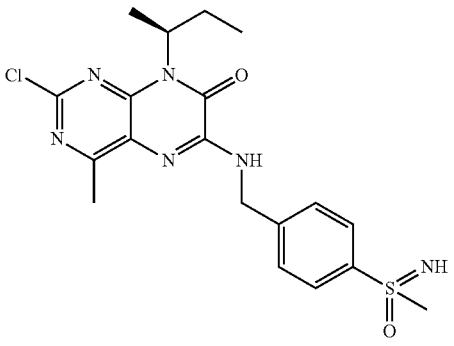
Intermediate	Structure	Synthetic Method	m/z $[M + H]^+$
EEE		1	451.2
FFF		2	438.1
GGG		2	491.1
HHH		2	434.9

TABLE 2-continued

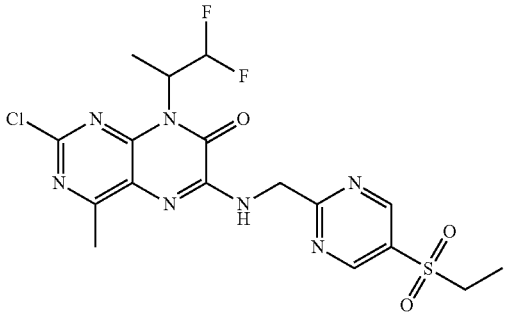
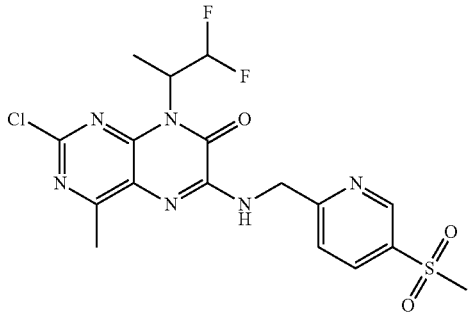
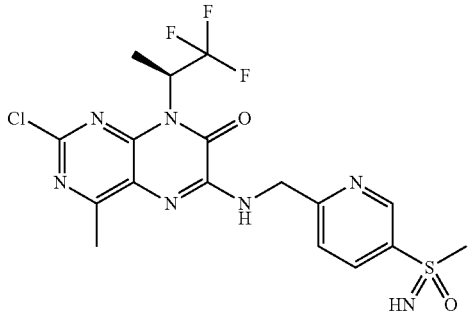
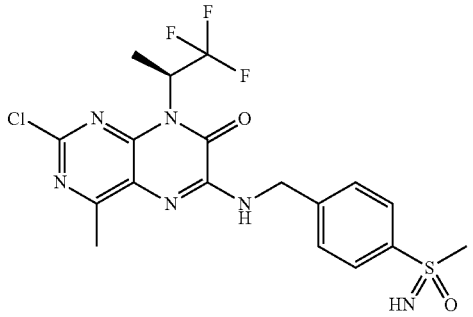
Intermediate	Structure	Synthetic Method	m/z [M + H]+
III		2	474.2
JJJ		2	459.2
KKKa		2	475.1
KKKb		2	475.1

TABLE 2-continued

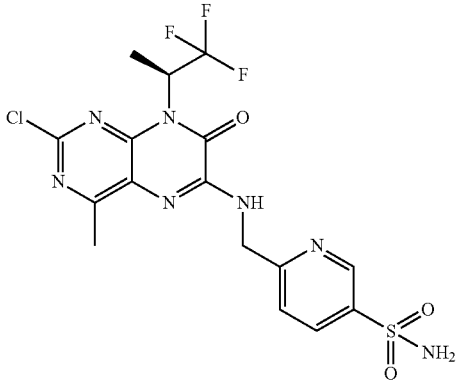
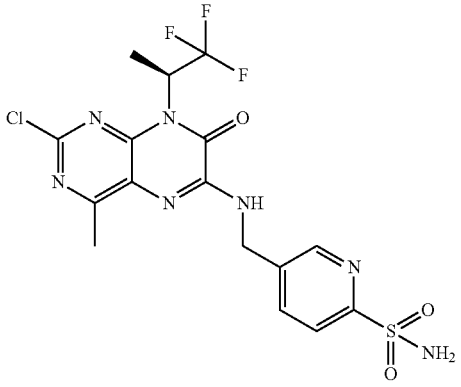
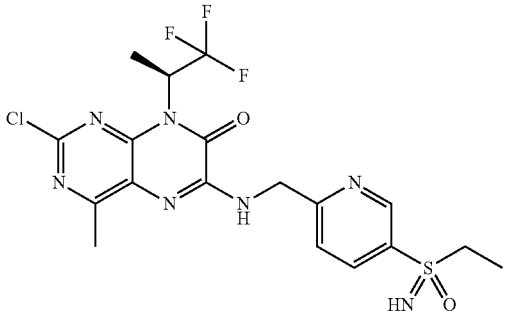
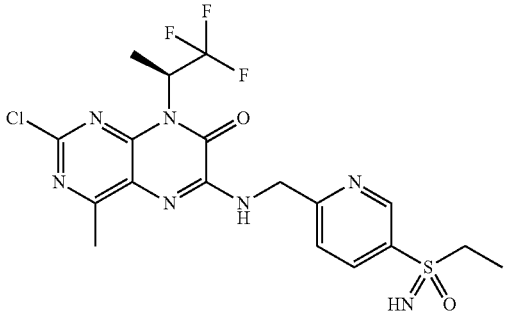
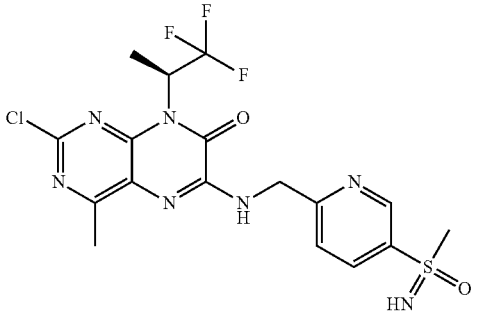
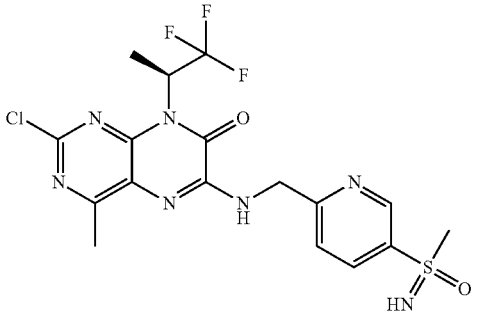
Intermediate	Structure	Synthetic Method	m/z [M + H]+
MMM		2	478.1
NNN		2	478.1
OOOa		2	490.1
OOOb		2	490.2

TABLE 2-continued

Intermediate	Structure	Synthetic Method	m/z [M + H]+
QQQa		2	476.1
QQQb		2	476.2

[0260] Final compounds 1-106b are prepared from the appropriate intermediate, above by coupling with the appropriate pyrimidine boronic acid intermediate, as described in Methods 13-15 or by modification of R^5 on another final product as illustrated by Methods 16 and 19.

Biological Activity

[0261] The compounds of the present invention have activity as modulators of RORγ (retinoid acid receptor-related orphan receptor y).

Reporter Gene Assay (RGA)

[0262] A nuclear receptor transactivation assay is performed to quantitate the ability of test compounds to inhibit RORγ transactivation of a luciferase reporter. A similar assay is described in: Khan et al., Bioorganic & Medicinal Chemistry Letters 23 (2013), 532-536. The system uses transiently transfected HEK 293 cells cotransfected with two plasmids (pGL4.3, luc2P/GAL4UAS/Hygro, and pBIND, Gal4DBD hRORC LBD1-3). The positive control is co-transiently transfected with both plasmids, and the negative control contains the pGL4.3 promoter sequence. Assays are assembled in 384 well plates where transiently transfected cells and test compound at varying concentrations are incubated for 20-24 h. The next day, assays plates are taken out and equilibrated at RT for 20-30 minutes. Bright-Glo™ Luciferase Assay System is used to detect Luciferase production. After addition of Bright GLO detection reagent, the plates are incubated at RT for 20 minutes. The plates are read on an Envision plate reader to measure luminescence signal. The RLU signal is converted to POC relative to control and blank wells.

Cell Seeding Media:

[0263] RPMI 1640-Invitrogen #11875135), 2.5% FBS-Invitrogen #26140, IxPenicillin-Streptomycin-Gibco #15140

Compound Dilution Buffer:

1×HBSS-Invitrogen #14025126

Assay Plates: Greiner #781080-020

Bright Glo Luciferase Assay System: Promega #E2620

[0264] Thaw lysis buffer provided in kit, add 100 mL lysis buffer to substrate powder.

[0265] Table 3 presents the results obtained when the compounds of the present invention were tested in the above assay, demonstrating their activity as modulators of RORγ. Table 3 also shows data from the metabolic stability assay in human liver microsomes, described below.

Assessment of Metabolic Stability

[0266] The 5 time point, high-throughput human liver microsome (HLM) metabolic stability assay is designed to determine in vitro compound metabolism. Compounds are incubated with HLMs at a concentration of 1 uM, at 37° C., for a total of 60 min. The percent of compound remaining at 5, 15, 30, and 60 min is used to calculate the t1/2 (min), CL_{int} (mL/min/kg), CL_h (mL/min/kg), and % Q_h. The assay is based on a 96-well format and can accommodate up to 92 compounds per plate (n=1).

[0267] Using the 96-well multi-channel head, the Biomek FX, equipped with a Peltier heating block/shaker, is programmed to accomplish the following steps:

[0268] 1. Pipette 175 uL of 1.15 mg/mL microsomes into each of the 96 conical inserts (Analytical Sales and Products, catalog number 96PL05) that fit into the plate of the Peltier heating block/shaker (the incubation plate)

[0269] 2. Add 5 uL of compounds from the assay plate to the microsomes and shake the mixture at 600 rpm at 42.1° C. for 10 min (a setting of 42.1° C. on the Peltier is required for the samples to incubate at 37° C.)

[0270] 3. After 10 min, prompt the user to add the NADPH plate to the deck and add 20 uL from the NADPH plate to the incubation plate to start the reaction

[0271] 4. Add 215 uL of 100%, cold acetonitrile containing an internal standard(s) to a 0 minute, 5 minute, 15 minute, 30 minute, and 60 minute "quench" plate

[0272] 5. At 0 min, 5 min, 15 min, 30 min, and 60 min into the incubation, aspirate 12 uL from the incubation mixture and add it to the quench solution to stop the reaction

[0273] 6. Add 185 uL HPLC grade water to each well of the 0, 5, 15, 30 and 60 minute quench plates to dilute compounds to the appropriate concentration for the mass spectrometer

[0274] After all time points are collected, the quench plates are sealed with 96-well pierceable plate mats or heat sealing foil and centrifuged at 3000 rpm for 15 min to pellet the microsomes.

[0275] The plates are analyzed using LC/MS/MS with electron spray ionization (ESI) and the previously determined MRM transitions. The LC method includes the following parameters:

Injection volume: 5 uL

Mobile Phases: 0.1% Formic Acid in Water (A) and 0.1% Formic Acid in Acetonitrile (B) (HPLC grade)

Left and Right Temperature: 35° C.

Run Time: 4.0 min

[0276] Column: Thermo Scientific, Aquasil C18, 50×2.1 mm, 5a, part number 77505-052130, or equivalent

LC Pump Gradient:

[0277]

Total Time (min)	Flow Rate (uL/min)	% A	% B
0	500	90.0	10.0
0.5	500	90.0	10.0
1.5	500	1.0	99.0
2.5	500	1.0	99.0
3.3	500	90.0	10.0
4.0	500	90.0	10.0

[0278] If peak shape is poor and cannot be integrated properly, the following LC method can be used:

Injection volume: 5 uL

Mobile Phases: 2.5 mM Ammonium Bicarbonate (A) and 100% Acetonitrile (B) (HPLC grade)

Aqueous Wash: 90% Water, 10% Acetonitrile (HPLC grade)

Organic Wash: 90% Acetonitrile, 10% Water (HPLC grade)

Left and Right Temperature: 35° C.

Run Time: 4.5 min

Column: Phenomex Luna 3u C18(2) 100A, 50×2.00 mm

LC Pump Gradient:

[0279]

Total Time (min)	Flow Rate (uL/min)	% A	% B
0	500	90.0	10.0
0.5	500	90.0	10.0
1.5	500	1.0	99.0
2.5	500	1.0	99.0
3.30	500	90.0	10.0
4.50	500	90.0	10.0

[0280] Using an Excel template in Activitybase, the peak areas corresponding to 5, 15, 30 and 60 min are compared to the peak area at 0 min to calculate the percent of remaining compound using the following equation:

[0281] Percent compound remaining=(AUC at Time t min/AUC at Time 0 min)×100 where t=0, 5, 15, 30 or 60 min.

[0282] Time (min) is plotted against the natural logarithm (Ln) of the percent compound remaining to determine the slope. The slope is used to calculate t1/2 (min) using the equation, t1/2=0.693/slope.

Clint, Intrinsic Clearance

[0283] 0.693/t1/2*Avg liver wt in g/avg body wt in kg*f(u)/protein concentration in incubation in mg/mL*mg microsomal protein/g liver

[0284] 0.693/t1/2*26 g/kg*1/1.0 mg/mL*45 mg/g

Clh, Hepatic Clearance

[0285] Hepatic flow*f(u)*Clint/(hepatic flow+f(u)*Clint)

Qh, % Hepatic Blood Flow

[0286] (Clh/Hepatic flow)*100

[0287] IC_{50} data in RORγ Reporter Gene Assay (RGA) and Metabolic stability data (% Qh) for compounds from Table 1 are shown in Table 3 below. Preferred compounds have % Qh values of less than 24.

TABLE 3

Example	RGA IC_{50} (nM)	HLM (% Qh)
1	200	<24
2	110	<24
3	88	<24
4	180	<24
5	73	28
6	87	<24

TABLE 3-continued

Example	RGA IC_{50} (nM)	HLM (% Qh)
7	70	33
8	75	<24
9	70	<24
10	97	27
11	135	26
12	140	<24
13	99	<24
14	115	<24
15	150	<24
16	113	<24
17	130	39
18	175	55
19	165	62
20	175	29
21	1900	<24
22	140	<24
23	178	<24
24	120	69
25	155	26
26b	170	25
27b	265	<24
26a	109	25
29a	235	73
29b	170	48
31	850	55
27a	210	<24
33	100	41
34a	210	25
34b	170	<24
36b	245	<24
37	455	<24
38a	160	<24
38b	110	<24
36a	260	<24
41	1250	<24
42b	390	<24
43a	730	<24
43b	400	<24
42a	270	<24
46	1050	66
47	1050	56
48	1205	<24
49	4200	<24
50	2700	<24
51	230	<24
52	335	<24
53	160	33
54	225	41
55	265	<24
56	1100	<24
57	500	<24
58	71	<24
59	98	78
60	80	<24
61	185	<24
62	125	27
63	100	<24
64	95	<24
65	135	<24
66	64	25
67	110	<24
68	60	<24
69	116	<24
70	1300	<24
71	65	35
72	205	<24
73	155	<24
74	77	<24
75		
76	275	34
77	680	<24
78	275	<24
79	130	<24
80	255	<24

TABLE 3-continued

Example	RGA IC_{50} (nM)	HLM (% Qh)
81	185	<24
82	225	<24
83	250	32
84	195	33
85	270	<24
86	73	<24
87	97	37
88	102	38
89	225	<24
90	235	<24
91a	295	<24
91b	255	<24
93	185	<24
94	205	<24
95	150	40
96	280	<24
97	320	46
98	1100	<24
99a	230	41
99b	260	41
101a	365	<24
102a	535	<24
101b	315	<24
102b	640	<24
105a	890	<24
106a	1300	<24
105b	510	27
106b	840	28

Methods of Therapeutic Use

[0288] On the basis of their biological properties the compounds of formula (I) according to the invention, or their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for treating autoimmune and allergic disorders in that they exhibit good modulatory effect upon RORγ.

[0289] The present invention is therefore directed to compounds of general formula (I), and the pharmaceutically acceptable salts thereof, and all tautomers, racemates, enantiomers, diastereomers, mixtures thereof, which are useful in the treatment of a disease and/or condition wherein the activity of RORγ modulators is of therapeutic benefit, including but not limited to the treatment of autoimmune or allergic disorders.

[0290] Such disorders that may be treated by the compounds of the invention include for example: rheumatoid arthritis, psoriasis, systemic lupus erythromatosis, lupus nephritis, systemic sclerosis, vasculitis, scleroderma, asthma, allergic rhinitis, allergic eczema, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, type I diabetes, Crohn's disease, ulcerative colitis, graft versus host disease, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, atherosclerosis, uveitis and non-radiographic spondyloarthropathy.

[0291] For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range of approximately 0.01 mg to about 10 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 5 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be approximately 0.7 mg to about 750 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 350 mg per dosage.

Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

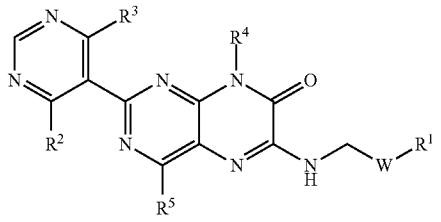
[0292] When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and generally comprise at least one compound of the invention and at least one pharmaceutically acceptable carrier. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased antagonist activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

[0293] Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by Remington: The Science and Practice of Pharmacy, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; Handbook of Pharmaceutical Additives, Michael & Irene Ash (eds.), Gower, 1995; Handbook of Pharmaceutical Excipients, A. H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H. C. Ansel and N. G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art. As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that are required for the formulation to be efficacious.

[0294] All patent and non-patent documents or literature cited in this application are herein incorporated by reference in their entirety.

1. A compound of formula (I)

(I)



wherein:

R^1 is selected from $—S(O)_nR^6$, $—S(O)_nNR^7R$, and $—S(O)(NH)R^6$;

wherein:

R^6 is:

C_{1-3} alkyl

R^7 and R^8 are each —H; and

n is 1 or 2;

R^2 and R^3 are independently selected from

C_{1-3}alkyl;

cyclopropyl; and

methoxy;

R^4 is C_{1-6}alkyl, optionally substituted with one or two groups independently selected from

C_{3-6}cycloalkyl;

halogen;

$—CF_3$; and

—CN;

R^5 is selected from

C_{1-3}alkyl, optionally substituted with 1 to 3 fluoro groups;

$—CH_2OH$;

$—CH_2OC(O)C_{1-3}$alkyl; and

$—OC_{1-3}$alkyl;

W is selected from

pyridinyl;

pyrimidinyl;

pyrizinyl;

phenyl; and

piperidinyl;

and the pharmaceutically acceptable salts thereof.

2. The compound of formula (I) according to claim **1**, wherein

R^1 is selected from $—S(O)_nR^6$, $—S(O)_nNR^7R^8$, and $—S(O)(NH)R^6$;

wherein:

R^6 is C_{1-3} alkyl;

R^7 and R^8 are each —H; and

n is 2;

R^2 and R^3 are independently selected from

methyl;

cyclopropyl; and

methoxy;

R^4 is C_{1-4}alkyl, optionally substituted with one or two groups independently selected from

cyclopropyl;

—F;

$—CF_3$; and

—CN;

R^5 is selected from

$—CH_3$;

$—CH_2F$;

—CH_2OH;
—$CH_2OC(O)CH_3$; and
—OCH_3;
W is selected from
2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, 2-pyrizinyl and phenyl;
and the pharmaceutically acceptable salts thereof.

3. The compound of formula (I) according to claim **1**, wherein
R^1 is selected from —$S(O)_nR^6$, —$S(O)_nNR^7R^8$, and —$S(O)(NH)R^6$;
wherein:
R^6 is C_{1-2} alkyl;
R^7 and R^8 are each —H; and
n is 2;
R^2 and R^3 are independently selected from
methyl;
cyclopropyl; and
methoxy;
R^4 is C_{1-4}alkyl, optionally substituted with one or two groups independently selected from
cyclopropyl;
—F;
—CF_3; and
—CN;
R^5 is selected from
—CH_3;
—CH_2F;
—CH_2OH;
—$CH_2OC(O)CH_3$; and
—OCH_3;
W is selected from
2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, 2-pyrizinyl and phenyl;
and the pharmaceutically acceptable salts thereof.

4. The compound of formula (I) according to claim **1**, wherein
R^1 is selected from —$S(O)_nR^6$, —$S(O)_nNR^7R^8$, and —$S(O)(NH)R^6$;
wherein:
R^6 is C_{1-2} alkyl;
R^7 and R^8 are each —H; and
n is 2;
R^2 is methyl or methoxy;
R^3 is cyclopropyl;
R^4 is C_{1-4}alkyl, optionally substituted with a group selected from
cyclopropyl and —CF_3;
R^5 is selected from
—CH_3;
—CH_2F; and
—CH_2OH;
W is selected from
2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, and phenyl;
and the pharmaceutically acceptable salts thereof.

5. The compound of formula (I) according to claim **1**, wherein
R^2 is methyl or methoxy;
R^3 is cyclopropyl;
R^4 is C_{1-4}alkyl, optionally substituted with a group selected from cyclopropyl and —CF_3;
R^5 is —CH_3;
W is selected from
2-pyridinyl, 3-pyridinyl, 2-pyrimidinyl, and phenyl;
and the pharmaceutically acceptable salts thereof.

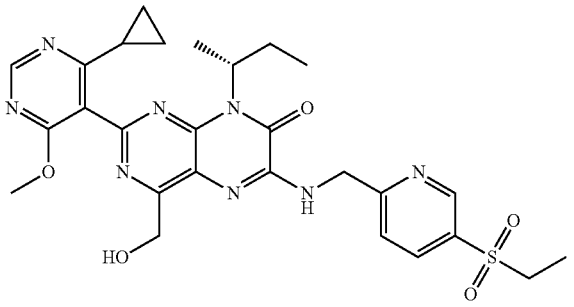
6. The compound of formula (I) according to claim **1**, wherein

W is selected from 2-pyridinyl and, 3-pyridinyl;

and the pharmaceutically acceptable salts thereof.

7. The compound according to claim **1** selected from the group consisting of:

1



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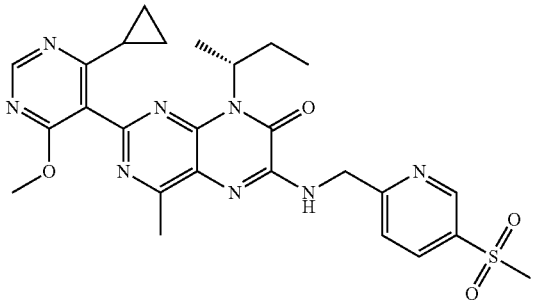

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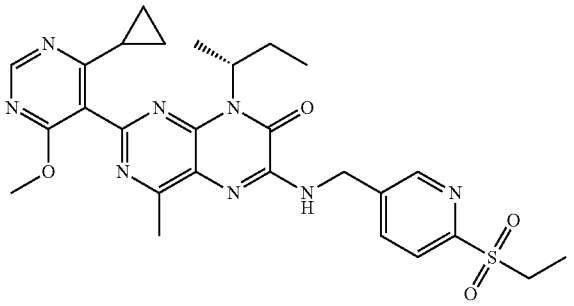

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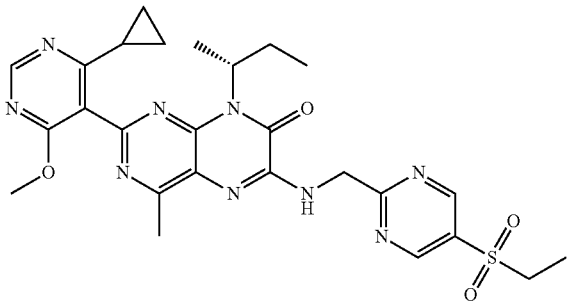

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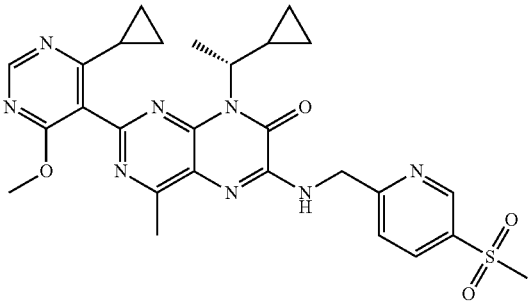

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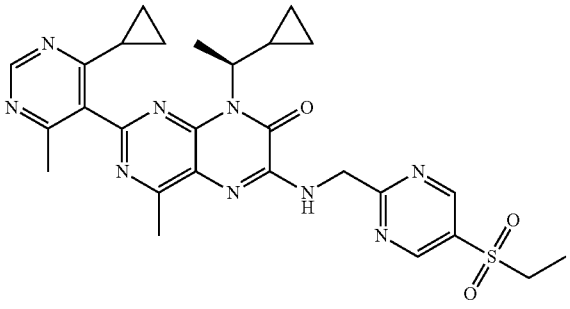

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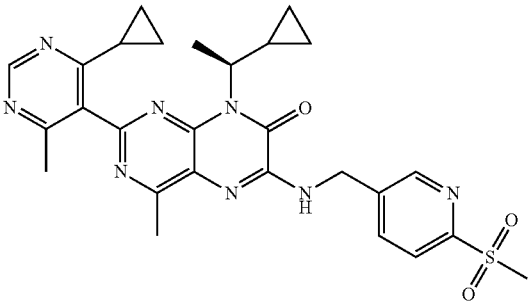

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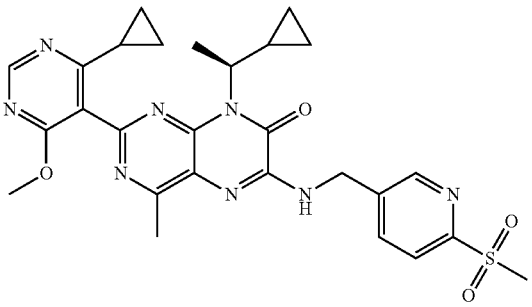

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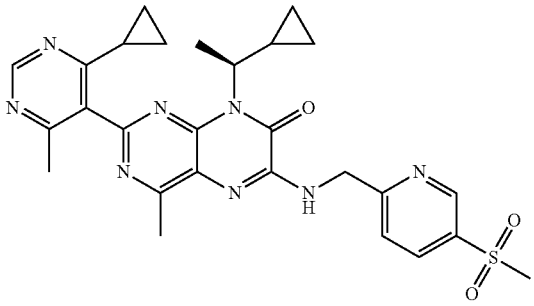

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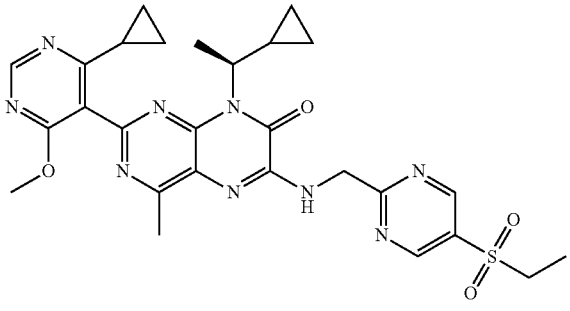

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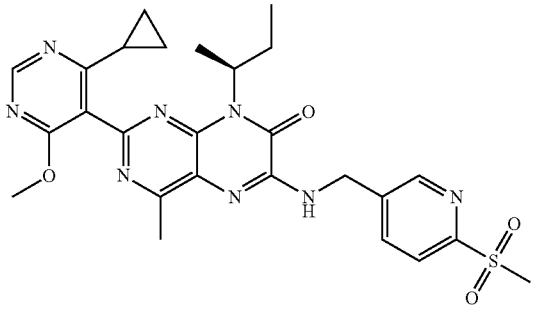

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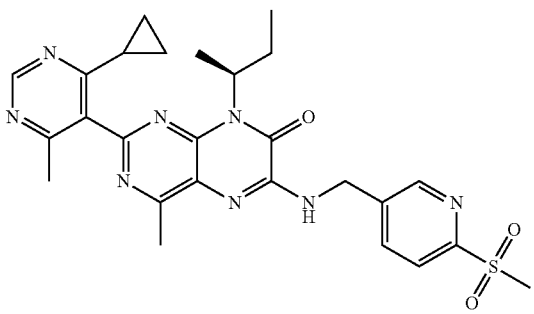

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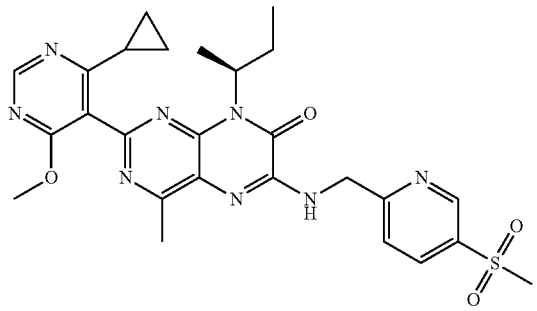

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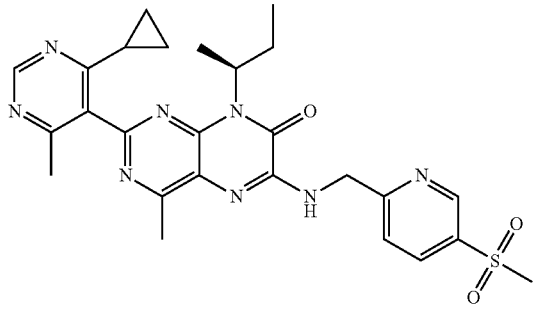

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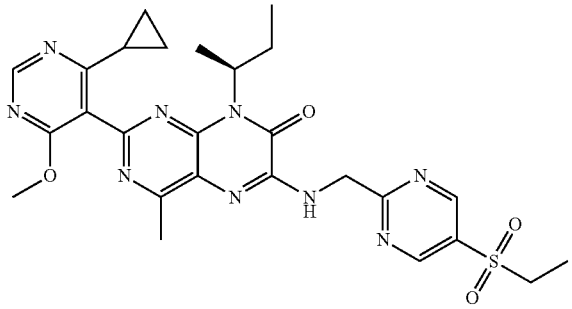

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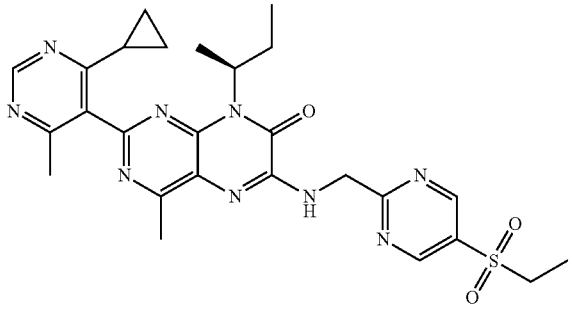

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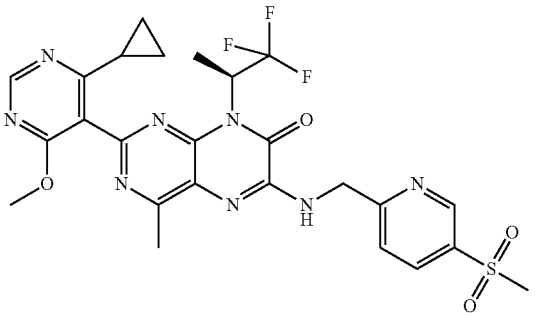

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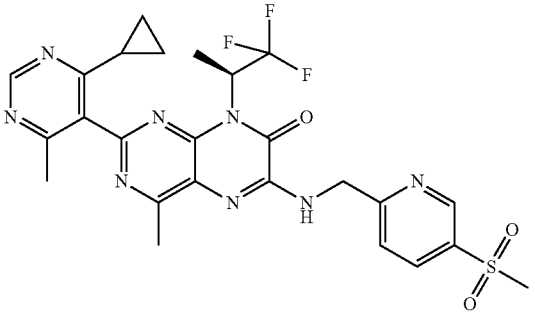

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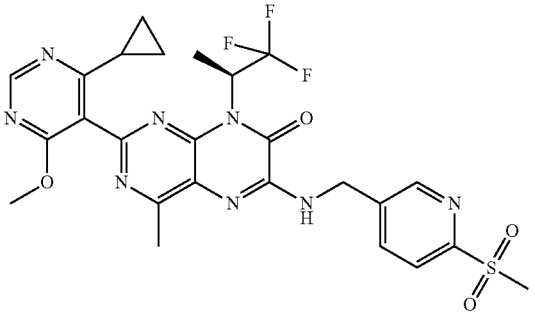

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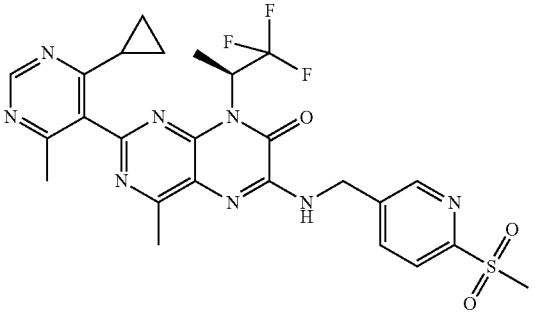

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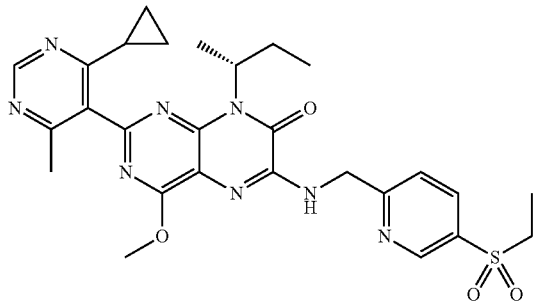

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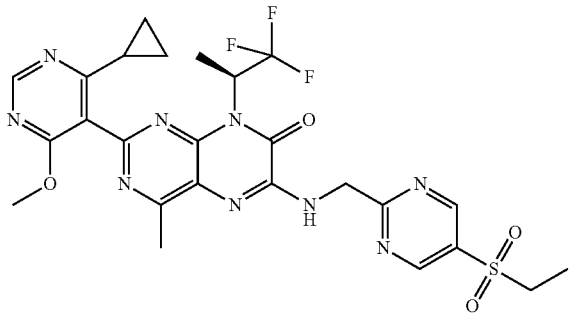

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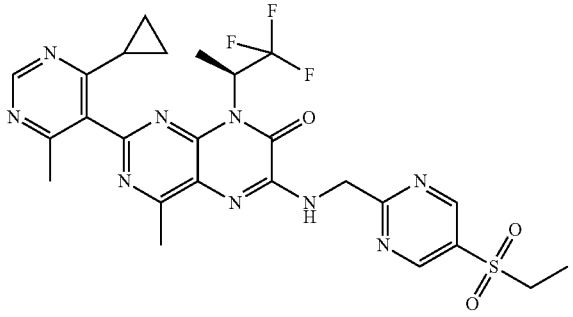

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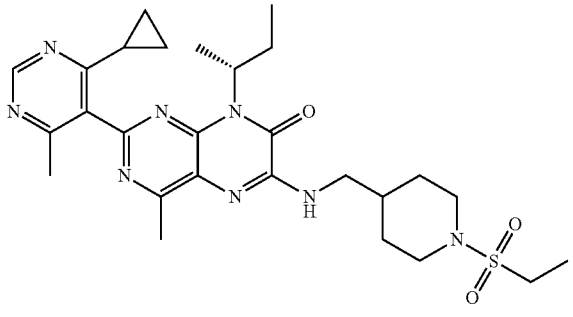

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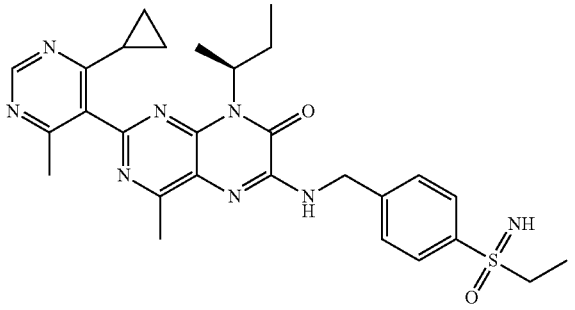

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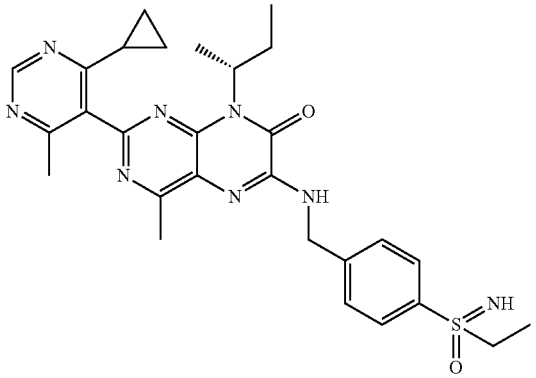

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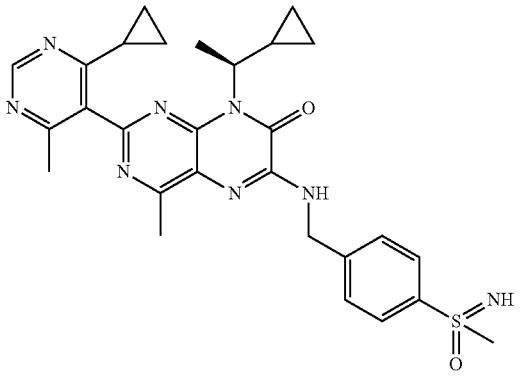

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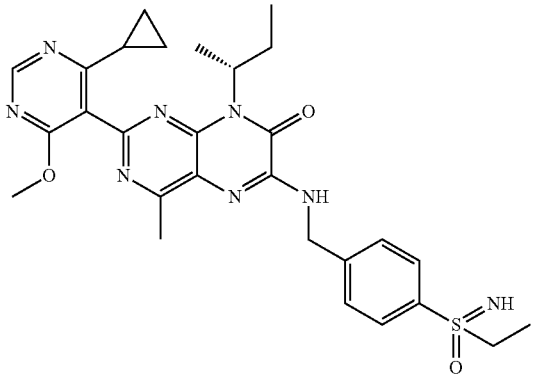

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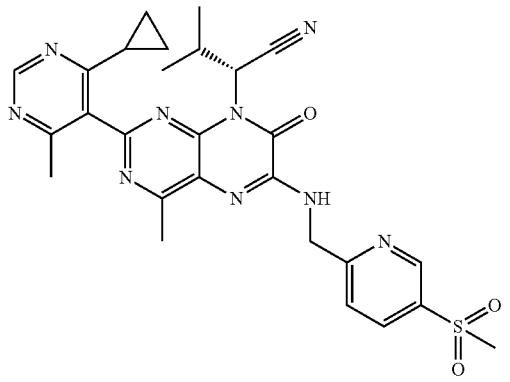

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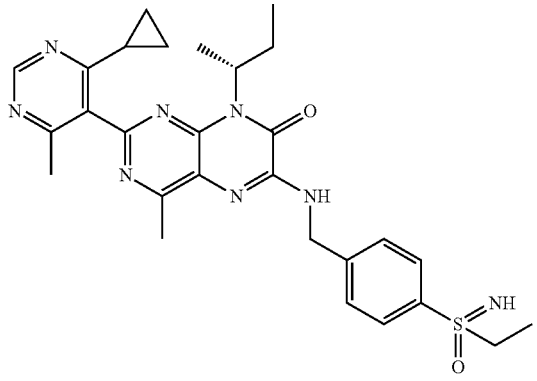

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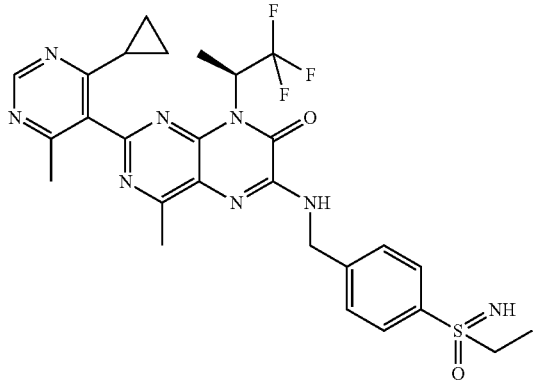

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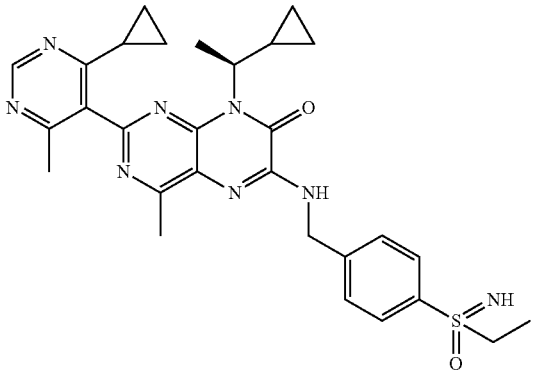

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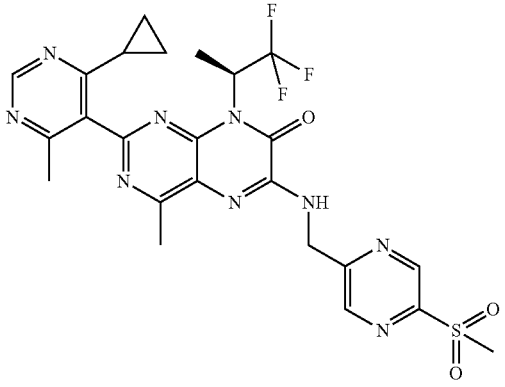

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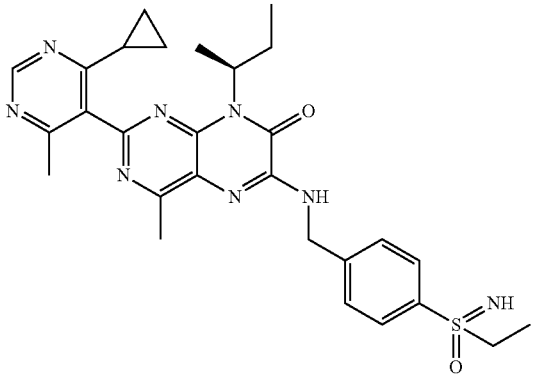

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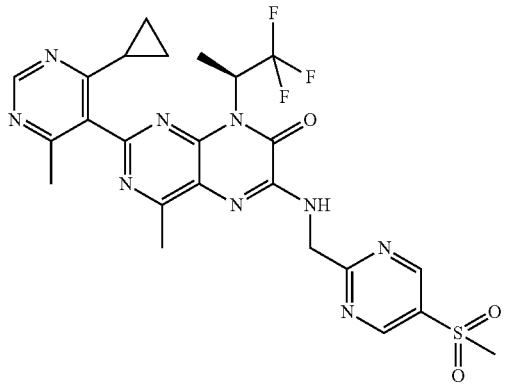

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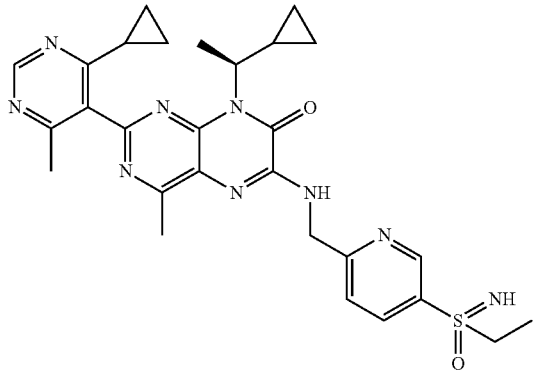

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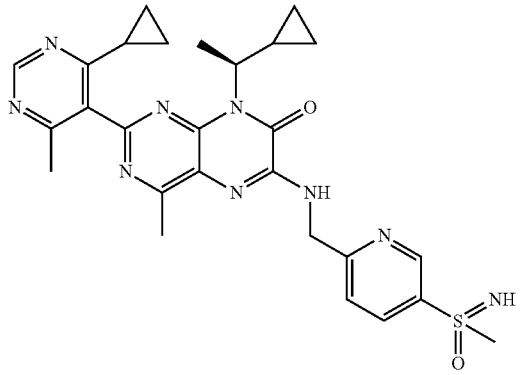

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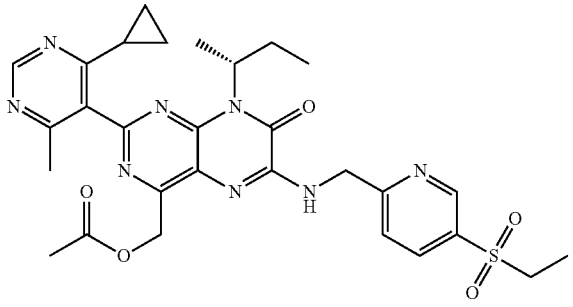

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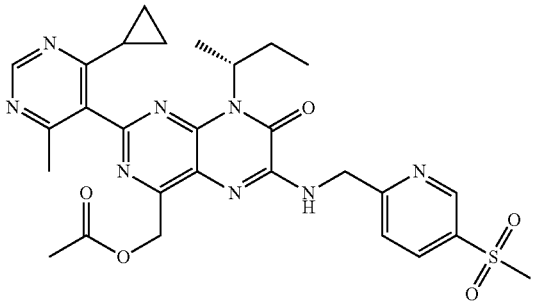

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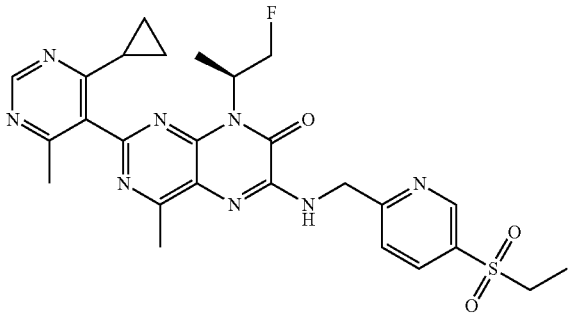

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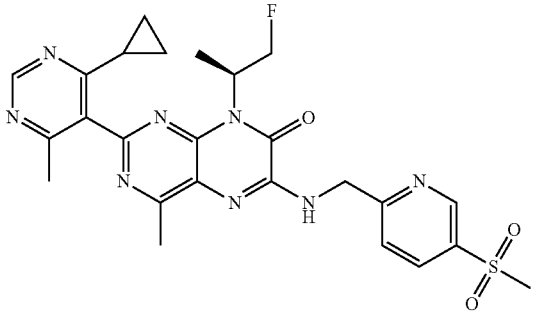

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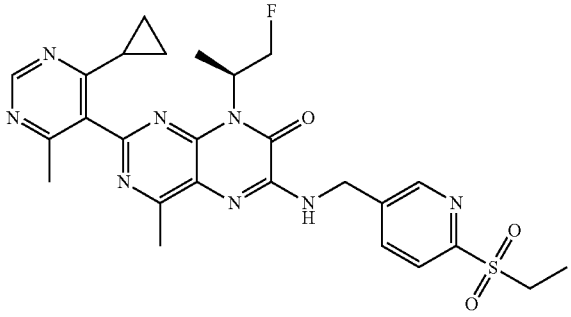

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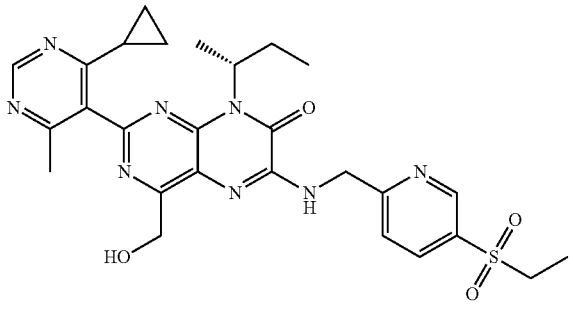

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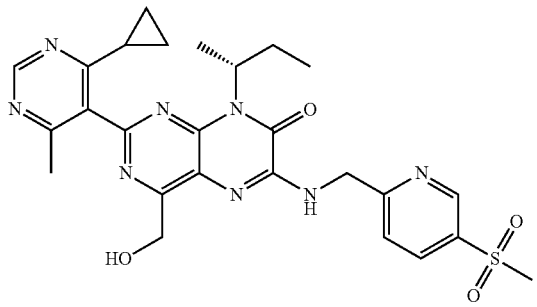

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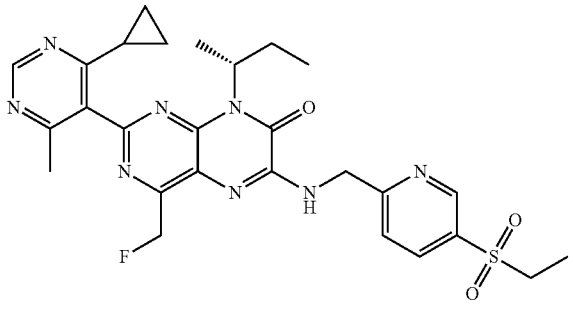

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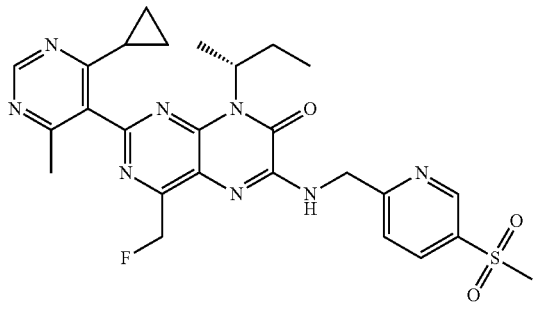

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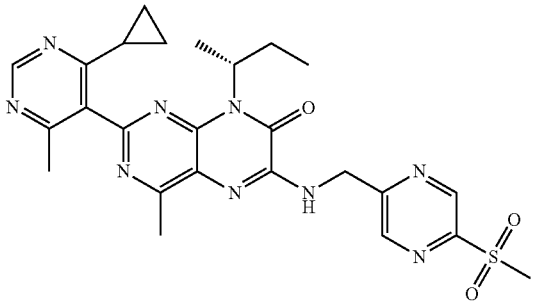

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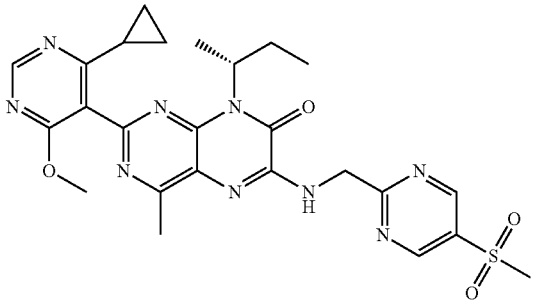

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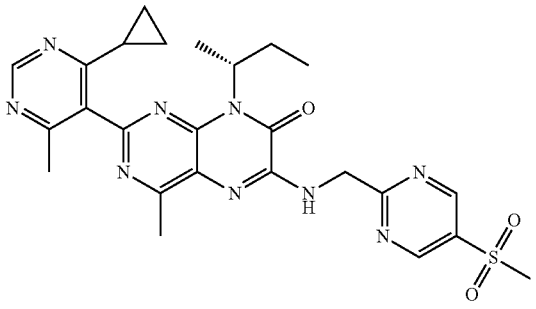

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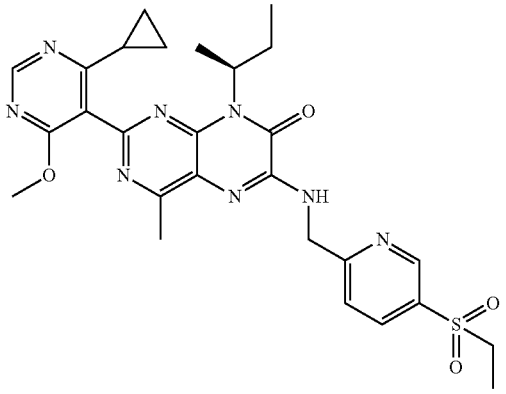

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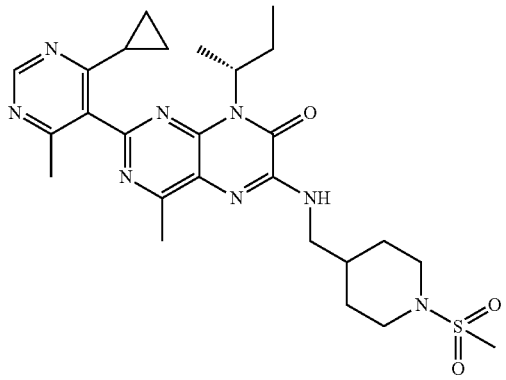

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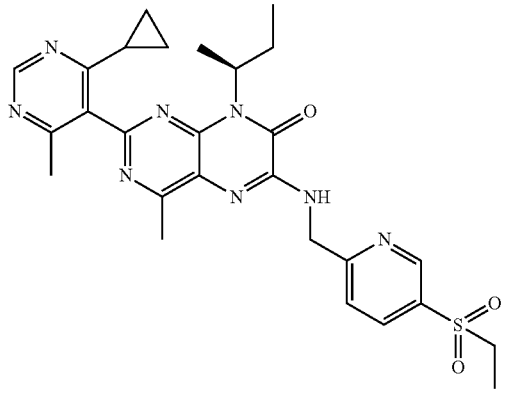

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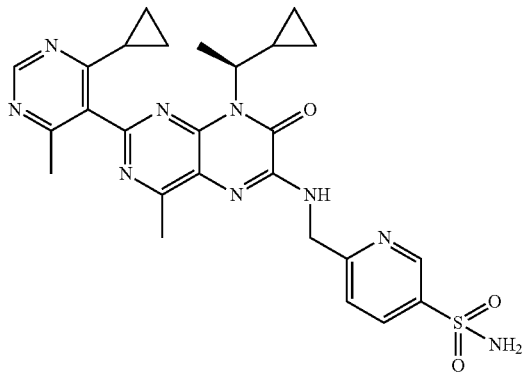

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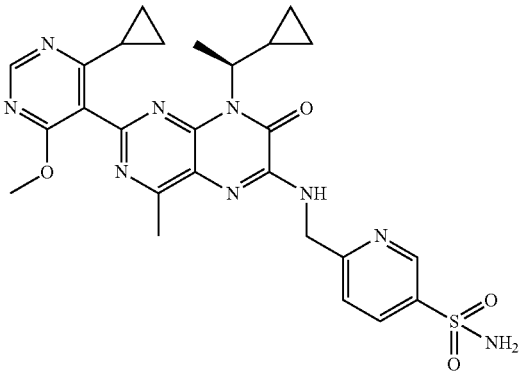

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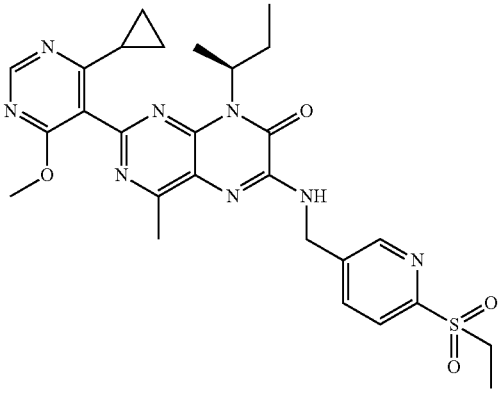

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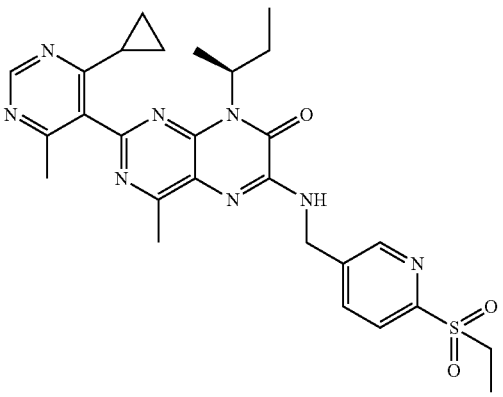

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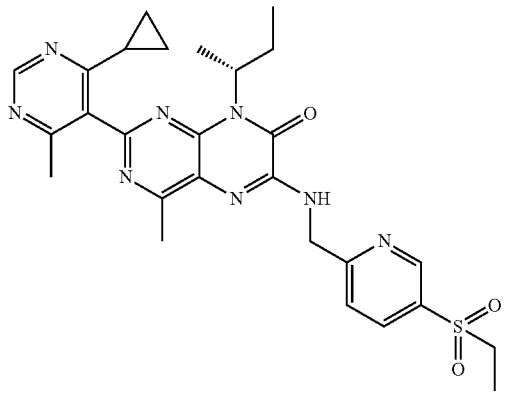

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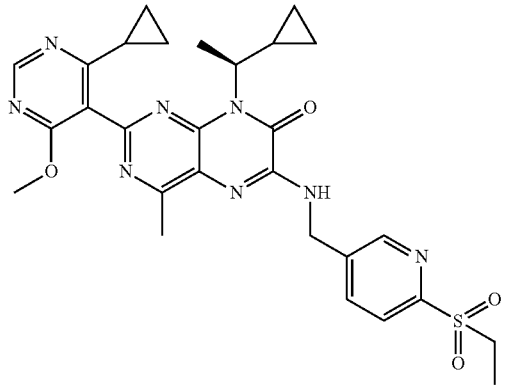

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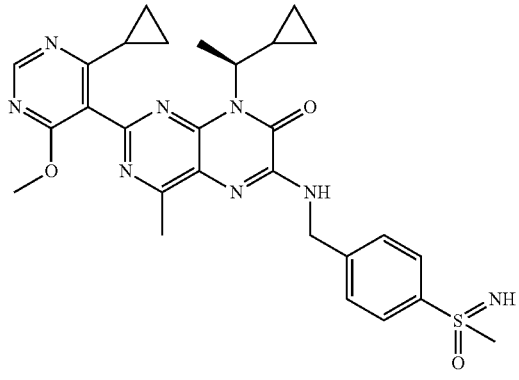

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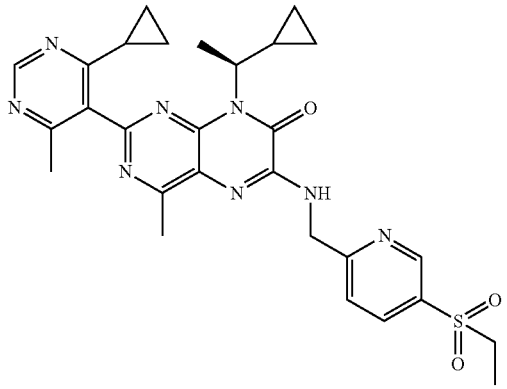

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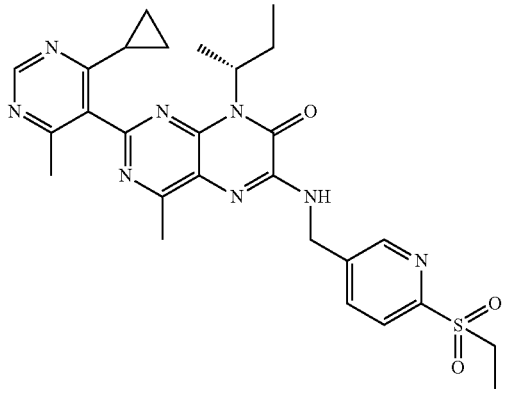

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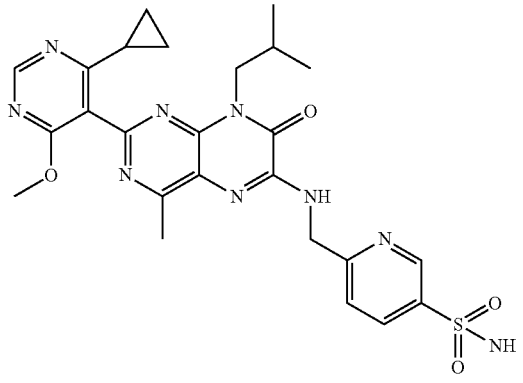

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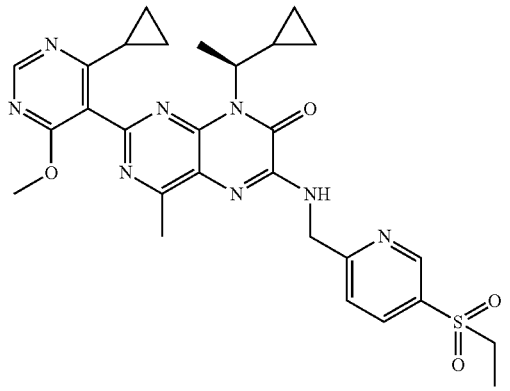

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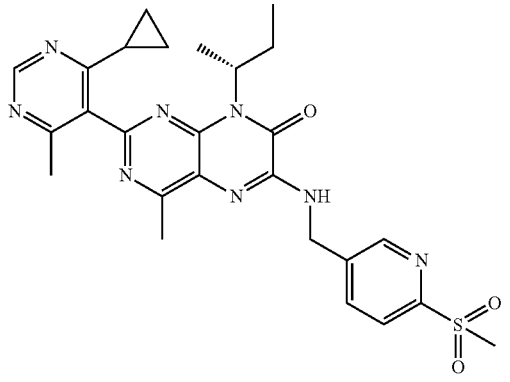

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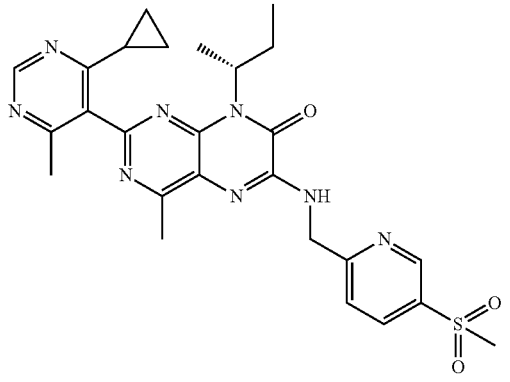

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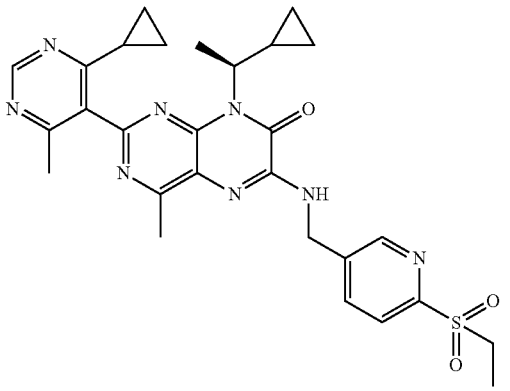

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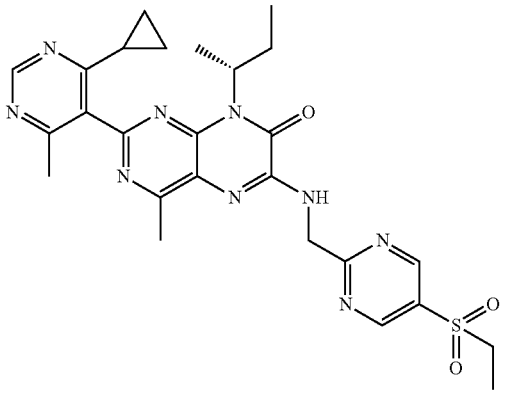

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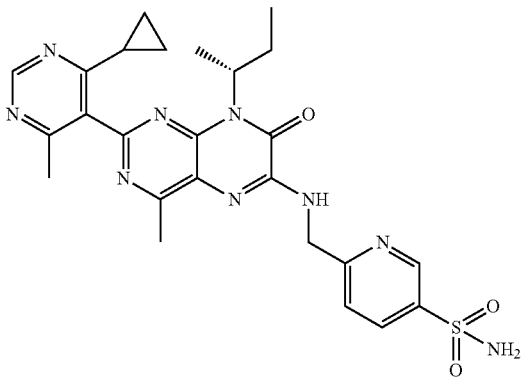

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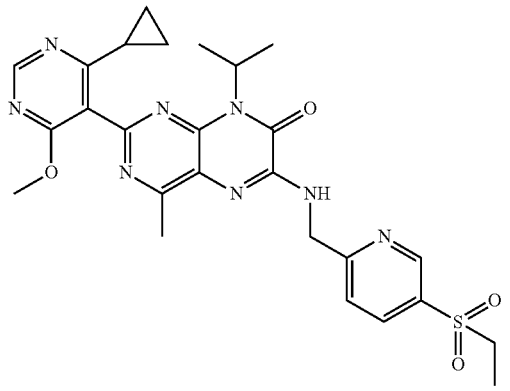

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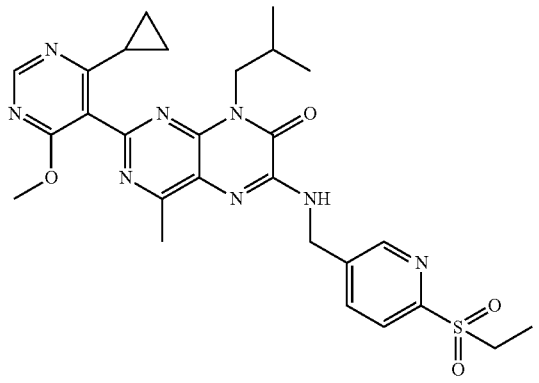

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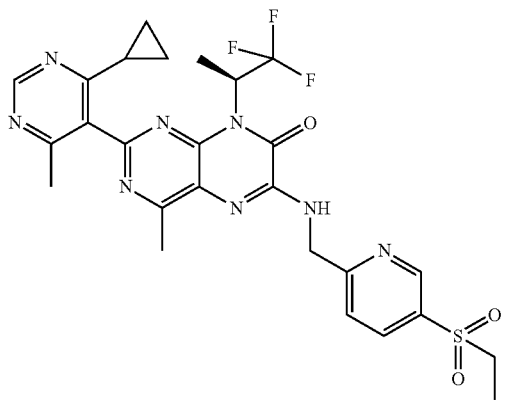

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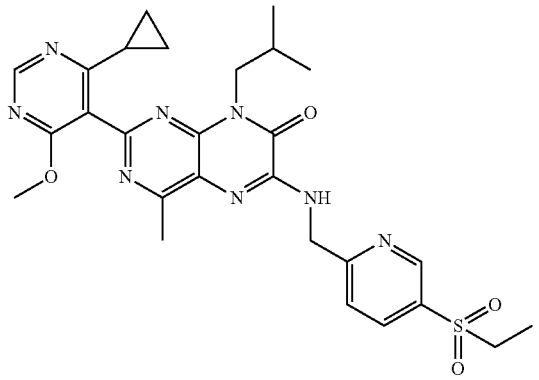

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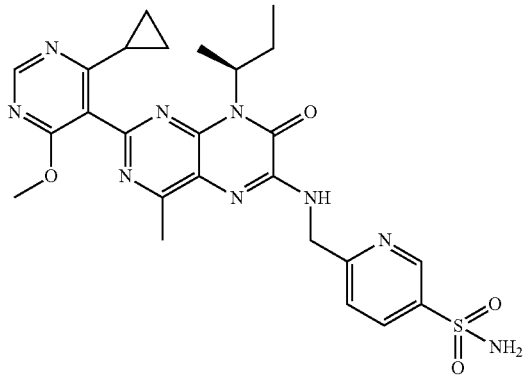

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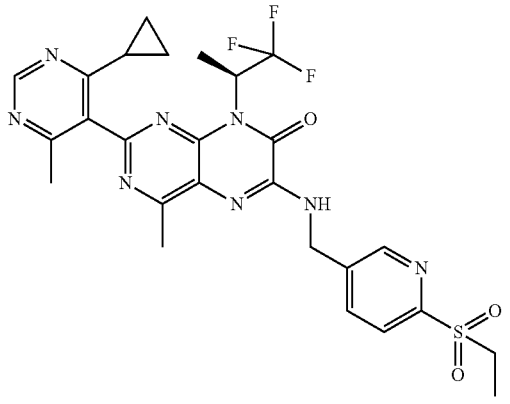

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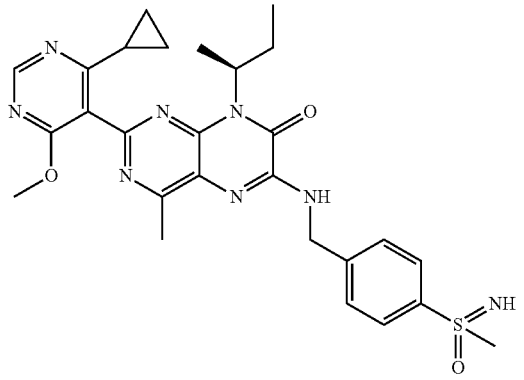

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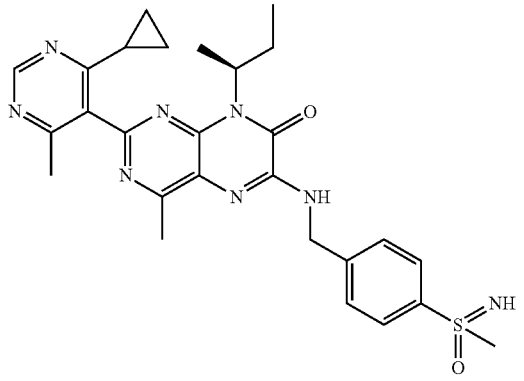

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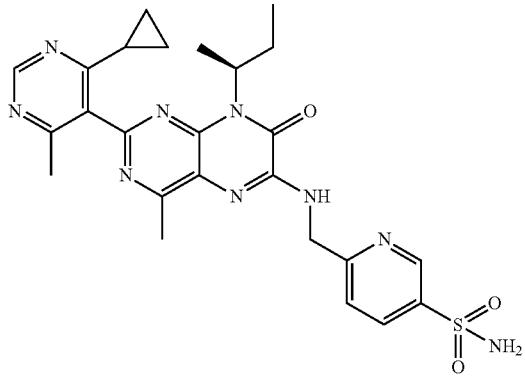

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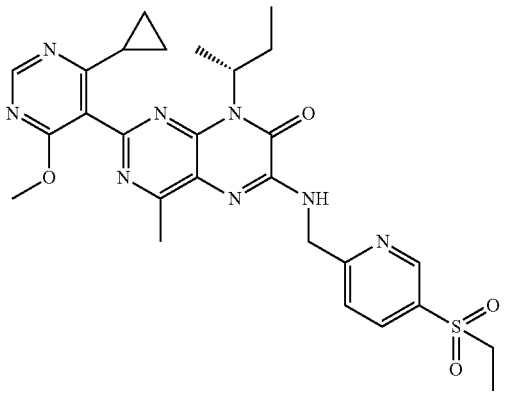

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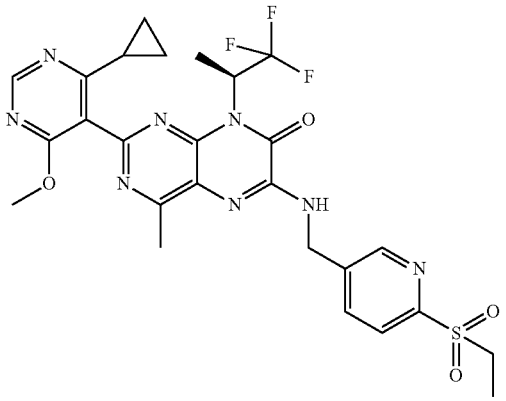

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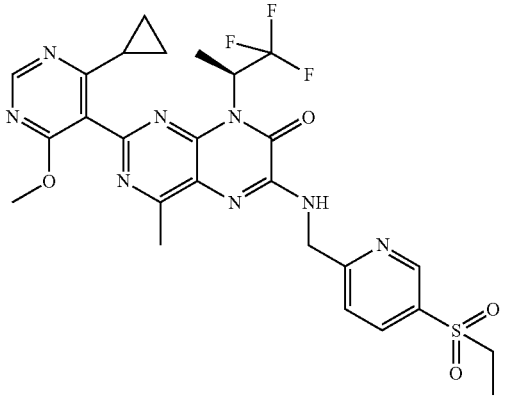

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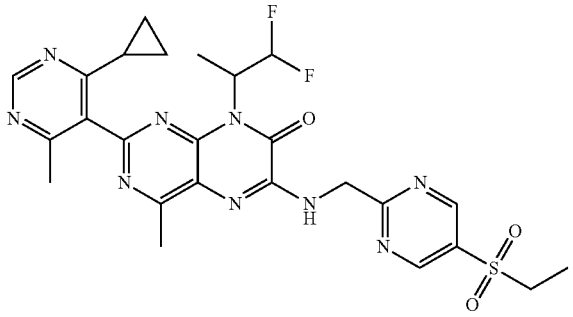

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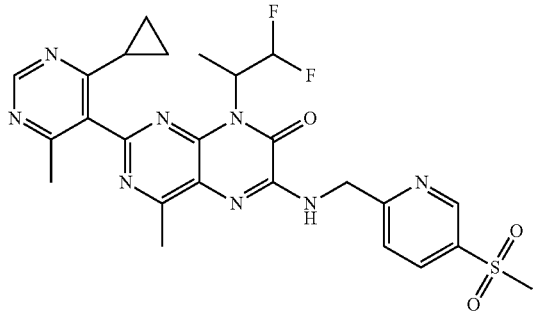

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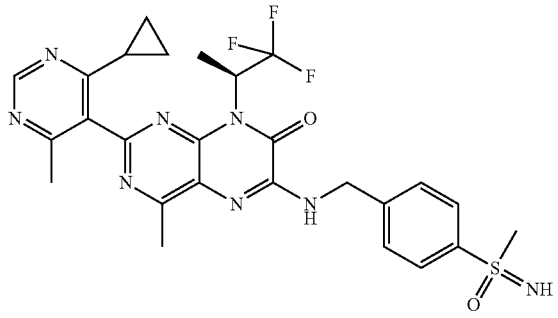

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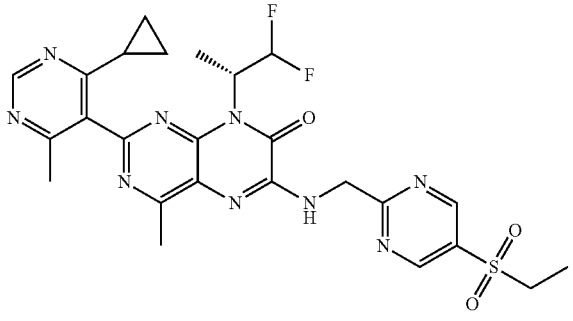

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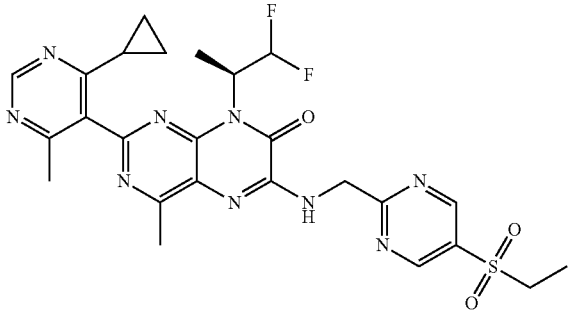

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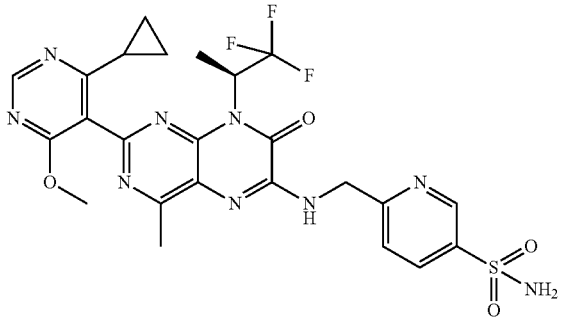

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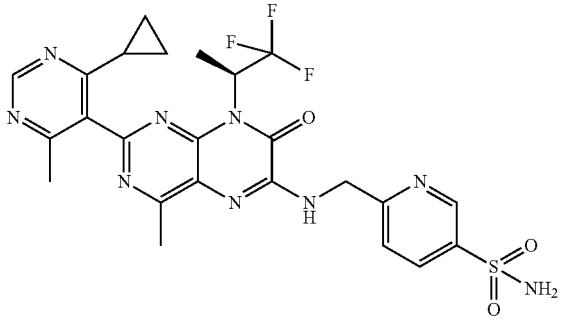

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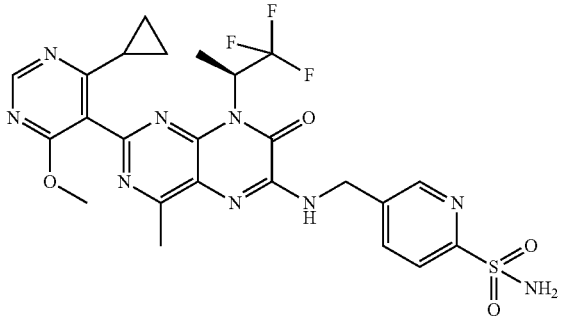

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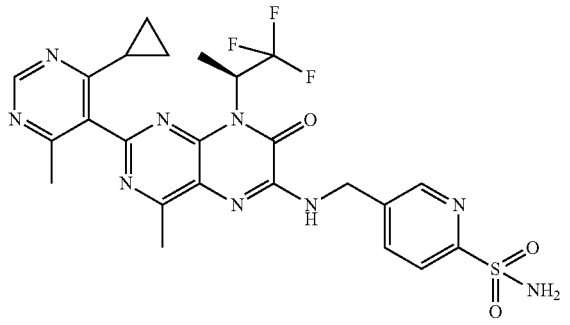

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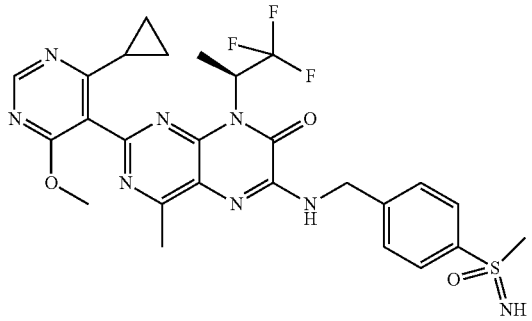

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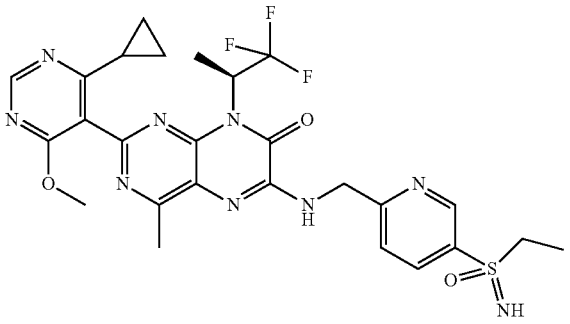

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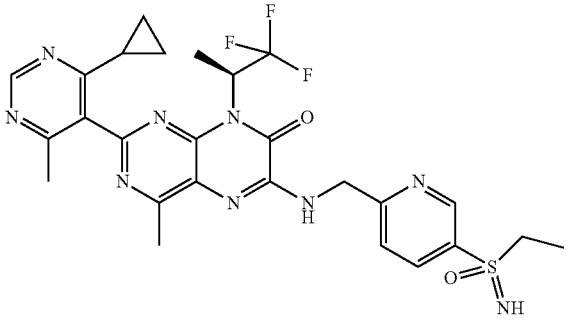

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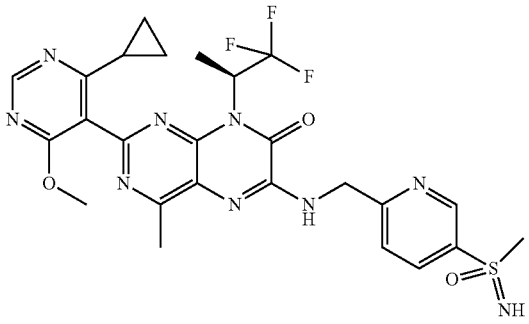

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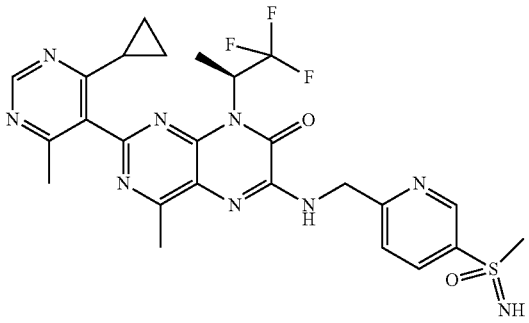

and the pharmaceutically acceptable salts thereof.

8. A pharmaceutical composition comprising a compound according to claim **1** and a pharmaceutically acceptable excipient or carrier.

9. A method for treating an autoimmune disease or allergic disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula (I) according to claim **1**, or a pharmaceutically acceptable salt thereof.

10. The method according to claim **9**, wherein the autoimmune disease or allergic disorder is selected from rheumatoid arthritis, psoriasis, systemic lupus erythromatosis, lupus nephritis, scleroderma, asthma, allergic rhinitis, allergic eczema, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, type I diabetes, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and uveitis.

11. A method of manufacture of a medicament for treatment of an autoimmune disease or allergic disorder in a patient, comprising combining an effective amount of a compound of formula (I) according to claim **1** or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient or carrier.

12. The method according to claim **11**, wherein the autoimmune disease or allergic disorder is selected from rheumatoid arthritis, psoriasis, systemic lupus erythromatosis, lupus nephritis, scleroderma, asthma, allergic rhinitis, allergic eczema, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, type I diabetes, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and uveitis.

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