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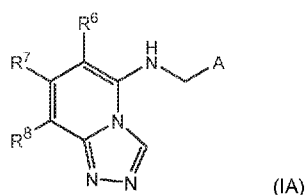
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(54) Title: TRIAZOLOPYRIDINE COMPOUNDS AND USES THEREOF

(57) Abstract: A compound of Formula (IA), or a pharmaceutically acceptable salt thereof, is provided that has been shown to be useful for treating a PRC2-mediated disease or disorder: wherein A, R⁶, R⁷ and R⁸ are as defined herein.



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TRIAZOLOPYRIDINE COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

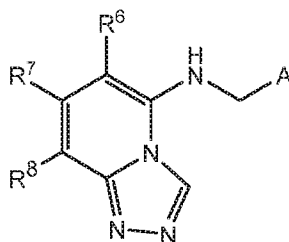
[0001] The present invention relates to triazolopyridine compounds, compositions comprising such compounds, and their use for the treatment of Polycomb Repressive Complex 2 (PRC2)-mediated diseases or disorders.

BACKGROUND

[0002] Polycomb group (PcG) proteins are chromatin modifying enzymes that are dysregulated in many human cancers. The Polycomb Repressive Complex 2 (PRC2), which includes SUZ12 (suppressor of zeste 12), EED (embryonic ectoderm development) and the catalytic subunit, EZH2 (enhancer of zeste homolog 2), represses genes by methylating the core histone H3 lysine 27 (H3K27me3) at and around the promoter regions of target genes. PRC2 is the critical component of cellular machinery involved in the epigenetic regulation of gene transcription and plays critical function in development and tissue differentiation and regeneration. Although EZH2 is the catalytic subunit, PRC2 requires at least EED and SUZ12 for its methyltransferase activity. EED, SUZ12 and EZH2 are overexpressed in many cancers, including but not limited to breast cancer, prostate cancer, hepatocellular carcinoma and etc. EZH2 activating mutations have been identified in DLBCL (diffused large B cell lymphoma) patients and FL (follicular lymphoma) patients. Inhibition of PRC2 methyltransferase activity by compounds competing with the cofactor S-adenosyl methionine (SAM) in DLBCL reverses H3K27 methylation, re-activates expression of target genes and inhibits tumor growth/proliferation. Therefore, PRC2 provides a pharmacological target for DLBCL and other cancers. In particular, the need exists for small molecules that inhibit the activity of PRC2.

SUMMARY

[0003] The present invention provides a compound of Formula (IA):



(IA)

wherein A, R⁶, R⁷ and R⁸ are as defined herein, including stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, or solvates thereof, which are useful for the treatment of PRC2-mediated diseases or disorders.

[0004] The present invention also provides processes and intermediates for making the compounds of the present invention.

[0005] The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the present invention and at least one pharmaceutically acceptable carrier, diluent or excipient. The pharmaceutical composition may further comprise at least one additional therapeutic agent. Of particular interest are additional therapeutic agents selected from: other anti-cancer agents, immunomodulators, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

[0006] The compounds of the present invention may be used in the treatment of diseases or disorders mediated by EED and/or PRC2.

[0007] The compounds of the present invention may be used in therapy.

[0008] The compounds of the present invention may be used for the manufacture of a medicament for the treatment of diseases or disorders mediated by EED and/or PRC2.

[0009] The present invention provides a method for the treatment of diseases or disorders mediated by EED and/or PRC2, comprising administering to a patient in need thereof a therapeutically effective amount of a first therapeutic agent optionally with a second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention and the second therapeutic agent is one other type of therapeutic agent.

[0010] Examples of diseases or disorders mediated by EED and/or PRC2 include, but are not limited to, diffused large B cell lymphoma (DLBCL), follicular lymphoma, other lymphomas, leukemia, multiple myeloma, mesothelioma, gastric cancer, malignant rhabdoid tumor, hepatocellular carcinoma, prostate cancer, breast carcinoma, bile duct and gallbladder cancers, bladder carcinoma, brain tumors including neuroblastoma, schwannoma, glioma, glioblastoma and astrocytoma, cervical cancer, colon cancer, melanoma, endometrial cancer, esophageal cancer, head and neck cancer, lung cancer, nasopharyngeal carcinoma, ovarian cancer, pancreatic cancer, renal cell carcinoma, rectal cancer, thyroid cancers, parathyroid tumors, uterine tumors, and soft tissue sarcomas such as rhabdomyosarcoma (RMS), Kaposi sarcoma, synovial sarcoma, osteosarcoma and Ewing's sarcoma.

[0011] The present invention provides a method for the treatment of diseases or disorders mediated by EED and/or PRC2, comprising administering to a patient in need thereof a therapeutically effective amount of a first therapeutic agent optionally with a second therapeutic agent, wherein the first therapeutic agent is an EED inhibitor and the second therapeutic agent is one other type of therapeutic agent; wherein the diseases or disorders are selected from diffused large B cell lymphoma (DLBCL), follicular lymphoma, other lymphomas, leukemia, multiple myeloma, gastric cancer, malignant rhabdoid tumor, and hepatocellular carcinoma.

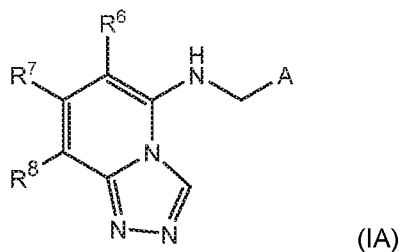
[0012] The compounds of the present invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s), simultaneously or sequentially.

[0013] Other features and advantages of the present invention will be apparent from the following detailed description and claims.

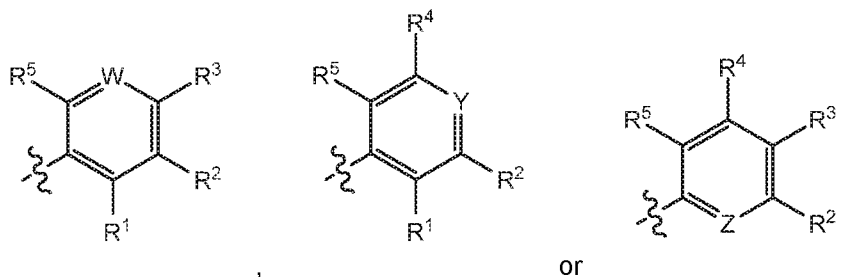
DETAILED DESCRIPTION

I. COMPOUNDS

[0014] In a first aspect, the present invention provides, *inter alia*, a compound of Formula (IA):

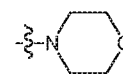


or a pharmaceutically acceptable salt thereof, wherein:



W is independently N or CR⁴;
Y is independently N or CR³;
Z is independently N or CR¹;

- R^1 is independently H, halogen, or NH_2 ;
 R^2 is independently H, OCH_3 , or halogen;
 R^3 is independently H or halogen;
 R^4 is independently H, halogen, CH_3 , or OCH_3 ;
 5 R^5 is independently H, halogen, CH_3 , OH, OCH_3 , OCH_2F , $OCHF_2$, or OCF_3 ;
 R^6 and R^7 are independently selected from: H and halogen;
 R^8 is independently selected from: halogen, phenyl, and a 5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^a , O, and $S(O)_p$; wherein said phenyl and heteroaryl are substituted with 0-3 R^{8A} ;
 10 each R^{8A} is independently selected from: halogen, CN, OH, $-(O)_m-(C_1-C_6 \text{ alkyl substituted with 0-1 } R^{8B})$, $C_1-C_6 \text{ haloalkyl}$, $C_1-C_6 \text{ haloalkoxy}$, R^{8C} , $-OR^{8C}$, $-C(=O)R^{8D}$, $NR^{8E}R^{8F}$, $-C(C_1-C_4 \text{ alkyl})=N(C_1-C_4 \text{ alkoxy})$, $-C(=O)NR^{8E}R^{8F}$, $-NHC(=O)R^{8D}$, $-NHC(=O)NR^{8E}R^{8F}$, $-S(=O)R^{8D}$, $-S(=O)_2R^{8D}$, $-S(=O)_2NR^{8E}R^{8F}$, $-NHS(=O)_2R^{8D}$, $-NR^{8E}(S(=O)_2(C_1-C_4 \text{ alkyl}))$, and $-CR^{8C}R^{8E}R^{8G}$;
 15 R^{8B} is independently selected from: CN, OH, NR^eR^f , $C_1-C_4 \text{ alkoxy}$, $-C(=O)NR^eR^f$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-N(\rightarrow O)(C_1-C_4 \text{ alkyl})_2$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$, and a 4- to 6-membered heterocycloalkyl comprising carbon atoms and 1-2 heteroatoms selected from N, NR^a , O, and $S(O)_p$; wherein said heterocycloalkyl is substituted with 0-2 R^c ;
 each R^{8C} is independently selected from: $C_3-C_6 \text{ cycloalkyl}$, phenyl, and a 4- to 7-
 20 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^a , O, and $S(O)_p$; wherein each moiety is substituted with 0-2 R^c ;
 each R^{8D} is independently selected from: $C_1-C_4 \text{ alkyl}$ and R^{8C} ;
 R^{8E} and R^{8G} are, at each occurrence, independently selected from: H and $C_1-C_4 \text{ alkyl}$;
 25 each R^{8F} is independently selected from: H and $C_1-C_4 \text{ alkyl}$ substituted with 0-1 R^d ;
 each R^a is independently selected from: H, $\rightarrow O$, $C_1-C_4 \text{ alkyl}$ substituted with 0-1 R^b , $-C(=O)H$, $-C(=O)(C_1-C_4 \text{ alkyl})$, $-CO_2(C_1-C_4 \text{ alkyl})$, $C_3-C_6 \text{ cycloalkyl}$, benzyl, and a 4- to 6-membered heterocycloalkyl comprising carbon atoms and 1-2 heteroatoms selected
 30 from N, NR^g , O, and $S(O)_p$;



R^b is independently selected from: halogen, OH, $C_1-C_4 \text{ alkoxy}$, and
 each R^c is independently selected from: $=O$, halogen, OH, $C_1-C_4 \text{ alkyl}$,
 $C_1-C_4 \text{ haloalkyl}$, $C_1-C_4 \text{ alkoxy}$, and $C_1-C_4 \text{ haloalkoxy}$;

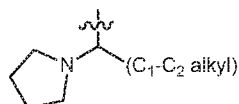
R^d is independently selected from: OH and NR^eR^f ;

R^e and R^f are, at each occurrence, independently selected from: H and C₁-C₄ alkyl;

R^g is independently selected from: H, C₁-C₄ alkyl, -C(=O)(C₁-C₄ alkyl), and -CO₂(C₁-C₄ alkyl);
 each p is independently selected from 0, 1 and 2; and
 m is independently selected from 0 and 1.

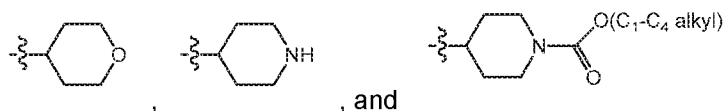
[0015] In a second aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of the first aspect; wherein:

each R^{8A} is independently selected from: halogen, CN, OH, -(O)_m-(C₁-C₆ alkyl substituted with 0-1 R^{8B}), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, R^{8C} , -C(=O) R^{8D} , $NR^{8E}R^{8F}$, -C(=O) $NR^{8E}R^{8F}$, -NHC(=O) R^{8D} , -NHC(=O) $NR^{8E}R^{8F}$, -S(=O) R^{8D} , -S(=O)₂ R^{8D} , -S(=O)₂NHR^{8F}, -NHS(=O)₂ R^{8D} , -NR^{8E}(S(=O)₂(C₁-C₄ alkyl)), -O-C₃-C₆ cycloalkyl, and



; and

each R^a is independently selected from: H, →O, C₁-C₄ alkyl substituted with 0-1 R^b , -C(=O)H, -C(=O)(C₁-C₄ alkyl), -CO₂(C₁-C₄ alkyl), C₃-C₆ cycloalkyl, benzyl,



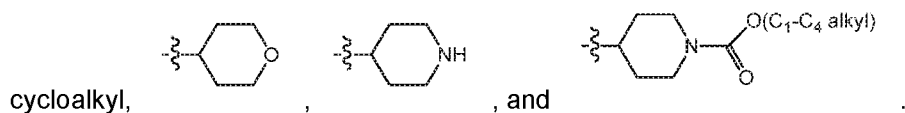
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[0016] In a third aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of the first or second aspect; wherein:

R^1 is independently H, F, or Cl;
 R^2 is independently H, OCH₃, or F;
 R^3 is independently H or F;
 R^4 is independently H, F, CH₃, or OCH₃;
 R^5 is independently H, F, CH₃, OH, OCH₃, OCH₂F, OCHF₂, or OCF₃;
 R^6 and R^7 are independently selected from: H and F; and

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R^a is independently selected from: H, C_1 - C_4 alkyl substituted with 0-1 R^b , C_3 - C_6



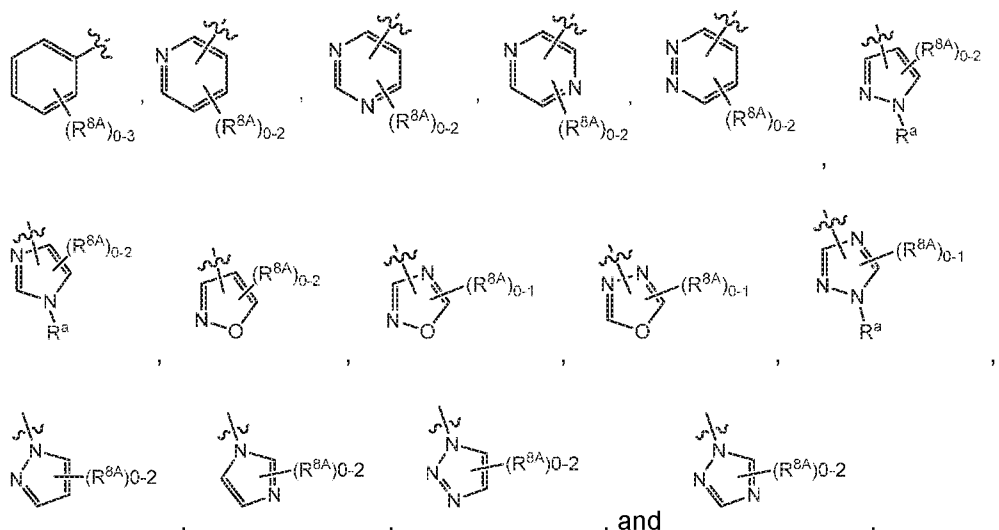
[0017] In a fourth aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any one of the first, second and third aspects; wherein:

R^6 and R^7 are H;

R^8 is independently selected from: phenyl, and a 6-membered heteroaryl comprising carbon atoms and 1-2 heteroatoms selected from N and NR^a ; wherein said phenyl and heteroaryl are substituted with 0-3 R^{8A} .

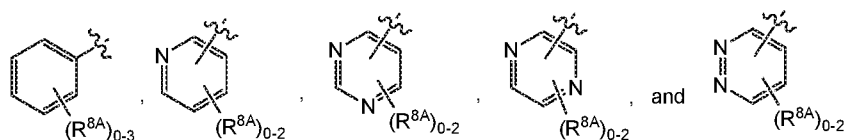
[0018] In a fifth aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to third aspects, wherein:

R^8 is independently selected from:



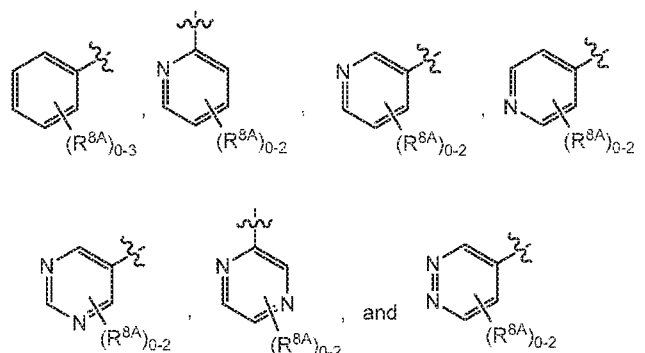
[0019] In another aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to fifth aspects, wherein:

R^8 is independently selected from:



[0020] In a sixth aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to fourth aspects, wherein:

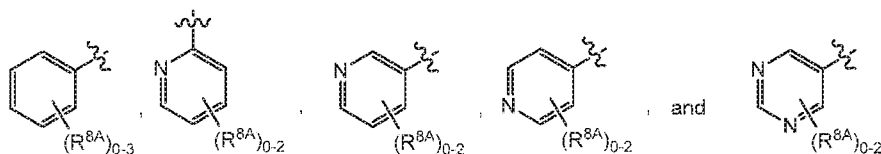
R^8 is independently selected from:



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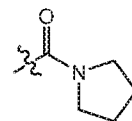
[0021] In a seventh aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to sixth aspects, wherein:

10 R^8 is independently selected from:

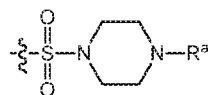
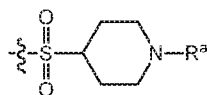
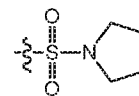
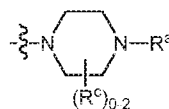
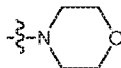
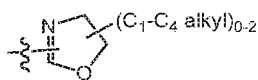
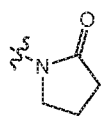


each R^{8A} is independently selected from: halogen, CN, OH, $-(O)_m-(C_1-C_6 \text{ alkyl})$ substituted with 0-1 R^{8B} , C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NH_2 , $-N(C_1-C_4 \text{ alkyl})_2$, C_3-C_6 cycloalkyl, $-O-C_3-C_6$ cycloalkyl, $-C(=O)(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-NHC(=O)N(C_1-C_4 \text{ alkyl})_2$, $-S(=O)(C_1-C_4 \text{ alkyl})$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$, $-S(=O)_2NH_2$,

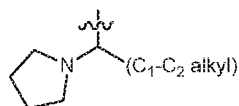
-S(=O)₂NH(C₁-C₄ alkyl substituted with 0-1 OH), -S(=O)₂N(C₁-C₄ alkyl)₂,



-NHS(=O)₂(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(S(=O)₂(C₁-C₄ alkyl)), tetrazolyl,



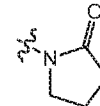
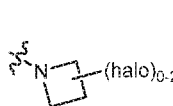
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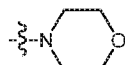
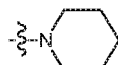
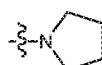
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R^{8B} is independently selected from: CN, OH, C₁-C₄ alkoxy, -N(C₁-C₄ alkyl)₂,

-C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -NHC(=O)(C₁-C₄ alkyl),



-N(\rightarrow O)(C₁-C₄ alkyl)₂, -S(=O)₂(C₁-C₄ alkyl), imidazolyl,



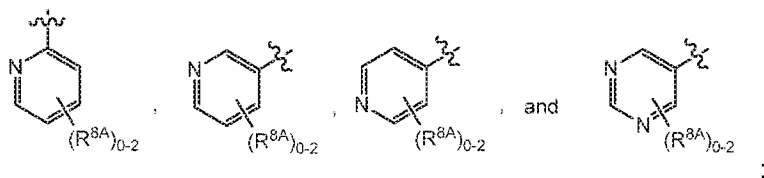
, and

5 R^a is independently selected from: H and C₁-C₄ alkyl; and

R^c is independently C₁-C₄ alkyl.

[0022] In an eighth aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to seventh aspects, wherein:

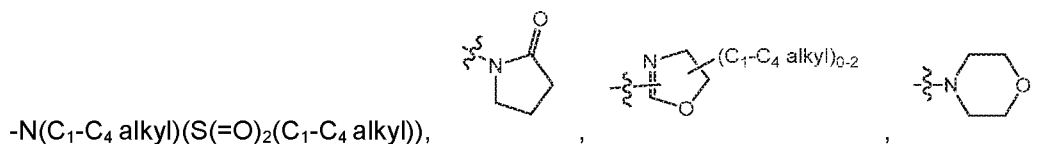
R^8 is independently selected from:



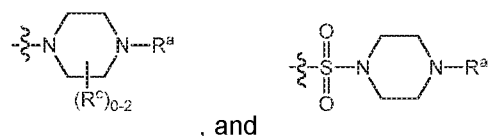
each R^{8A} is independently selected from: halogen, CN, OH, $-(O)_m-(C_1-C_6 \text{ alkyl})$ substituted with 0-1 R^{8B} , C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $N(C_1-C_4 \text{ alkyl})_2$,

C_3-C_6 cycloalkyl, $-O-C_3-C_6$ cycloalkyl, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$,

5 $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-NHC(=O)N(C_1-C_4 \text{ alkyl})_2$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$,



$-N(C_1-C_4 \text{ alkyl})(S(=O)_2(C_1-C_4 \text{ alkyl}))$,



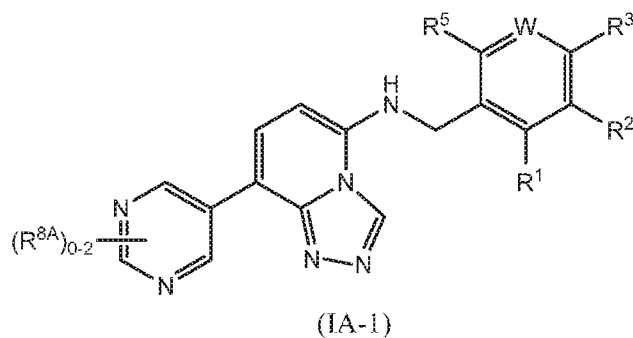
R^{8B} is independently selected from: CN, OH, C_1-C_4 alkoxy, $-N(C_1-C_4 \text{ alkyl})_2$, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$,

10 $-S(=O)_2(C_1-C_4 \text{ alkyl})$, and

R^a is independently selected from: H and C_1-C_4 alkyl; and

R^c is independently C_1-C_4 alkyl.

[0023] In a ninth aspect, the present invention provides a compound of Formula (IA-1):



or a pharmaceutically acceptable salt thereof, within the scope of any of the above aspects; wherein:

W is independently N or CR⁴;

R¹ is independently H or F;

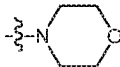
R² is independently H or F;


R³ is independently H or F;

R⁴ is independently H or F;

R⁵ is independently H or -OCH₃;

R^{8A} is independently selected from: C₁-C₆ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,

-N(C₁-C₄ alkyl)₂, C₃-C₆ cycloalkyl, -O-C₃-C₆ cycloalkyl, , and

; and

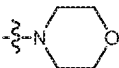
R⁸ is independently selected from: H and C₁-C₄ alkyl.

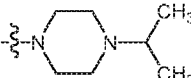
- 5 **[0024]** In a tenth aspect, the present invention includes a compound of Formula (IA-1) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to ninth aspects, wherein:

W is independently CR⁴;

R⁴ is independently H or F;

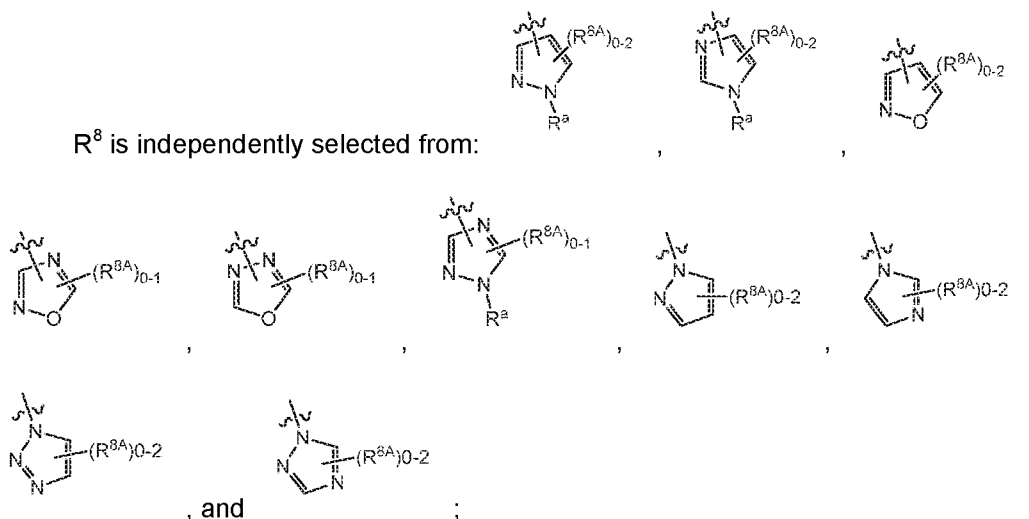
R^{8A} is independently selected from: CH₃, CH(CH₃)₂, CH(CH₃)(CH₂CH₃), OCH₃,

OCH₂CH₃, OCH(CH₃)₂, CHF₂, N(CH₃)₂, cyclopropyl, -O-cyclopropyl, , and

.

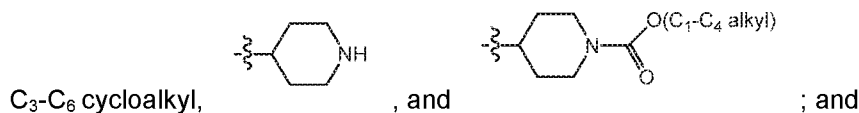
- 10 **[0025]** In an eleventh aspect, the present invention includes a compound of Formula (IA) or a pharmaceutically acceptable salt thereof, within the scope of any of the first to third and fifth aspects, wherein:

R⁶ and R⁷ are H;



each R^{8A} is independently selected from: C_1 - C_4 alkyl substituted with 0-1 OH, and C_1 - C_4 haloalkyl;

R^a is independently selected from: H, C_1 - C_4 alkyl substituted with 0-1 R^b ,



R^b is independently selected from: OH and .

[0026] In a twelfth aspect, the present invention includes a compound of Formula (IA) or (IA-1), or a pharmaceutically acceptable salt thereof, within the scope of any of the above aspects, wherein:

5 R^1 is F.

[0027] In a thirteenth aspect, the present invention provides a compound selected from the exemplified examples or a pharmaceutically acceptable salt thereof, including all compounds of Examples 1 to 374.

10

[0028] In another aspect, the present invention provides a compound selected from any subset list of compounds within the scope of the thirteenth aspect.

[0029] In an embodiment, R^1 is independently H, F, or Cl. In another embodiment, R^1 is independently H or F.

[0030] In an embodiment, R^2 is independently H, OCH_3 , or F. In another embodiment, R^1 is independently H or F.

[0031] In an embodiment, R^3 is independently H or F.

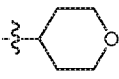
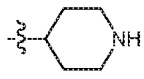
[0032] In an embodiment, R^4 is independently H, F, CH_3 , or OCH_3 . In another embodiment, R^4 is independently H or F.

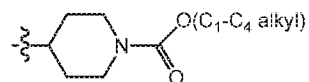
[0033] In an embodiment, R^5 is independently H, F, CH_3 , OH, OCH_3 , OCH_2F , $OCHF_2$, or OCF_3 . In another embodiment, R^5 is independently H or $-OCH_3$.

[0034] In an embodiment, R^6 is independently H or F. In another embodiment, R^6 is H.

[0035] In an embodiment, R^7 is independently H or F. In another embodiment, R^7 is H.

[0036] In an embodiment, R^a is independently selected from: H, C_1 - C_4 alkyl

substituted with 0-1 R^b , C_3 - C_6 cycloalkyl, , , and



[0036] In another embodiment, R^a is independently selected from: H and C_1 - C_4 alkyl.

[0037] In another embodiment, the compounds of the present invention have IC_{50} values $\leq 5 \mu M$, using the EED Alphascreen binding, LC-MS and/or ELISA assays disclosed herein, preferably, IC_{50} values $\leq 1 \mu M$, more preferably, IC_{50} values $\leq 0.5 \mu M$, even more preferably, IC_{50} values $\leq 0.1 \mu M$.

II. OTHER EMBODIMENTS

[0038] In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a pharmaceutically acceptable salt thereof.

- 5 **[0039]** In another embodiment, the present invention provides a pharmaceutical composition comprising at least one of the compounds of the present invention or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, diluent or excipient.

- [0040]** In another embodiment, the present invention provides a pharmaceutical composition, comprising a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, diluent or excipient.

[0041] The pharmaceutical composition is useful in the treatment of diseases or disorders mediated by EED and/or PRC2.

- 15 **[0042]** In another embodiment, the present invention provides a pharmaceutical composition as defined above further comprising additional therapeutic agent(s).

[0043] In another embodiment, the present invention provides a process for making a compound of the present invention.

- [0044]** In another embodiment, the present invention provides an intermediate for making a compound of the present invention.

[0045] In another embodiment, the present invention provides a compound of the present invention, for use in therapy, alone, or optionally in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

- [0046]** In another embodiment, the present invention provides a compound of the present invention for use in therapy, for the treatment of diseases or disorders mediated by EED and/or PRC2, alone, or optionally in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

- [0047]** In another embodiment, the present invention provides a method for the treatment of diseases or disorders mediated by EED and/or PRC2, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or optionally in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

- [0048]** In another embodiment, the present invention provides a method for the treatment of diseases or disorders mediated by EED and/or PRC2, comprising

administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention and the second therapeutic agent is one other type of therapeutic agent.

- 5 **[0049]** In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment of diseases or disorders mediated by EED and/or PRC2, alone, or optionally in combination with another compound of the present invention and/or at least one other type of therapeutic agent.
- 10 **[0050]** In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for use in therapy.
- [0051]** In another embodiment, the present invention provides a combination of a compound of the present invention and additional therapeutic agent(s) for simultaneous or separate use in therapy.
- 15 **[0052]** In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment of diseases or disorders mediated by EED and/or PRC2. The compound may be administered as a
- 20 pharmaceutical composition described herein.
- [0053]** Examples of diseases or disorders mediated by EED and/or PRC2 include, but are not limited to, diffused large B cell lymphoma (DLBCL), follicular lymphoma, other lymphomas, leukemia, multiple myeloma, mesothelioma, gastric cancer, malignant rhabdoid tumor, hepatocellular carcinoma, prostate cancer, breast carcinoma, bile duct
- 25 and gallbladder cancers, bladder carcinoma, brain tumors including neuroblastoma, glioma, glioblastoma and astrocytoma, cervical cancer, colon cancer, melanoma, endometrial cancer, esophageal cancer, head and neck cancer, lung cancer, nasopharyngeal carcinoma, ovarian cancer, pancreatic cancer, renal cell carcinoma, rectal cancer, thyroid cancers, parathyroid tumors, uterine tumors, and soft tissue
- 30 sarcomas selected from rhabdomyosarcoma (RMS), Kaposi sarcoma, synovial sarcoma, osteosarcoma and Ewing's sarcoma.
- [0054]** In another embodiment, the present invention provides a method for the treatment of diseases or disorders mediated by EED and/or PRC2, comprising administering to a patient in need thereof a therapeutically effective amount of a first
- 35 therapeutic agent optionally with a second therapeutic agent, wherein the first

therapeutic agent is an EED inhibitor and the second therapeutic agent is one other type of therapeutic agent; wherein the diseases or disorders are selected from diffused large B cell lymphoma (DLBCL), follicular lymphoma, other lymphomas, leukemia, multiple myeloma, gastric cancer, malignant rhabdoid tumor, and hepatocellular carcinoma.

- 5 **[0055]** In another embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of the following therapeutic agents: other anti-cancer agents, immunomodulators, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.
- 10 **[0056]** Various (enumerated) embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention. It is also understood that each individual element of the embodiments is its own independent embodiment.
- 15 **[0057]** Other features of the present invention should become apparent in the course of the above descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

III. DEFINITIONS

- 20 **[0058]** The general terms used hereinbefore and hereinafter preferably have within the context of this invention or disclosure the following meanings, unless otherwise indicated, where more general terms wherever used may, independently of each other, be replaced by more specific definitions or remain, thus defining more detailed embodiments of the invention.
- 25 **[0059]** All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.
- 30 **[0060]** The term "a," "an," "the" and similar terms used in the context of the present invention or disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.
- 35 **[0061]** As used herein, the term "heteroatoms" refers to nitrogen (N), oxygen (O) or sulfur (S) atoms, in particular nitrogen or oxygen.

[0062] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0063] As used herein, the terms "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1} . The alkane radical may be straight or branched. For example, the term "C₁-C₁₀ alkyl" or "C₁ to C₁₀ alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, heptyl, and the like).

[0064] The term "alkylene" refers to a divalent alkyl group. For example, the term "C₁-C₆ alkylene" or "C₁ to C₆ alkylene" refers to a divalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methylene (-CH₂-), ethylene (-CH₂CH₂-), n-propylene (-CH₂CH₂CH₂-), iso-propylene (-CH(CH₃)CH₂-), n-butylene, sec-butylene, iso-butylene, tert-butylene, n-pentylene, isopentylene, neopentylene, n-hexylene and the like).

[0065] The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as -O-R or -OR, wherein the R represents the alkyl group. "C₁-C₆ alkoxy" or "C₁ to C₆ alkoxy" is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

[0066] "Halogen" or "halo" may be fluorine, chlorine, bromine or iodine (preferred halogens as substituents are fluorine and chlorine).

[0067] "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with one or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with one or more fluorine atoms.

[0068] "Haloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C₁-C₆ haloalkoxy" or "C₁ to C₆ haloalkoxy" is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ haloalkoxy groups. Examples of haloalkoxy include, but are not limited to,

trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluoroethoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

- 5 **[0069]** The term "oxo" or -C(O)- refers to a carbonyl group. For example, a ketone, aldehyde, or part of an acid, ester, amide, lactone, or lactam group.

[0070] The term "cycloalkyl" refers to nonaromatic carbocyclic ring that is fully hydrogenated ring, including mono-, bi- or poly-cyclic ring systems. "C₃-C₈ cycloalkyl" or "C₃ to C₈ cycloalkyl" is intended to include C₃, C₄, C₅, C₆, C₇ and C₈ cycloalkyl groups.

- 10 Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl.

[0071] The term "aryl" refers to 6- to 10-membered aromatic carbocyclic moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene.). A typical aryl group is phenyl group.

- 15 **[0072]** The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

- [0073]** "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - and -S(O)₂-, wherein R is hydrogen, C₁₋₄alkyl or a nitrogen protecting group (for example, carbobenzyloxy, p-methoxybenzyl carbonyl, t-butyloxycarbonyl, acetyl, benzoyl, benzyl, p-methoxy-benzyl, p-methoxy-phenyl, 3,4-dimethoxybenzyl, and the like). For example, a 3 to 8 membered heterocycloalkyl includes epoxy, aziridinyl, azetidiny, imidazolidinyl, pyrazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, oxazolidinyl, thiazolidinyl, pyrrolidinyl, 20 pyrrolidinyl-2-one, morpholino, piperazinyl, piperidinyl, piperidinylone, pyrazolidinyl, hexahydropyrimidinyl, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, thiomorpholino, sulfanomorpholino, sulfonomorpholino, octahydropyrrolo[3,2-b]pyrrolyl, and the like.

- [0074]** The term "partially saturated heterocycle" refers to a nonaromatic ring that is partially hydrogenated and may exist as a single ring, bicyclic ring (including fused 30 rings). Unless specified otherwise, said heterocyclic ring is generally a 5- to 10-membered ring containing 1 to 3 heteroatoms selected from -O-, -N=, -NR-, and -S-, (preferably 1 or 2 heteroatoms). Partially saturated heterocyclic rings include groups such as dihydrofuranyl, dihydrooxazolyl, dihydropyridinyl, imidazolinyl, 1H-dihydroimidazolyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl and the like. A 35 partially saturated heterocyclic ring also includes groups wherein the heterocyclic ring is

fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, indolinyl (or 2,3-dihydroindolyl), 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydropyrido[3,4-b]pyrazinyl, and the like).

- 5 **[0075]** The term "partially or fully saturated heterocycle" refers to a nonaromatic ring that is either partially or fully hydrogenated and may exist as a single ring, bicyclic ring (including fused rings) or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 12-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from sulfur, oxygen and/or nitrogen. When the
- 10 term "partially or fully saturated heterocycle" is used, it is intended to include "heterocycloalkyl", and "partially saturated heterocycle". Examples of spiral rings include 2,6-diazaspiro[3.3]heptanyl, 3-azaspiro[5.5]undecanyl, 3,9-diazaspiro[5.5]undecanyl, and the like.

- [0076]** The term "heteroaryl" refers to aromatic moieties containing at least one
- 15 heteroatom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, triazinyl, pyrimidinyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzopyranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, 1H-
- 20 benzo[d][1,2,3]triazolyl, and the like.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and
- 25 nitrogen. The fused heteroaryl ring system may consist of two heteroaryl rings fused together or a heteroaryl fused to an aryl (e.g., phenyl).

[0077] When the term "heterocycle" is used, it is intended to include "heterocycloalkyl", "partially or fully saturated heterocycle", "partially saturated heterocycle", "fully saturated heterocycle" and "heteroaryl".

- 30 **[0078]** The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na⁺), potassium (K⁺), ammonium (R_nNH_m⁺, where n=0-4, m=0-4 and m+n=4) and the like.

- [0079]** When a dotted ring is used within a ring structure, this indicates that the ring
- 35 structure may be saturated, partially saturated or unsaturated.

[0080] As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (*e.g.*, carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (*i.e.*, within) of the ring. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

[0081] In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[0082] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group may be unsubstituted or substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R. For example, with reference to the first aspect, this applies to 0-4 R^{8A} in the R⁸ definition, such that when R⁸ is phenyl or 5- to 6-membered heteroaryl, these groups are either unsubstituted (not substituted with R^{8A}) or substituted with one, two, three or four R^{8A} groups which are independently selected at each occurrence from the given definitions for R^{8A}. This similarly applies to the definitions for 0-2 R^c in the R^{8B} and R^{8C} definitions, and to 0-1 R^d in the R^{8F} definition.

[0083] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

[0084] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0085] As a person of ordinary skill in the art would be able to understand, for example, a ketone (-CH-C=O) group in a molecule may tautomerize to its enol form

(-C=C-OH). Thus, this invention is intended to cover all possible tautomers even when a structure depicts only one of them.

[0086] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other

5 ingredients comprising a formulation, and/or the mammal being treated therewith.

[0087] Unless specified otherwise, the term "compounds of the present invention" or "compounds of the present disclosure" refers to compounds of Formula (I), (IA) or (IA-1), as well as isomers, such as stereoisomers (including diastereoisomers, enantiomers and racemates), geometrical isomers, conformational isomers (including rotamers and

10 astropisomers), tautomers, isotopically labeled compounds (including deuterium substitutions), and inherently formed moieties (e.g., polymorphs, solvates and/or hydrates). When a moiety is present that is capable of forming a salt, then salts are included as well, in particular pharmaceutically acceptable salts.

[0088] It will be recognized by those skilled in the art that the compounds of the

15 present invention may contain chiral centers and as such may exist in different isomeric forms. As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms.

[0089] "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic"

20 mixture. The term is used to designate a racemic mixture where appropriate. When designating the stereochemistry for the compounds of the present invention, a single stereoisomer with known relative and absolute configuration of the two chiral centers is designated using the conventional RS system (e.g., (1S,2S)); a single stereoisomer with known relative configuration but unknown absolute configuration is designated with stars (e.g., (1R*,2R*)); and a racemate with two letters (e.g., (1RS,2RS) as a racemic mixture

25 of (1R,2R) and (1S,2S); (1RS,2SR) as a racemic mixture of (1R,2S) and (1S,2R)).

"Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure

30 enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (–) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Alternatively, the resolved compounds can be defined by the respective retention times for the corresponding

35 enantiomers/diastereomers *via* chiral HPLC.

[0090] Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

5 **[0091]** Geometric isomers may occur when a compound contains a double bond or some other feature that gives the molecule a certain amount of structural rigidity. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration.

10 **[0092]** Conformational isomers (or conformers) are isomers that can differ by rotations about one or more a bonds. Rotamers are conformers that differ by rotation about only a single a bond.

[0093] The term "atropisomer" refers to a structural isomer based on axial or planar chirality resulting from restricted rotation in the molecule.

15 **[0094]** Unless specified otherwise, the compounds of the present invention are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques (e.g., separated on chiral SFC or HPLC chromatography columns, such as
20 CHIRALPAK® and CHIRALCEL® available from DAICEL Corp. using the appropriate solvent or mixture of solvents to achieve good separation).

[0095] The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the
25 present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization.

[0096] Depending on the process conditions the end products of the present
30 invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the
35 individual isomers.

[0097] Pharmaceutically acceptable salts are preferred. However, other salts may be useful, e.g., in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention.

[0098] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. For example, pharmaceutically acceptable salts include, but are not limited to, acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate/hydroxymalonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phenylacetate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, salicylates, stearate, succinate, sulfamate, sulfosalicylate, tartrate, tosylate, trifluoroacetate or xinafoate salt form.

[0099] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[00100] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[00101] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Allen, L.V., Jr., ed., *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

[00102] Compounds of the invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present invention by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present invention with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of the present invention.

[00103] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I respectively. The present invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{13}C , and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this present invention can generally be prepared by carrying out the procedures disclosed in the

schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00104] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[00105] Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

[00106] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $\text{S}(\text{O})_2\text{H}$, or $\text{S}(\text{O})\text{H}$ group.

[00107] The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may

comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanlates, methanlates, and isopropanolates. Methods of solvation are generally known in the art.

- 5 **[00108]** As used herein, "polymorph(s)" refer to crystalline form(s) having the same chemical structure/composition but different spatial arrangements of the molecules and/or ions forming the crystals. Compounds of the present invention can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds of the present invention as a solid.
- 10 **[00109]** "EED" refers to the protein product of the gene embryonic ectoderm development.
- [00110]** "PRC2" refers to Polycomb Repressive Complex 2.
- [00111]** The term "PRC2-mediated disease or disorder" refers to any disease or disorder which is directly or indirectly regulated by PRC2. This includes, but is not limited
- 15 to, any disease or disorder which is directly or indirectly regulated by EED.
- [00112]** The term "diseases or disorders mediated by EED and/or PRC2" refers to diseases or disorders which are directly or indirectly regulated by EED and/or PRC2.
- [00113]** As used herein, the term "patient" encompasses all mammalian species.
- [00114]** As used herein, the term "subject" refers to an animal. Typically the animal is
- 20 a mammal. A "subject" also refers to any human or non-human organism that could potentially benefit from treatment with an EED inhibitor. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human. Exemplary subjects include human beings
- 25 of any age with risk factors for cancer disease.
- [00115]** As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment (preferably, a human).
- [00116]** As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the
- 30 reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.
- [00117]** As used herein, the term "treat", "treating" or "treatment" of any disease/ disorder refers the treatment of the disease/disorder in a mammal, particularly in a human, and include: (a) ameliorating the disease/disorder, (*i.e.*, slowing or arresting or
- 35 reducing the development of the disease/disorder, or at least one of the clinical

symptoms thereof); (b) relieving or modulating the disease/disorder, (*i.e.*, causing regression of the disease/disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both); (c) alleviating or ameliorating at least one physical parameter including those which may not
5 be discernible by the subject; and/or (d) preventing or delaying the onset or development or progression of the disease or disorder from occurring in a mammal, in particular, when such mammal is predisposed to the disease or disorder but has not yet been diagnosed as having it.

[00118] As used herein, "preventing" or "prevention" cover the preventive treatment
10 (*i.e.*, prophylaxis and/or risk reduction) of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and
15 (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

[00119] As used herein, "risk reduction" or "reducing risk" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and
20 secondary prevention therapies are examples of risk reduction.

[00120] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of EED and/or PRC2, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease
25 or disorder mediated by PRC2. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

[00121] Abbreviations as used herein, are defined as follows: "1x" for once, "2x" for twice, "3x" for thrice, "°C" for degrees Celsius, "aq" for aqueous, "Col" for column, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "nM" for nanomolar, "mol" for mole or moles, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "ON" for overnight, "atm" for atmosphere, "psi" for
35 pounds per square inch, "conc." for concentrate, "aq" for aqueous, "sat" or "sat'd" for

saturated, "MW" for molecular weight, "mw" or "μwave" for microwave, "mp" for melting point, "Wt" for weight, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectrometry, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "¹H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, "ee" for "enantiomeric excess" and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

[00122] The following abbreviations used herein below have the corresponding meanings:

	B ₂ Pin ₂	bis(pinacolato)diboron
15	Bn	benzyl
	Boc	<i>tert</i> -butoxy carbonyl
	Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
	Bu	butyl
	CDI	N,N'-carbonyldiimidazole
20	Cs ₂ CO ₃	cesium carbonate anhydrous
	CHCl ₃	chloroform
	DAST	diethylaminosulfurtrifluoride
	DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine
	DCM	dichloromethane
25	DIEA	N,N-diisopropylethylamine
	DMAc	dimethylacetamide
	DMAP	4-dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
30	DPPA	diphenylphosphoryl azide
	Et	ethyl
	EtOH	ethanol
	EtOAc	ethyl acetate
	HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
35		hexafluorophosphate

	HCl	hydrochloric acid
	<i>i</i> -Bu	isobutyl
	<i>i</i> -Pr	isopropyl
	KOAc	potassium acetate
5	LDA	lithium diisopropylamide
	LiAlH ₄	lithium Aluminium Hydride
	Me	methyl
	MeMgBr	methylmagnesium bromide
	mCPBA	3-Chloroperoxybenzoic acid
10	MeCN	acetonitrile
	MnO ₂	manganese dioxide
	N ₂	nitrogen
	NaBH ₄	sodium borohydride
	NaHCO ₃	sodium bicarbonate
15	NaHMDS	sodium bis(trimethylsilyl)amide
	NaOMe	sodium methoxide
	Na ₂ SO ₄	sodium sulphate
	NBS	N-bromosuccinimide
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium
20	PE	petroleum ether
	Ph	phenyl
	PPh ₃	triphenylphosphine
	Ph ₃ P=O	triphenylphosphine oxide
	pTSA	<i>p</i> -toluenesulfonic acids
25	<i>p</i> TSH	<i>p</i> -toluenesulfonhydrazide
	s-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
	TBAF	tetrabutylammonium fluoride
	<i>t</i> -Bu or Bu ^t	<i>tert</i> -butyl
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	Xant-phos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
	X-phos	2-dicyclohexylphosphino-2',4',6'-tri- <i>i</i> -propyl-1,1'-biphenyl

IV. SYNTHESIS

[00123] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis in view of the methods, reaction schemes and examples provided herein. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention

[00124] The starting materials are generally available from commercial sources such as Sigma-Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York (1967-1999 ed.), Larock, R.C., *Comprehensive Organic Transformations*, 2nd-ed., Wiley-VCH Weinheim, Germany (1999), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

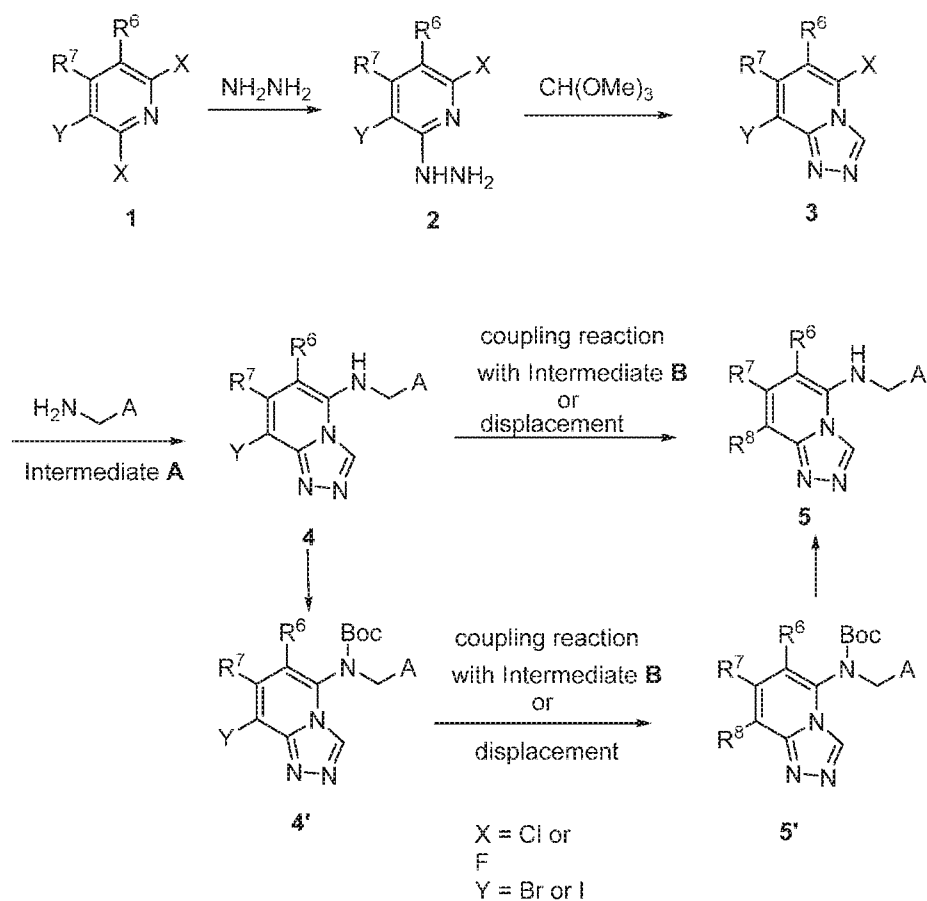
[00125] For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[00126] In the preparation of compounds of the present invention, protection of remote functionality of intermediates may be necessary. The need for such protection

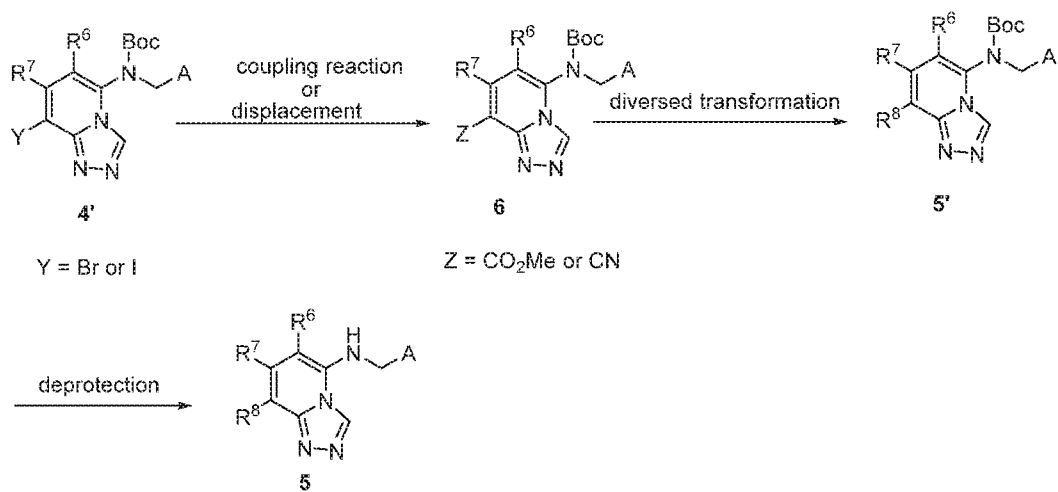
will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see Greene, T.W. et al., *Protecting Groups in Organic Synthesis*, 4th Ed., Wiley (2007). Protecting groups incorporated in making of the compounds of the present invention, such as the trityl protecting group, may be shown as one regioisomer but may also exist as a mixture of regioisomers.

- [00127]** Schemes 1 to 4 (below) describe potential routes for producing the compounds of the present invention which include compounds of Formula (IA).
- 10 Compounds of Formula (IA) can be made substantially optically pure by either using substantially optically pure starting material or by separation chromatography, recrystallization or other separation techniques well-known in the art. For a more detailed description, see the Example section below.

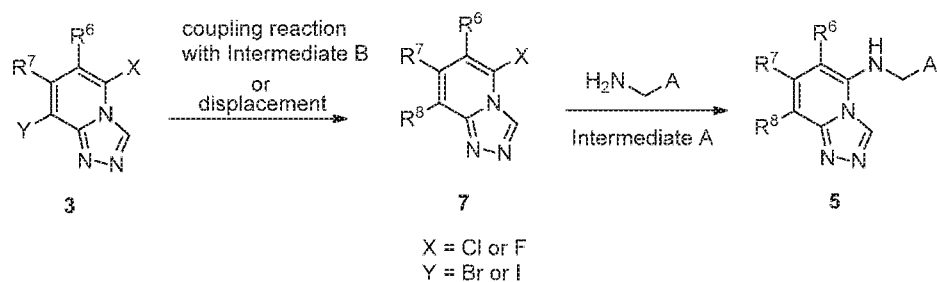
Scheme 1



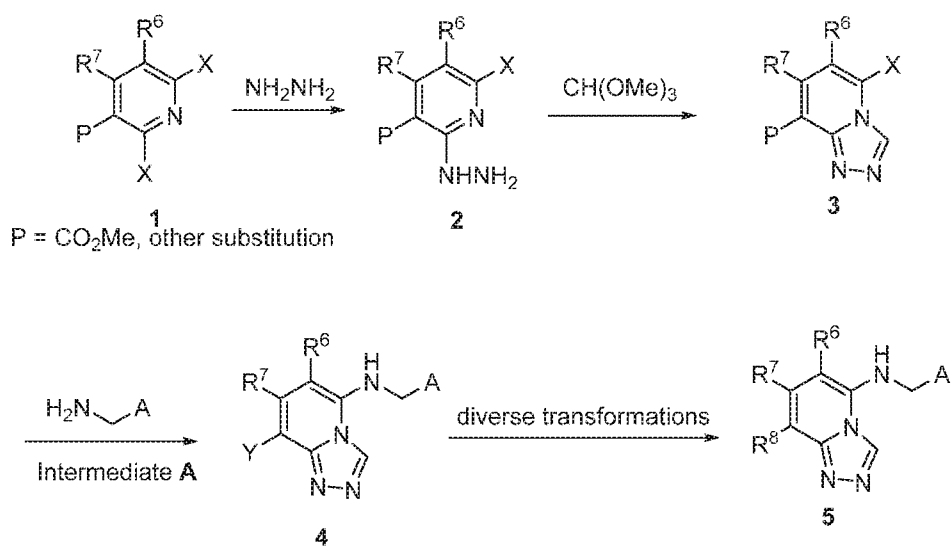
Scheme 2



Scheme 3



Scheme 4



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[00128] In general, under Scheme 1, substituted pyridine **1** was treated with hydrazine to form intermediate **2**, which was transformed to the cyclized product **3** upon treatment with trimethyl orthoformate or triethyl orthoformate. Subsequently, **3** was treated with appropriate amine to generate **4**, which was transformed to product **5** via cross-coupling reaction with appropriate R^8 reagent (e.g., various boronic acid or equivalent with appropriate R^8 group). In some circumstances, the protected **4'** was used in the coupling or displacement step leading to compound **5'**, which afforded compound **5** after deprotection.

[00129] Alternatively, under Scheme 2, the C8 aryl substitution was built from the appropriately substituted and protected intermediate **6** to give compound **5'** which was subsequently transformed to **5**.

[00130] In other cases, under Scheme 3, C-8 substitution could be installed first to give intermediate **7**, which was transformed to compound **5** through corresponding displacements.

[00131] In other cases, as described in Scheme 4, compound **5** could be obtained with similar reaction sequence described as in Scheme 1 by starting from differently substituted pyridine **1a**. The C-8 aryl ring was constructed by diverse method in the last steps to furnish compound **5**.

GENERAL METHODS

[00132] The following methods were used in the exemplified Examples, except where noted otherwise.

[00133] Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out using prepacked SiO₂ cartridges eluting with either gradients of hexanes and ethyl acetate or DCM and MeOH unless otherwise indicated. For highly polar amines, gradients of DCM and 1M NH₃ in MeOH were used. Reverse phase preparative HPLC was carried out using C18 columns with UV 214 nm and 254 nm or prep LCMS detection eluting with gradients of Solvent A (water with 0.1% TFA) and Solvent B (acetonitrile with 0.1% TFA) or with gradients of Solvent A (water with 0.05% TFA) and Solvent B (acetonitrile with 0.05% TFA) or with gradients of Solvent A (water with 0.05% ammonia) and Solvent B (acetonitrile with 0.05% ammonia).

LC/MS Methods Employed in Characterization of Examples

[00134] Reverse phase analytical HPLC/MS was performed on Agilent LC1200 systems coupled with 6110 (Methods A-D), or 6120 (Method E and F), or 6130 (Method G) Mass Spectrometer.

Method A: Linear gradient of 5% to 95% B over 1.2 min, with 1 min hold at 95% B;
UV visualization at 214 nm and 254 nm

Column: SunFire® C18 4.6 x 50 mm 3.5 µm
Flow rate: 2 mL/min
Solvent A: 0.1% trifluoroacetic acid, 99.9% water
Solvent B: 0.1% trifluoroacetic acid, 99.9% acetonitrile.

Method B: Linear gradient of 5% to 95% B over 1.5 min, with 1 min hold at 95% B;

- UV visualization at 214 nm and 254 nm
Column: XBridge® C18 4.6 x 50 mm 3.5 µm
Flow rate: 2 mL/min
Solvent A: water with 10mM Ammonium hydrogen carbonate
5 Solvent B: acetonitrile.
- Method C: Linear gradient of 5% to 95% B over 1.2 min, with 1.3 min hold at 95% B,
95% to 5% B over 0.01 min;
UV visualization at 214 nm and 254 nm
10 Column: SunFire® C18 4.6 x 50 mm 3.5 µm
Flow rate: 2 mL/min
Solvent A: 0.1% trifluoroacetic acid, 99.9% water
Solvent B: 0.1% trifluoroacetic acid, 99.9% acetonitrile.
- 15 Method D: Linear gradient of 5% to 95% B over 1.4 min, with 1.6 min hold at 95% B,
95% to 5% B over 0.01 min;
UV visualization at 214 nm and 254 nm
Column: XBridge® C18 4.6 x 50 mm 3.5 µm
Flow rate: 1.8 mL/min
20 Solvent A: water with 10mM Ammonium hydrogen carbonate
Solvent B: acetonitrile.
- Method E: Linear gradient of 5% to 95% B over 1.5 min, with 1 min hold at 95% B;
UV visualization at 214 nm and 254 nm
25 Column: XBridge® C18 4.6 x 50 mm 3.5 µm
Flow rate: 2 mL/min
Solvent A: water with 10mM Ammonium hydrogen carbonate
Solvent B: acetonitrile.
- 30 Method F: Linear gradient of 5% to 95% B over 1.5 min, with 1 min hold at 95% B;
UV visualization at 214 nm and 254 nm and 300 nm
Column: XBridge® C18 4.6 x 30 mm 2.5 µm
Flow rate: 1.8 mL/min
Solvent A: water with 0.1% ammonia
35 Solvent B: acetonitrile.

Method G: Linear gradient of 10% to 95% B over 2 min, with 1 min hold at 95% B;
UV visualization at 214 nm, 254 nm and 300 nm
Column: Sunfire[®] C18 4.6 x 30 mm 2.5 μ m
5 Flow rate: 1.8 mL/min
Solvent A: water
Solvent B: MeOH with 0.1% formic acid.

NMR Employed in Characterization of Examples

- 10 **[00135]** ¹H NMR spectra were obtained with Bruker Fourier transform spectrometers operating at frequencies as follows: ¹H NMR: 400 MHz (Bruker). ¹³C NMR: 100 MHz (Bruker). Spectra data are reported in the format: chemical shift (multiplicity, number of hydrogens). Chemical shifts are specified in ppm downfield of a tetramethylsilane internal standard (δ units, tetramethylsilane = 0 ppm) and/or referenced to solvent peaks,
15 which in ¹H NMR spectra appear at 2.49 ppm for CD₂HSOCD₃, 3.30 ppm for CD₂HOD, 1.94 for CD₃CN, and 7.24 ppm for CDCl₃, and which in ¹³C NMR spectra appear at 39.7 ppm for CD₃SOCD₃, 49.0 ppm for CD₃OD, and 77.0 ppm for CDCl₃. All ¹³C NMR spectra were proton decoupled.

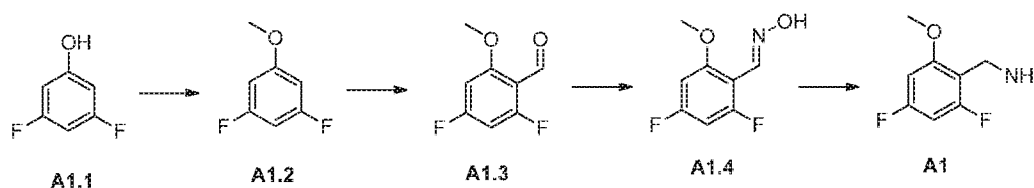
20 V. EXAMPLES

[00136] The following Examples have been prepared, isolated and characterized using the methods disclosed herein. The following examples demonstrate a partial scope of the invention and are not meant to be limiting of the scope of the disclosure.

- [00137]** Unless specified otherwise, starting materials are generally available from a
25 non-excluding commercial sources such as TCI Fine Chemicals (Japan), Shanghai Chemhere Co., Ltd.(Shanghai, China), Aurora Fine Chemicals LLC (San Diego, CA), FCH Group (Ukraine), Aldrich Chemicals Co. (Milwaukee, Wis.), Lancaster Synthesis, Inc. (Windham, N.H.), Acros Organics (Fairlawn, N.J.), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, N.J.), AstraZeneca
30 Pharmaceuticals (London, England), Chembridge Corporation (USA), Matrix Scientific (USA), Conier Chem & Pharm Co., Ltd (China), Enamine Ltd (Ukraine), Combi-Blocks, Inc. (San Diego, USA), Oakwood Products, Inc. (USA), Apollo Scientific Ltd. (UK), Allichem LLC. (USA) and Ukrorgsyntez Ltd (Latvia). Sigma-Aldrich Corporation, PharmaBlock (Nanjing) R&D Co. Ltd, Accela ChemBio Co., Ltd, Alputon (SHANGHAI)
35 Phamatech Co., Ltd., J&K Scientific Ltd

INTERMEDIATES

Intermediate **A1**: (2,4-Difluoro-6-methoxyphenyl)methanamine



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[00138] 1,3-Difluoro-5-methoxybenzene (**A1.2**): To a stirred suspension of **A1.1** (12.5 g, 96 mmol) and K_2CO_3 (66.0 g, 480 mmol) in acetone (400 mL) was added methyl iodide (27 mL, 480 mmol) in one portion. Then the reaction mixture was heated at 60 °C for 18 h. After cooling to rt, excess solvent was removed under vacuum and 150 mL of H_2O was added, which was extracted with Et_2O (2 \times 300 mL). The combined organic layers were washed with aq. NaOH (0.1 M, 100 mL) and H_2O (100 mL) in sequence, dried over Na_2SO_4 , filtrated and concentrated under reduced pressure to give the title compound (12.0 g, 80%) as a colorless oil. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 3.81 (s, 3H), 6.43 - 6.46 (m, 3H).

[00139] 2,4-Difluoro-6-methoxybenzaldehyde (**A1.3**): To a solution of **A1.2** (11.0 g, 76.4 mmol) in 100 mL of DCM at 0 °C was added $TiCl_4$ (12.5 mL, 114.8 mmol) dropwise, followed by dichloro(methoxy)methane (9.0 mL, 91.7 mmol). The mixture was stirred at 0 °C for 90 min and allowed to warm up to rt for 30 min. After dilution with 150 mL of DCM, the mixture was poured into crushed ice. The organic layer was collected and washed with brine (50 mL) and concentrated under reduced pressure. The residue was purified with silica gel chromatography column eluted with PE/ $EtOAc$ = 10/1 to give the title compound (4.5 g, 31 %) as a white solid. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 3.95 (s, 3H), 6.50 - 6.53 (m, 2H), 10.35 (s, 1H).

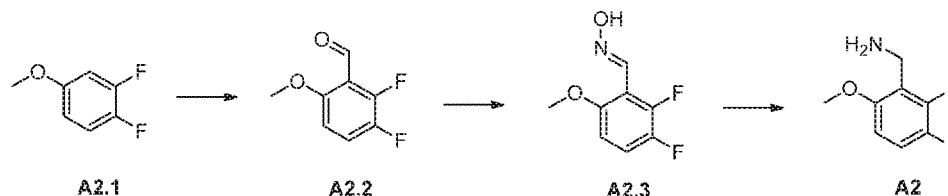
[00140] (E)-2,4-Difluoro-6-methoxybenzaldehyde oxime (**A1.4**): To a mixture of **A1.3** (4.5 g, 26.2 mmol), $NH_2OH \cdot HCl$ (3.6 g, 52.4 mmol) in a mixed solvent of MeOH (50 mL) and H_2O (50 mL) was added NaOH (3.1 g, 78.5 mmol). The reaction mixture stirred at 25 °C for 1 h. The solvent was concentrated and the residue was diluted with $EtOAc$ (100 mL). the obtained solution was washed with HCl (1N, 80 mL), $NaHCO_3$ (50 mL) and brine (50 mL). The combined organic phase was concentrated to give the title compound (4.8 g, 96%). LC-MS: $[MH]^+ = 188.1$.

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[00141] *Intermediate A1*: A mixture of **A1.4** (1000 mg, 5.2 mmol) and Raney Ni (0.92 g, 10.7mmol) in MeOH (100 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (14 mL) was stirred at rt under H_2 balloon overnight. The suspension was filtered through a pad of celite. The filtrate was concentrated to give the title compound (900 mg, 98%). LC-MS: $[\text{MH}]^+ = 174.1$.

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Intermediate A2: (2,3-Difluoro-6-methoxyphenyl)methanamine

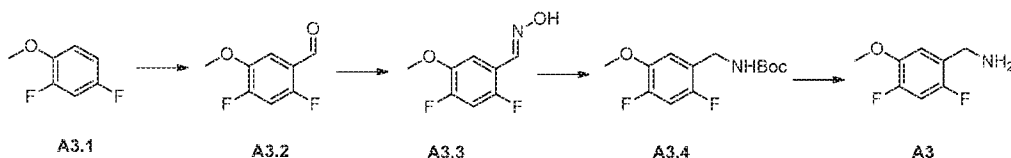


[00142] *1,3-Difluoro-5-methoxybenzene (A2.2)*: To a solution of LDA (23.4 mL) in 25 mL of THF was added **A2.1** (4.68 g, 32.5 mmol) in 10 mL THF dropwise at -70°C under N_2 . The mixture was stirred for 1 h at -70°C , then DMF (3.74 mL) was added dropwise, the reaction mixture was stirred for another 1 h at -70°C , and then warmed to rt. The reaction was quenched by 3 mL CH_3COOH and 40 mL H_2O , extracted with ethyl acetate (100 mL \times 3), the combined organic layers were washed with H_2O (100 mL), 1N HCl (100 mL), and brine (100 mL), dried over Na_2SO_4 , concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5:1) to give the title compound (2.9 g, 51.8%) as a yellow solid. LC-MS: $[\text{MH}]^+ = 173.2$.

[00143] *(E)-2,3-Difluoro-6-methoxybenzaldehyde oxime (A2.3)*: A mixture of **A2.2** (2.9 g, 16.9 mmol), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (2.3 g, 33.8 mmol), CH_3OH (45 mL) and NaOH (2.7 g, 67.6 mmol) in water (45 mL) was stirred at rt for 3 h. The mixture was concentrated and the residue was added ethyl acetate (200 mL). Then the organic layers were washed with 1N HCl (50 mL \times 2), saturated NaHCO_3 (100 mL) and brine (100 mL), dried over Na_2SO_4 , evaporated to give the title compound (2.2 g, 70%) as a white solid. LC-MS: $[\text{MH}]^+ = 187.8$.

[00144] *Intermediate A2*: A mixture of **A2.3** (2.2 g, 11.8 mmol), CH_3OH (200 mL), NH_4OH (30 mL), and Raney Ni (1.5 g) was stirred for 16 h at 20°C under H_2 atmosphere. The mixture was filtered and the filtrate was concentrated to give the title compound (2 g, 98%) as a colorless oil. LCMS: $[\text{MH}]^+ = 173.9$.

Intermediate A3: (2,4-difluoro-5-methoxyphenyl)methanamine



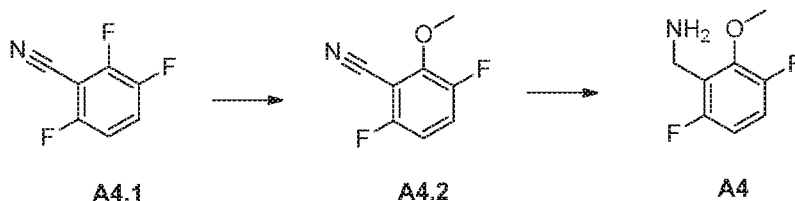
[00145] *2,4-Difluoro-5-methoxybenzaldehyde (A3.2)*: The title compound was prepared by a method similar to that of **A1.3** by replacing **A1.2** with **A3.1**. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ ppm 3.94 (s, 3 H), 6.99 (t, 1 H), 7.44 (dd, 1 H), 10.31 (s, 1 H).

5 **[00146]** *(E)-2,4-Difluoro-5-methoxybenzaldehyde oxime (A3.3)*: The title compound was prepared by a method similar to that of **A1.4** by replacing **A1.3** with **A3.2**. LC-MS: $[\text{MH}]^+ = 188.1$.

[00147] *tert-Butyl 2,4-difluoro-5-methoxybenzylcarbamate (A3.4)*: To a solution of **A3.3** (11.7 g, 62.6 mmol) and Boc_2O (20.5 g, 93.9 mmol) in 400 mL of MeOH was added
10 Pd/C (2.5 g, 10% wt). The mixture was evacuated under vacuum followed by back filling with H_2 via a balloon for four times. Then it was stirred at 40 °C under H_2 (4.0 MPa) overnight. The reaction mixture was filtered through celite pad and washed with MeOH (200 mL \times 2). The filtrate was concentrated under reduced pressure to give the title compound (15.6 g, 91%) as a white solid. LC-MS: $[\text{MH}]^+ = 218.1$.

15 **[00148]** *Intermediate A3*: To a solution of **A3.4** (4.0 g, 14.65 mmol) in dioxane (120 mL) was added 30 mL of HCl (4 mol/L). The reaction was stirred at rt for 2 h, then concentrated under reduced pressure to give the crude product as HCl salt form. The residue was diluted with MeOH/MeCN (1/4, 250 mL), followed by K_2CO_3 (6.7 g, 43.95 mmol) and stirred at 60 °C for 3 h. After cooling to rt, the solid was filtered off, and the
20 filtrate was evacuated under vacuum, purified by Flash Column Chromatography (MeOH/EtOAc = 0% to 25%) to give the title compound (2.0 g, 80.0%) as a yellow oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 3.88 (s, 2H), 3.90 (s, 3H), 6.86 (dd, 1H), 6.98 (dd, 1H). LC-MS: $[\text{MH}]^+ = 174.1$.

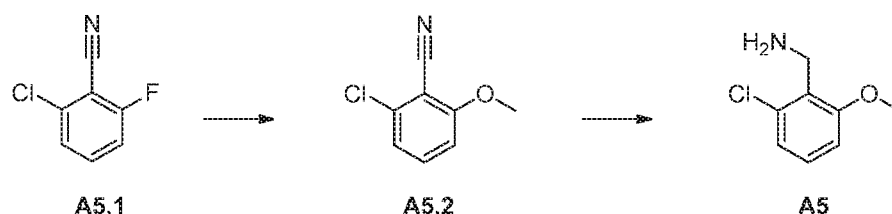
25 *Intermediate A4: (3,6-Difluoro-2-methoxyphenyl)methanamine*



[00149] 3,6-Difluoro-2-methoxybenzonitrile (**A4.2**): Methanol (10 mL) was treated portionwise with sodium (162 mg, 7 mmol). The sodium methoxide solution was cooled to rt and added dropwise to a solution of **A4.1** (1g, 6.4 mol) in methanol (10 mL) at rt. The mixture was stirred for 16 h at 60 °C, concentrated to remove the solvent under reduced pressure. The residue was purified by column chromatography (EA/PE = 0-50%) to give the title compound (600 mg, 55%). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.18 (s, 3H), 6.80 - 6.85 (m, 1H), 7.27 - 7.34 (m, 1H).

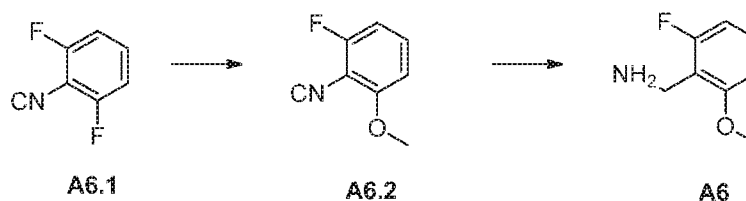
[00150] Intermediate **A4**: To a solution of **A4.2** (600 mg, 3.55 mmol) and NH₄OH (5 mL) in CH₃OH (50 mL) was added Raney Ni (0.6 g), the mixture was stirred for 16 h at 20 °C under H₂ atmosphere. The mixture was filtered and the filtrate was concentrated to give the title compound (400 mg, 65%). LC-MS: [MH]⁺ = 174.1.

Intermediate **A5**: (2-Chloro-6-methoxyphenyl)methanamine

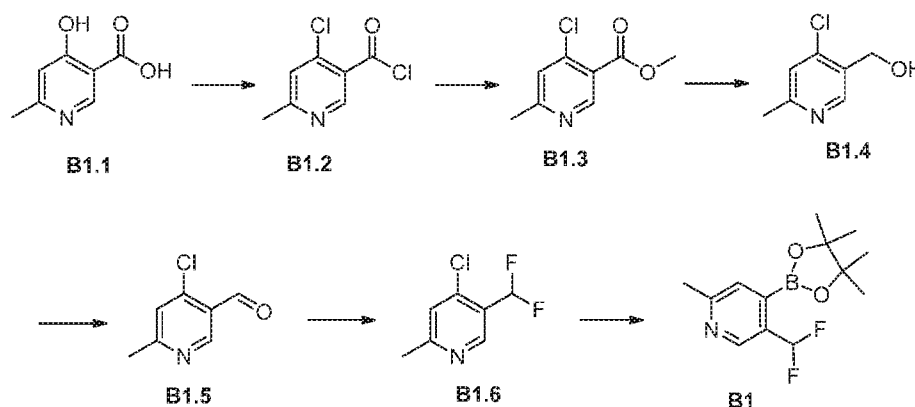


[00151] 2-Chloro-6-methoxybenzonitrile (**A5.2**): To a solution of **A5.1** (1.55 g, 10.0 mmol) in 100 mL of anhydrous methanol was added sodium methoxide (4.32 g, 80 mmol). The mixture was heated at 85 °C and stirred overnight, then concentrated under reduced pressure to remove solvents. The residue was diluted with 400 mL DCM, washed with Sat. NH₄Cl (2 × 20 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum. The crude product was purified by column chromatography (PE:EA = 10:1) to give the title compound (1.5 g, 89.8%) as a pale yellow solid. LC-MS: [MH]⁺ = 168.0.

[00152] Intermediate **A5**: To a solution of **A5.2** (334 mg, 2.0 mmol) in 10.0 mL THF was added of borane (2.0 mol/L). The mixture was heated at 90 °C for 3 h, then cooled to rt and quenched with methanol. The mixture was concentrated under vacuum, the residue was diluted with another 50 mL methanol, and then removed again. The process was repeated for four times to give the title compound (300 mg, 88%) as the crude product, which will used in next step without further purification. LC-MS: [MH]⁺ = 172.1

Intermediate **A6**: (2-Fluoro-6-methoxyphenyl)methanamine

- [00153]** 2-Fluoro-6-methoxybenzonitrile (**A6.2**): To a solution of **A6.1** (500 g, 3.6 mol) in 2.5 L MeOH was added sodium methoxide (388 g, 7.2 mol) in portions slowly. The mixture was stirred at rt overnight. The reaction mixture was poured into 15 L H₂O and the precipitate was filtered off and washed twice with 2.0 L H₂O to give the title compound (1140 g) as a white solid, the crude product will be used in next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ ppm 3.96 (s, 3H), 6.79 (dd, 2H), 7.52 (dd, 1H).
- 10 **[00154]** Intermediate **A6**: To a solution of **A6.2** (228 g, crude) and 145 mL NH₄OH in 1.0 L MeOH was added 30 g Raney Ni. The mixture was stirred in an autoclave at 40 °C under hydrogen atmosphere (25 atm) for 8 h. After filtration, the filtrate was concentrated under reduced pressure to get a pale yellow oil, which was purified by reduced pressure distillation to give the title compound (60 g, 54 %) as a colorless oil. ¹H NMR (500 MHz,
- 15 DMSO-*d*₆) δ ppm 1.58 (s, 2H), 3.67 (s, 1H), 6.75 (t, 1H), 6.82 (d, 1H), 7.22 (dd, 1H). LC-MS: [MH]⁺ = 156.1.

Intermediate **B1**: 5-(Difluoromethyl)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

[00155] *4-Chloro-6-methylnicotinoyl chloride (B1.2)*: A mixture of **B1.1** (15.3 g, 0.1 mol) in POCl₃ (200 mL) was heated to 120 °C and stirred for 3 h. The mixture was cooled to rt and concentrated. The residue was diluted with DCM (100 mL) and concentrated to give the title compound (18 g, 100 %) as pale yellow oil. The crude product will be used in next without further purification.

[00156] *Methyl 4-chloro-6-methylnicotinate (B1.3)*: A mixture of **B1.2** (18 g, 0.1 mol) in DCM (150 mL) was added MeOH (30 mL) and stirred at rt for 20 mins. The solvent was removed. The residue was purified with silica gel chromatography eluted with PE/EtOAc = 5/1 to give title compound as a colorless oil (15.9 g, 86%). LC-MS: [MH]⁺ = 186.1.

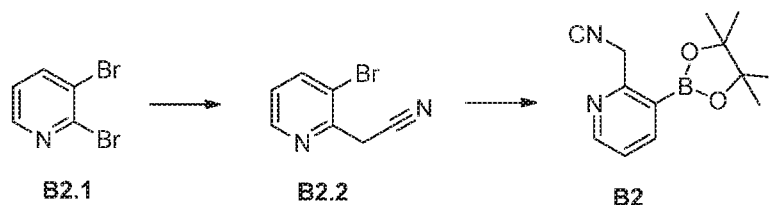
[00157] *4-Chloro-6-methylpyridin-3-yl)methanol (B1.4)*: To a solution of **B1.3** (1.0 g, 5.4 mmol) in 30 mL of methanol was added NaBH₄ (1.0 g, 27.0 mmol) at rt. Then the reaction mixture was stirred at rt for 5 h. The solvent was removed. EtOAc (20 mL) and water (15 mL) were added. The organic phase was separated and concentrated to give title compound (700 mg, 82%) as a colorless oil. LC-MS: [MH]⁺ = 158.1.

[00158] *4-Chloro-6-methylnicotinaldehyde (B1.5)*: To a mixture of **B1.4** (700 mg, 4.458 mmol) in DCM (15 mL) was added MnO₂ (1.94 g, 22.29 mmol) at rt. The mixture was stirred at rt for 18 h, filtered, the filtrate was removed to give the title compound (650 mg, 93%) as a pale yellow solid. LC-MS: [MH]⁺ = 174.1.

[00159] *4-Chloro-5-(difluoromethyl)-2-methylpyridine (B1.6)*: A mixture of **B1.5** (650 mg, 4.19 mmol) in DCM (10 mL) was added DAST (1.1 mL, 8.38 mmol) at 0 °C. Then the mixture was stirred at 0 °C for 2 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added. The organic phase was separated and concentrated. The residue was purified with silica gel chromatography eluted with PE/EtOAc = 3/1 to give the title compound (600 mg, 81%) as a pale yellow oil. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.60 (s, 3H), 6.93 (t, 1H), 7.26 (s, 1H), 8.71 (s, 1H).

[00160] *Intermediate B1*: A mixture of **B1.6** (150 mg, 0.85 mmol), B₂Pin₂ (237 mg, 0.93 mmol), KOAc (250 mg, 2.55 mmol), s-Phos (15 mg, 0.037 mmol) and Pd(OAc)₂ (40 mg, 0.18 mmol) in 1,4-dioxane (6 mL) was purged with N₂ for 3 times. Then the sealed reaction was stirred at 120 °C for 2 h. Solvent was removed and the residue was dissolved with DCM (5 mL). The solid was filtered, and the filtrate was concentrated to give the title compound (300 mg, 60%) as a brown oil. The crude product will be used in next without further purification. LC-MS: [MH]⁺ = 270.1.

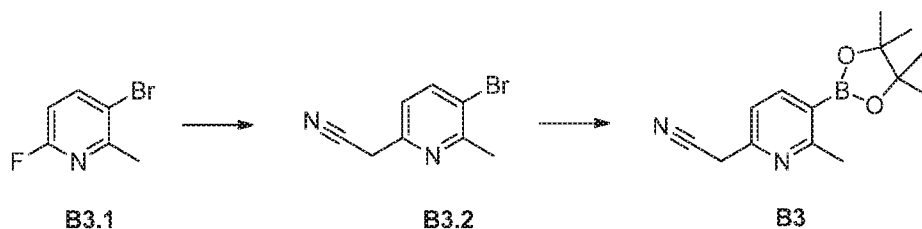
Intermediate B2: 2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetonitrile



[00161] *2-(3-Bromopyridin-2-yl)acetonitrile (B2.2)*: To the solution of MeCN (87 mg, 2.13 mmol) in THF (8 mL) was added n-BuLi (1.78 mL, 4.26 mmol) at -78 °C and stirred at -78 °C for 1 h. Then **B2.1** (500 mg, 2.13 mmol) in THF (2 mL) was added slowly at -78 °C. The reaction was stirred at -78 °C for 1.5 h, and warmed to rt, quenched with saturated NH₄Cl solution, extracted with EA (100 mL × 3), washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by Prep-HPLC (Mobile Phase: MeCN/H₂O (10 mM) NH₄HCO₃) to give the title compound (110 mg, 22%) as a white solid. LCMS: [MH]⁺ = 197.

10 **[00162]** *Intermediate B2*: To a solution of **B2.2** (110 mg, 0.56 mmol) and
4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (285 mg, 1.12 mmol) in 6 mL
dioxane was added KOAc (165mg, 1.68 mmol) and Pd(dppf)Cl₂ (41 mg, 0.056mmol).
The suspension was stirred at 95 °C under N₂ for 2 h. The reaction was concentrated
under vacuum, the residue was washed with PE (20 mL × 2). The filtration was
15 concentrated under vacuum to give the title compound (200 mg, 48%) as a yellow oil.
LC-MS: [MH]⁺ = 245.

Intermediate **B3**: 2-(6-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetonitrile

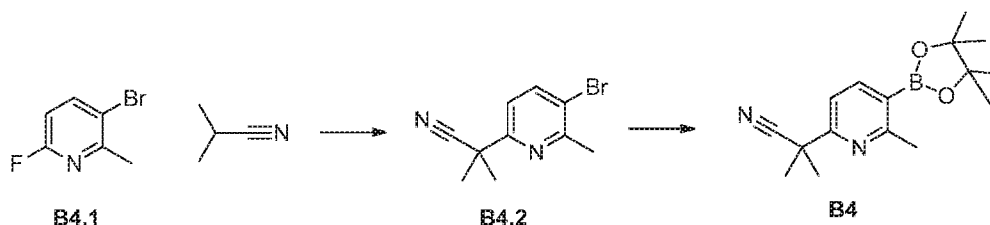


[00163] *2-(5-Bromo-6-methylpyridin-2-yl)acetonitrile (B3.2)*: To the solution of MeCN (142 mg, 3.47 mmol) in THF (5 mL) was added n-BuLi (3.47 mL, 3.47 mmol) at -78 °C and stirred at -78 °C for 1 h, then **B3.1** (200 mg, 1.05 mmol) was added slowly at -78 °C. The mixture was warmed to rt and stirred at rt for 2 h. The reaction mixture was quenched with saturated NH₄Cl, extracted with EtOAc (100 mL × 3), washed with brine,

dried over Na₂SO₄ and concentrated. The residue was purified by Prep-HPLC (Mobile Phase: MeCN/H₂O (10 mM NH₄HCO₃)) to give the title compound (220 mg, 64%) as a white solid. LC-MS: [MH]⁺ = 211.1.

- [00164] *Intermediate B3*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B3.2**. LC-MS: [MH]⁺ = 259.2.

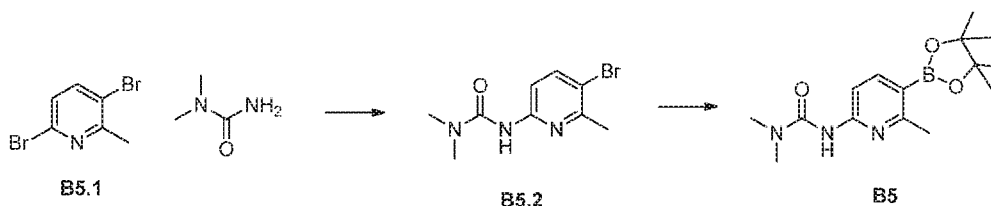
Intermediate B4: 2-Methyl-2-(6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propanenitrile



- [00165] *2-(5-Bromo-6-methylpyridin-2-yl)-2-methylpropanenitrile (B4.2)*: To a solution of **B4.1** (1.0 g, 5.26 mmol) and isobutyronitrile (1.87 mL) in toluene (20 mL) was added NaHMDS (5 mL, 15.8 mmol), it was stirred at 120 °C for 2h. The mixture was concentrated and diluted with water (20 mL), then extracted with EA (20 mL × 3). The organic layer was dried and concentrated, which was purified by flash chromatography (normal phase, silica gel; EtOAc:PE=1:4) to give the title compound (480 mg, 38%) as a gray oil. LC-MS: [MH]⁺ = 241.1.

[00166] *Intermediate B4*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B4.2**. LC-MS: [MH]⁺ = 287.1.

- [00167] *Intermediate B5: 1,1-Dimethyl-3-(6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)urea*

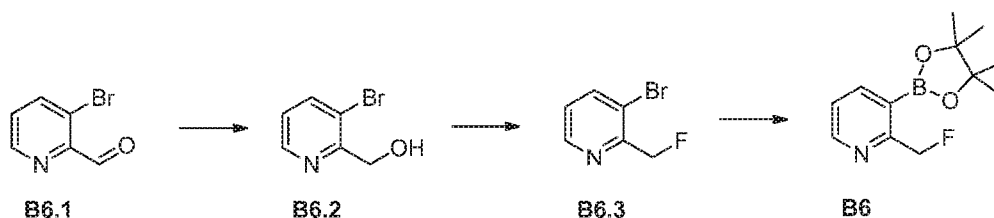


- [00167] *3-(5-Bromo-6-methylpyridin-2-yl)-1,1-dimethylurea (B5.2)*: To a solution of **B5.1** (502 mg, 2.0 mmol), 1,1-dimethylurea (352 mg, 4.0 mmol), Pd₂(dba)₃ (280 mg, 0.4 mmol), Xant-phos (23 mg, 0.4 mmol) and Cs₂CO₃ (1.3 g, 4.0 mmol) in dioxane (10 mL)

was sealed in a tube stirred at 100 °C for 1 h under N₂. The mixture was concentrated and diluted with water (10 mL), extracted with EA (10 mL × 3). The organic layer was dried and concentrated, purified by flash chromatography(normal phase, silica gel; EA:PE=1:17) to give the title compound (68 mg, 13%) as a yellow solid. LC-MS: [MH]⁺ = 257.7.

[00168] *Intermediate B5*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B5.2**. LC-MS: [MH]⁺ = 306.2.

Intermediate B6: 2-(Fluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

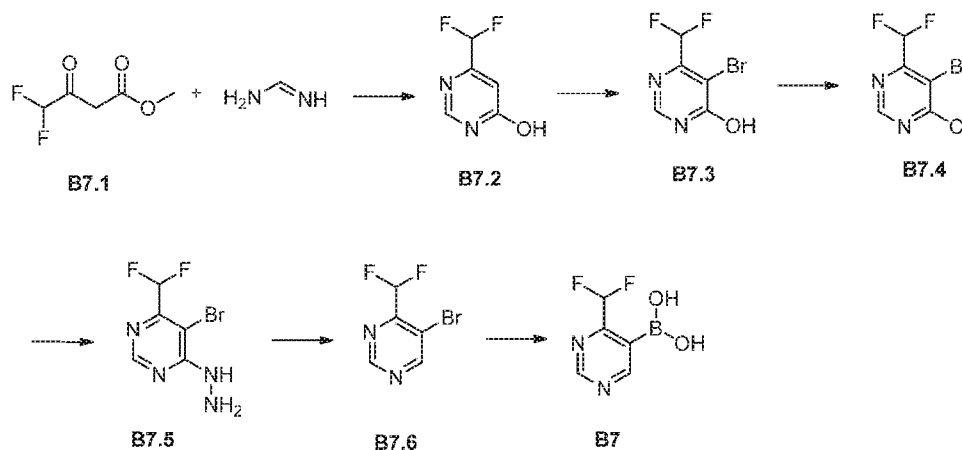


[00169] *(3-Bromopyridin-2-yl)methanol (B6.2)*: A mixture of **B6.1** (480 mg, 2.58 mmol) in MeOH(10 mL) and THF(5 mL) was cooled to 0 °C, NaBH₄ (390 mg, 10.32 mmol) was added in portions. The mixture was stirred for 4 h, then concentrated, and diluted with water(30 mL), extracted with DCM (30 mL × 3). The organic layer was washed with brine (30 mL), dried over Na₂SO₄, concentrated to give the title compound (400 mg, 82%) as a white solid. LC-MS: [MH]⁺ = 188.0.

[00170] *3-Bromo-2-(fluoromethyl)pyridine (B6.3)*: To a mixture of **B6.2** (300 mg, 1.6 mmol) in DCM (20 mL) was added DAST(1.03 g, 6.4 mmol) at 0 °C dropwise. The mixture was stirred for 3 h at 0 °C, then quenched by sat. NaHCO₃(40 mL), extracted with DCM (40 mL × 2), the organic layer was washed with brine (40 mL), dried over Na₂SO₄, concentrated and purified on silica gel (0-50% EtOAc in PE) to give the title compound (120 mg, 39%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 5.60 (d, 2H), 7.22 (dd, 1H), 7.93 (d, 1H), 8.61 (d, 1H).

[00171] *Intermediate B6*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B6.3**. LC-MS: [MH]⁺ = 238.2.

Intermediate B7: (4-(Difluoromethyl)pyrimidin-5-yl)boronic acid



[00172] *6-(Difluoromethyl)pyrimidin-4-ol (B7.2)*: A mixture of methyl **B7.1** (6.4 g, 38.5 mmol), formimidamide (4.0 g, 38.5 mmol) and CH₃ONa (2.7 g, 50.1 mmol) in MeOH (100 mL) was stirred at rt for 18 h. The solvent was removed. The residue was dissolved in 50 mL of water. The solution was adjusted to pH~4. After cooling to 5°C, the solid was filtered to give the title compound (6.0 g, 98%) as a yellow solid. LC-MS: [MH]⁺ = 147.1.

[00173] *5-Bromo-6-(difluoromethyl)pyrimidin-4-ol (B7.3)*: A mixture of **B7.2** (6.0 g, 38.5 mmol) and NBS (7.5 g, 42.4 mmol) in DMF (15 mL) was stirred at 40 °C for 4 h. Water 100 mL and EA (100 mL) were added. The organic phase was separated and concentrated to give the title compound (4.5 g, 49 %) as a yellow solid. LC-MS: $[MH]^+ = 224.9$.

[00174] *5-Bromo-4-chloro-6-(difluoromethyl)pyrimidine (B7.4)*: A mixture of **B7.3** (4.5 g, 20.1 mmol) in POCl₃ (20 mL) stirred at 110 °C for 2 h. After cooling to rt, the mixture was concentrated, the residue was poured into ice water (10 mL), then extracted with DCM (20 mL × 2). The organic phase was concentrated and purified with silica gel chromatography column eluted with PE/EA=5/1 to give the title compound (3.2 g, 67%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 6.87 (t, 1H), 9.02 (s, 1H).

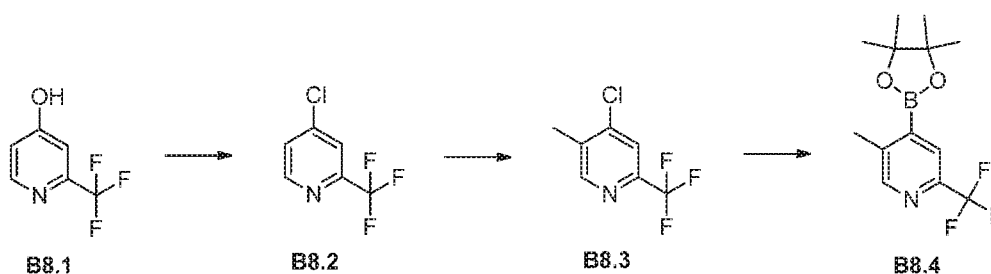
[00175] *5-Bromo-4-(difluoromethyl)-6-hydrazinylpyrimidine (B7.5)*: To a mixture of **B7.4** (2.0 g, 8.2 mmol) in EtOH (10 mL) was added hydrazine hydrate (1.03 g, 20.6 mmol) in EtOH (10 mL) drop wise at 0 °C. After 10 mins stirring, H₂O (5 mL) was added. The solid was filtered to give the title compound (1.8g, 90%) as a yellow solid. LC-MS: [MH]⁺ = 239.1.

[00176] *5-Bromo-4-(difluoromethyl)pyrimidine (B7.6)*: A mixture of MnO₂ (6.6 g, 75.3 mmol) in CHCl₃ (20 ml) was added **B7.5** (1.8 g, 7.53 mmol) in CHCl₃ (10 ml) at 0 °C. The

mixture was stirred at rt for 0.5 h. The MnO₂ filtered and the filtrate was concentrated. The residue was purified with silica gel chromatography column eluted with PE/EtOAc=5/1 to give the title compound (0.7 g, 44%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 6.80 (t, 1H), 9.00 (s, 1H), 9.25 (s, 1H).

- 5 **[00177]** *Intermediate B7*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B7.6**. LC-MS: [MH]⁺ = 175.1.

Intermediate B8: 5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine



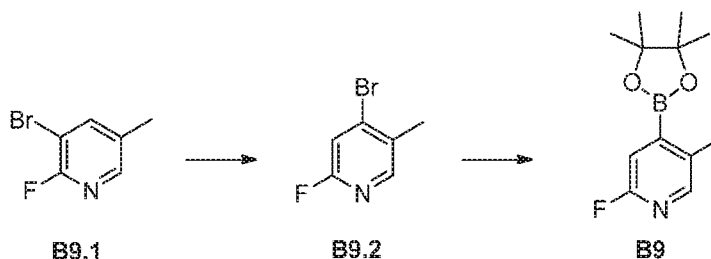
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- [00178]** *4-Chloro-2-(trifluoromethyl)pyridine (B8.2)*: A mixture of **B8.1** (2.0 g, 12.3 mmol) in POCl₃ (10 mL) was stirred at 110 °C for 2 h. Then the extra POCl₃ was removed. The residue was poured into ice water (30 mL). The solid was filtered to give the title compound (1.5 g, 68%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.54 (d, 1H), 7.74 (s, 1H), 8.68 (d, 1H).
- 15

- [00179]** *4-Chloro-5-methyl-2-(trifluoromethyl)pyridine (B8.3)*: To a mixture of **B8.2** (1.5 g, 8.3 mmol) in THF (20 mL) was added LDA (6 mL, 12 mmol) dropwise at -78 °C. The mixture was stirred at the at -78 °C for 30 min. Then methyl iodide (1.4 g, 9.96 mmol) was added. The reaction was allowed to warm to RT and stirred over night, then quenched by Ssatd. NH₄Cl (15 mL), extracted with Et₂O (20mL × 2). The combined organic phase was concentrated to give the title compound (1.5 g, 94%) as a yellow oil.
- 20

- [00180]** *Intermediate B8*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B8.3**. LC-MS: [MH]⁺ = 288.1.
- 25

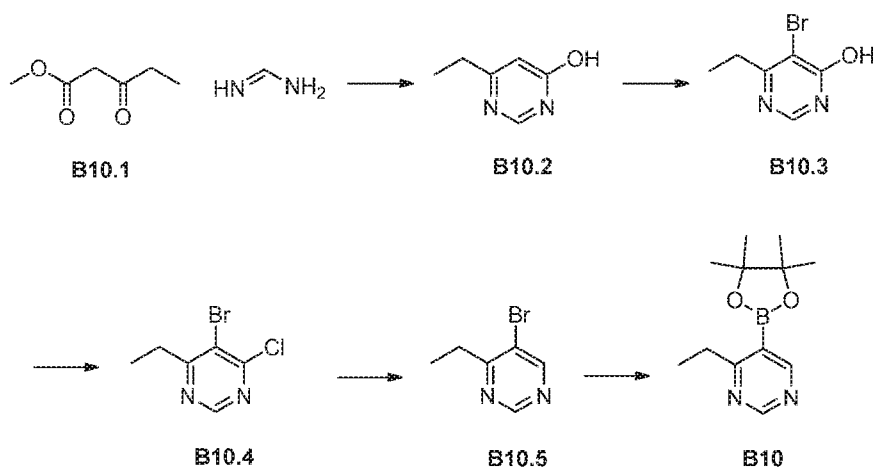
Intermediate B9: 2-Fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00181] *4-Bromo-2-fluoro-5-methylpyridine (B9.2)*: To a solution of **B9.1** (300 mg, 1.596 mmol) in THF (10 mL) at -78 °C was added LDA (2 M, 0.8 mL) and the mixture was stirred at -78 °C for 2 h. The mixture was quenched by 10 mL H₂O and extracted with EtOAc (10 mL x 3). The combined organic phase was concentrated to give the crude product, which was purified by flash chromatography (Normal phase, silica gel, PE:EtOAc=0-100%, UV254 & UV280) to give the title compound (130 mg, 43%) as a yellow oil. ¹H-NMR (400 MHz, CDCl₃) δ ppm 2.37 (s, 3H), 7.19 (d, 1H), 8.05 (s, 1H).

[00182] *Intermediate B9*: The title compound was prepared by a method similar to that of **B2** by replacing 2-(3-bromopyridin-2-yl)acetonitrile (**B2.2**) with 4-bromo-2-fluoro-5-methylpyridine (**B9.2**). LC-MS: [MH]⁺ = 238.1.

Intermediate B10: 4-Ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



[00183] *6-Ethylpyrimidin-4-ol (B10.2)*: A mixture of methyl **B10.1** (20 g, 154 mmol), formamidine acetate (20 g, 192 mmol), CH₃ONa (20 g, 370 mmol) and CH₃OH (160 mL) was stirred for 16 h at 20 °C. The mixture was diluted with water (40 mL), CH₃COOH (20 mL) was added to adjust pH to 7, evaporated, then diluted with water (40 mL), extracted with EA (100 mL x 4), dried over Na₂SO₄ and concentrated. The resulting solid was

trituated with EtOAc (30 mL), filtered to give the title compound (7 g, 37%) as white solid. LC-MS: $[MH]^+ = 125.2$.

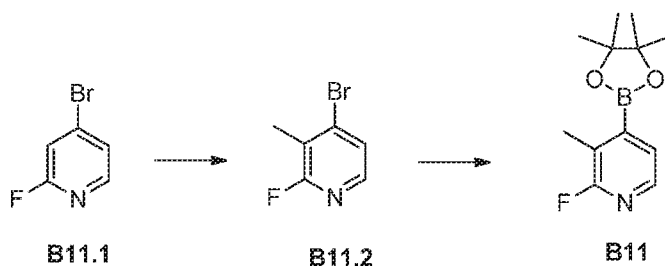
[00184] *5-Bromo-6-ethylpyrimidin-4-ol (B10.3)*: To a mixture of **B10.2** (5 g, 40 mmol), $NaHCO_3$ (3.36 g, 40 mmol) in H_2O (15 mL) was added Br_2 (6.39 g, 40 mmol) dropwise at 0 °C,. The mixture was stirred for 3 h at rt, extracted with EtOAc (30 mL x 3), concentrated and purified on silica gel (PE/EA = 0-100%) to give the title compound (4 g, 47%) as white solid. LC-MS: $[MH]^+ = 205.2$.

[00185] *5-Bromo-4-chloro-6-ethylpyrimidine (B10.4)*: A mixture of **B10.3** (2 g, 10 mmol), mmol) in $POCl_3$ (10 mL) was heated to 70 °C and stirred for 16 h, The mixture was poured into ice-water and neutralized with 30% NaOH solution to pH = 5-7 at 0 °C, extracted with EA (50mL x 2), concentrated and purified on silica gel (PE/EA=0-50%) to give the title compound (1.3 g, 58%) as colorless oil. 1H -NMR (400 MHz, $DMSO-d_6$) δ ppm 1.22 (t, 3H), 2.93 (q, 2H), 8.89 (s, 1H).

[00186] *5-Bromo-4-ethylpyrimidine (B10.5)*: A mixture of **B10.4** (1.3 g, 5.9 mmol), $pTSH$ (3.3 g, 17.7 mmol) in CH_3Cl (20 mL) was heated to 90 °C and stirred for 16 h. The mixture was concentrated, then added 10% Na_2CO_3 (20 mL) and stirred for 2 h at 90 °C. The mixture was extracted with EtOAc (30 mL x 3), the combined organics was washed with brine (50 mL), dried over Na_2SO_4 , concentrated and purified on silica gel (PE/EtOAc = 0-30%) to give the title compound (450 mg, 40%) as a colorless oil. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 1.31 (t, 3H), 2.95 (q, 2H), 8.72 (s, 1H), 9.02 (s, 1H).

[00187] *Intermediate B10*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B10.5**. LC-MS: $[MH]^+ = 235.1$.

Intermediate **B11**: *2-Fluoro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine*

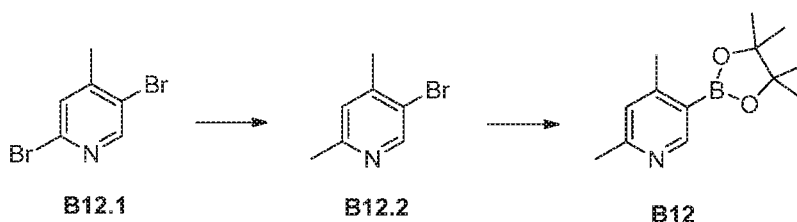


[00188] *4-Bromo-2-fluoro-3-methylpyridine (B11.2)*: To a mixture of **B11.1** (2 g, 11.3 mmol) in THF (40 mL) was added a solution of LDA (2 M, 8.5 mL) dropwise at -78 °C. The mixture was stirred for 1 h at -78 °C, and then methyl iodide (4.8 g, 34 mmol) was

added dropwise. The mixture was stirred for 1 h at -78 °C, and warmed to rt over 1 h. The mixture was quenched by sat. NH₄Cl (50 mL) at 0 °C, then extracted with EA (60 mL × 3), the organics layer was washed with brine (60 mL), dried over Na₂SO₄, concentrated. The residue was purified on silica gel (PE/EtOAc = 0-50%) to give the title compound (1 g, 47%) as a yellow solid. ¹H-NMR (400 MHz, CDCl₃) δ ppm 2.35 (s, 3H), 7.36 (d, 1H), 7.86 (d, 1H).

[00189] *Intermediate B11*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B11.2**. LC-MS: [MH]⁺ = 238.1.

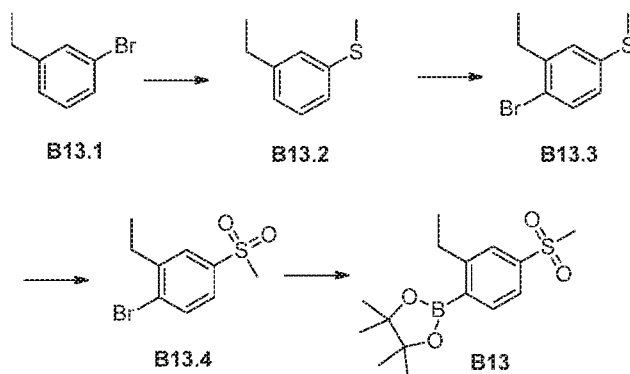
10 *Intermediate B12: 2,4-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine*



[00190] *5-Bromo-2,4-dimethylpyridine (B12.2)*: To a three-neck flask, was placed **B12.1** (2.51 g, 10.0 mmol) in dry THF (50 mL), Pd(PPh₃)₄ (1.15 g, 1.0 mmol). The mixture was protected under N₂ and stirred at 0 °C. MeMgBr/THF (15 mL, 15.0 mmol, 1 mol/L) was added slowly. After addition, the mixture was refluxed for 3 h, cooled to rt, quenched the reaction mixture with 1N HCl and extracted with EtOAc (100 mL × 3). The organic layer was washed with H₂O (50 mL × 2) and brine (50 mL), then dried over anhydrous Na₂SO₄ and concentrated under vacuum and the crude product was purified by Biotage flash chromatography (PE/EtOAc = 5%-10%) to afford the title compound (301 mg, 16.2%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.35 (d, 3H), 2.47 (s, 3H), 7.04 (s, 1H), 8.50 (s, 1H).

[00191] *Intermediate B12*: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B12.2**. LC-MS: [MH]⁺ = 234.2.

25 *Intermediate B13: 2-(2-Ethyl-4-(methylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane*



[00192] (3-Ethylphenyl)(methyl)sulfane (**B13.2**): To a mixture of **B13.1** (3 g, 16 mmol) in THF (30 mL) was added n-BuLi (7.7 mL) dropwise at -78 °C. The mixture was stirred for 1 h at -78 °C, and then 1,2-dimethyldisulfane (3 g, 32 mmol) was added dropwise.

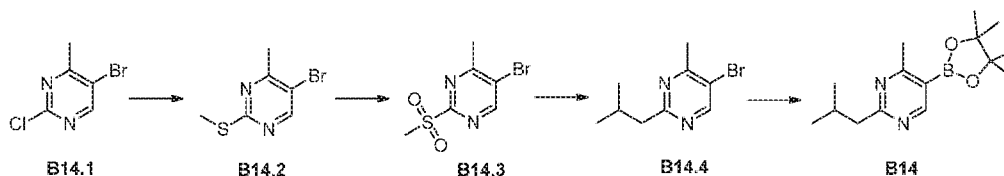
5 The mixture was stirred for 1 h at -78 °C, and warmed to rt over 1 h. The mixture was cooled to 0 °C, added saturated NH₄Cl (50 mL), then extracted with EA (50 mL \times 3), the organic layer was washed with H₂O (10 mL) and brine (100 mL), dried over Na₂SO₄, concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 0-20%) to give the title compound (1.7 g, 70%) as colorless oil.

10 **[00193]** (4-Bromo-3-ethylphenyl)(methyl)sulfane (**B13.3**): A mixture of **B13.2** (456 g, 3 mmol) in AcOH (10 mL) was cooled to 0 °C, Br₂ (479 g, 3 mmol) was added dropwise. The mixture was stirred for 3 h at 25 °C, concentrated and purified by column chromatography on silica gel (PE) to give the title compound (600 mg, 86%) as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ ppm 1.25 (t, 3H), 2.49 (s, 3H), 2.75 (q, 2H),
 15 6.95 (dd, 1H), 7.14 (d, 1H), 7.44 (d, 1H).

[00194] 1-Bromo-2-ethyl-4-(methylsulfonyl)benzene (**B13.4**): To a mixture of **B13.3** (600 mg, 2.6 mmol) in DCM (20 mL) was added mCPBA (1.34 g, 7.8 mmol) at 0 °C. The mixture was stirred for 16 h at 25 °C then added 1N NaOH (40 mL), extracted with DCM (50 mL \times 2). The combined organics was washed with brine (50 mL), dried over Na₂SO₄,
 20 concentrated. The residue was purified on silica gel (PE/EtOAc = 0-50%) to give the title compound (350 mg, 51%) as a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 1.21 (t, 3H), 2.81 (q, 2H), 3.25 (s, 3H), 7.67 (dd, 1H), 7.87 - 7.90 (m, 1H).

[00195] Intermediate **B13**: The title compound was prepared by a method similar to that of **B2** by replacing 2-(3-bromopyridin-2-yl)acetonitrile (**B2.2**) with 1-bromo-2-ethyl-4-(methylsulfonyl)benzene (**B13.4**).
 25

Intermediate **B14**: 2-iso-Butyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



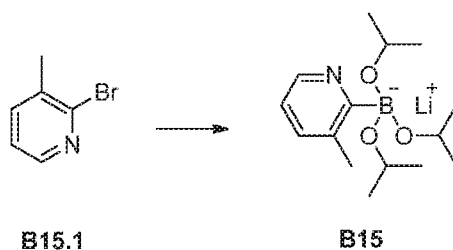
5 **[00196]** 5-Bromo-4-methyl-2-(methylthio)pyrimidine (**B14.2**): Sodium methanethiolate (1.04 g, 11.6 mmol) was added in portions into a solution of **B14.1** (2.0 g, 9.66 mmol) in DMF (20 mL) at 0 °C. After addition, the mixture was stirred at rt for 16 h, then poured into water (100 mL) and extracted with EtOAc (50 mL × 3). The organic layer was washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄, then concentrated under vacuum to give the title compound (2.0 g, 94.5 %) as a yellow oil. LC-MS: [MH]⁺ = 218.8.

[00197] 5-Bromo-4-methyl-2-(methylsulfonyl)pyrimidine (**B14.3**): m-CPBA (7.4 g, 36.5 mmol) was added into a solution of **B14.2** (2.0 g, 9.1 mmol) in DCM (100 mL) at 0 °C. The mixture was stirred at rt for 16H, then quenched with H₂O (200 mL), extracted with DCM (100 mL × 3). The organic layer was washed with aqueous Na₂CO₃ (100 mL × 2), H₂O (100 mL), brine (100 mL), then dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by flash chromatography (PE/EtOAc = 10%~30%) to get the title compound as a light yellow solid (1.8 g, 71.4%). LC-MS: [MH]⁺ = 251.0.

[00198] 5-Bromo-2-isobutyl-4-methylpyrimidine (**B14.4**): To a suspension of **B14.3** (1.2 g, 4.78 mmol) in dry ether (100 mL), was added isobutylmagnesium bromide (5.74 mL, 5.74 mmol) dropwise at 0 °C. After addition, the mixture was stirred for 2 h at rt, quenched with NH₄Cl solution and extracted with EtOAc (50 mL×3). The organic layer was washed with H₂O (50 mL), brine (50 mL) and dried over Na₂SO₄, then concentrated under vacuum. The crude product was purified by flash chromatography (PE/EtOAc = 10:1) to get the title compound as a colorless oil (1.0 g, 75.6%). LC-MS: [MH]⁺ = 229.1.

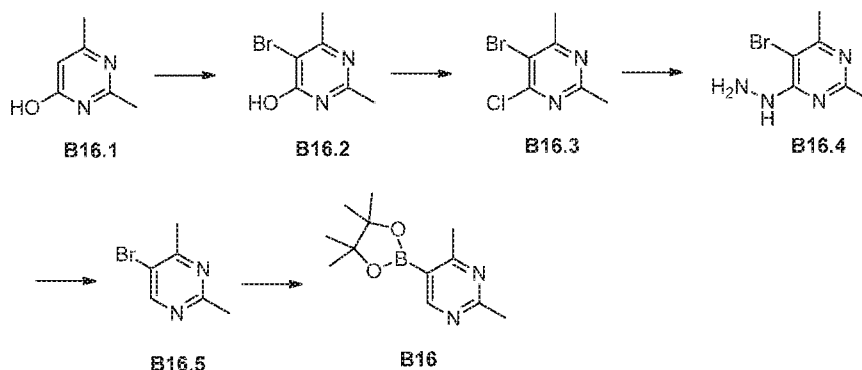
[00199] Intermediate **B14**: The title compound was prepared by a method similar to that of **B2** by replacing **B2.2** with **B14.4**. LC-MS: [MH]⁺ = 277.2.

Intermediate **B15**: *lithium triisopropoxy(3-methylpyridin-2-yl)borate*pyrimidine



[00200] **B15.1** (1 g, 5.81 mmol) was dissolved in THF (5 mL). The resulting solutions were cooled to -78 °C for 10 min at which point n-BuLi/cyclohexane (2M, 3.2mL) was added slowly over 20 min. After maintaining the temperature below -78 °C for 40 min, triisopropylborate was added dropwise over 10 min, then stirred at -78 °C for 1 h, subsequently warmed to rt and stirred at rt for 18 h. Isopropanol was added (1 mL), then the reaction mixture was stirred for 10 min, the allowed to stand without stirring for an additional 10 min. The resulting precipitate was collected by filtration then washed with THF and dried under N₂ for 1.5 h to give the title compound (1.2 g, 72%). LC-MS: [MH]⁺ = 138 (the mass came from the corresponding boronic acid).

Intermediate **B16**: 2,4-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



[00201] 5-Bromo-2,6-dimethylpyrimidin-4-ol (**B16.2**): Bromine (153.4 g, 0.96 mol, 1.2 eq) was added dropwise to a solution of **B16.1** (100 g, 0.8 mol, 1.0 eq) in 1.0 L chloroform. Then the mixture was stirred at 50 °C overnight. After cooling to rt, excess solvent was evaporated and 500 mL of ethyl acetate was added, which was removed under reduced pressure again. This process was repeated three times. The yellow solid was stirred in 100 mL of ethyl acetate for 30 min. at rt. After filtration, the residue was

washed with ethyl acetate (100 mL × 2) to give the title compound (135 g, 82%) as a white solid. LC-MS: [MH]⁺ = 205.

[00202] 5-Bromo-4-chloro-2,6-dimethylpyrimidine (**B16.3**): A mixture of **B16.2** (134 g, 0.66 mol) in 500 mL of POCl₃ was stirred at 110 °C for 18 h. Excess POCl₃ was

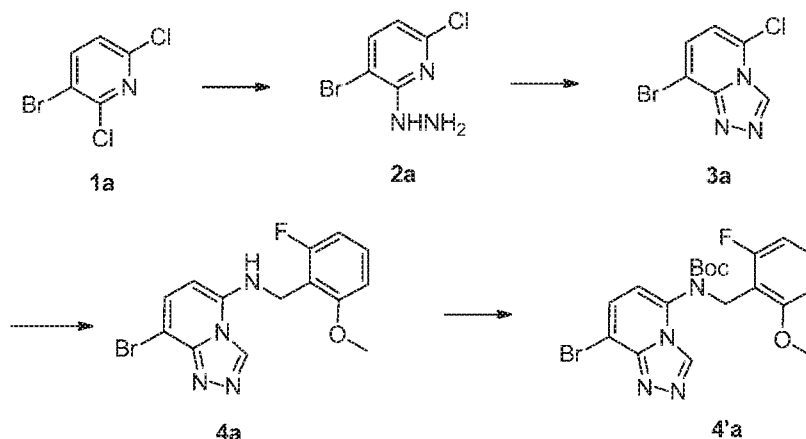
5 removed under vacuum, the residue was poured into 1000 g crushed ice. Then solid NaHCO₃ was added carefully to adjust pH to 8-9. The aqueous was extracted with ethyl acetate (1.5 L × 3), and the combined organic layers were washed with brine (1.0 L × 2), dried over Na₂SO₄, concentrated to give the title compound (71 g, 48%) as a white solid. LC-MS: [MH]⁺ = 223.

10 **[00203]** 5-Bromo-4-hydrazinyl-2,6-dimethylpyrimidine (**B16.4**): To a mixture of Hydrazine hydrate (NH₂NH₂•H₂O, 32 g, 0.64 mol, 98%) in 350 mL ethanol was added a solution of **B16.3** (70 g, 0.32 mol) in 350 mL methanol dropwise at 0 °C. The reaction mixture was stirred at rt for 16 h. The solvent was removed by reduced pressure, the residue was diluted with 500 mL of water, extracted with CHCl₃ (500 mL × 3). The
15 combined organic layers were washed with 500 mL brine, dried over Na₂SO₄, and concentrated to give the title compound (63 g, 91%) as a yellow solid. LC-MS: [MH]⁺ = 219.

[00204] 5-Bromo-2,4-dimethylpyrimidine (**B16.5**): To a suspension of MnO₂ (96 g, 1.1 mol) in 1.0 L CHCl₃ was added a solution of **B16.4** (47 g, 0.22 mol) in 1.0 L CHCl₃
20 dropwise at 0 °C. The mixture was stirred for 2 h at rt. After filtration and concentration, the residue was purified on 100-200 mesh silica gel column (PE:EA = 100:0 to 50:50) to give the title compound (30 g, 73%) as a yellow solid. LC-MS: [MH]⁺ = 189.

[00205] Intermediate **B16**: A mixture of **B16.5** (12 g, 64 mmol), bis(pinacolato)diboron (22.8 g, 89.6 mmol, 1.4 eq), KOAc (18.8 g, 192 mmol, 3.0 eq), and Pd(dppf)Cl₂ (2.34 g, 3.2 mmol) in 200 mL of anhydrous dioxane was heated at 90 °C and stirred for 4 h under N₂. The solvent was removed under reduced pressure, the residue was diluted with 300 mL mixed solvent (PE:EtOAc = 4:1), filtered and concentrated. The crude product was purified by flash column chromatography (PE:EtOAc = 2:1 to 1:1) to give the title
25 compound (10 g, 66%) as a yellow oil. LC-MS: [MH]⁺ = 235.

30 Intermediate **4'a**: *tert*-Butyl (8-bromo-[1,2,4]triazolo[4,3-a]pyridin-5-yl)(2-fluoro-6-methoxybenzyl)carbamate



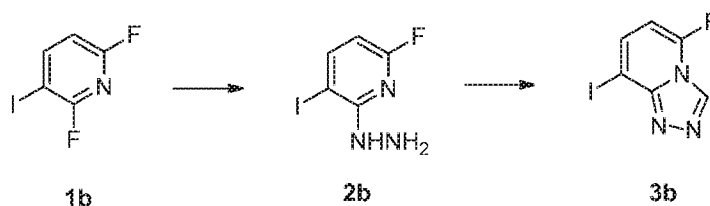
[00206] 3-Bromo-6-chloro-2-hydrazinylpyridine (**2a**): A mixture of **1a** (4 g, 17.63 mmol) and hydrazine hydrate (4 mL, 98%) in EtOH (80 mL) was heated 80 °C for 18 h. After cooling, the solid was filtered and washed with EtOH (10 mL). The solid was dried under vacuum to give the title compound (2.1 g, 44%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 4.30 (s, 2H), 6.57 (d, 1H), 7.73 (d, 1H), 7.84 (s, 1H). LC-MS: [MH]⁺ = 222.

[00207] 8-Bromo-5-chloro-[1,2,4]triazolo[4,3-*a*]pyridine (**3a**): A mixture of **2a** (2.1 g, 9.44 mmol) in trimethoxymethane (15 mL, 137 mmol) was heated at 110 °C for 1.5 h. After cooling, the solid was filtered and washed with PE, then the solid was dried under vacuum to give the title compound (1.5 g, 68%). LC-MS: [MH]⁺ = 232.

[00208] 8-Bromo-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine (**4a**): To a solution of **3a** (1 g, 4.33 mmol) in EtOH (0.5 mL) was added (2-fluoro-6-methoxyphenyl)methanamine (1.5 g, 9.68 mmol) and the mixture was stirred at 85 °C for 8 h. 5 mL of EtOAc was added and filtered to give a white solid, which was purified by flash chromatography to afford the title compound (0.45 g, 30%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 3.88 (s, 3H), 4.45 (s, 2H), 5.98 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.36 - 7.45 (m, 1H), 7.60 (d, 1H), 9.55 (s, 1H). LC-MS: [MH]⁺ = 351.

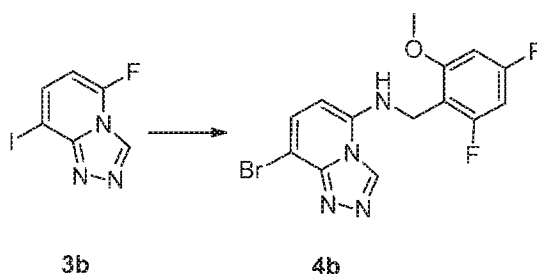
[00209] Intermediate **4'a**: The mixture of **4a** (4.9 g, 14.0 mmol), (Boc)₂O (6.1 g, 28.0 mmol), DIEA (5.4 g, 42.0 mmol) and DMAP (340 mg, 2.8 mmol) in MeCN (100 mL) was degassed with N₂ and then stirred at 90 °C for 18 hours. The reaction mixture was poured into saturated NaHCO₃ solution, extracted with EA (150 mL × 3), washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (PE : EA:OAc = 5 : 1 to 1 : 2) to give the title compound (5.8 g, 92%) as a yellow solid. LCMS: [MH]⁺ = 453.0.

[00210] Intermediates **4b** and **4c** were prepared using similar procedure as that of **4a** and with modification from their respective Intermediate **3b** and **3c**. For example Intermediate **3b**: 5-fluoro-8-iodo-[1,2,4]triazolo[4,3-a]pyridine was prepared as follows:

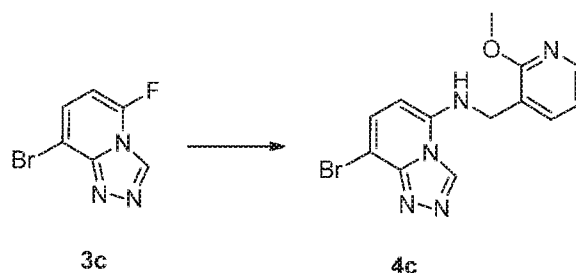


5 **[00211]** 6-Fluoro-2-hydrazinyl-3-iodopyridine (**2b**): To a mixture of **1b** (3.5 g, 12.78 mmol) in EtOH (28 mL) was added hydrazine hydrate (3.5 mL). The mixture was heated at 30 °C for 4 h, then solid was collected by filtering and washed with cold EtOH. The crude product was recrystallized with EtOH to afford the title compound (900 mg, 28%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 6.14 (dd, 1 H), 7.99 (t, 1 H). LC-MS: [MH]⁺ = 254.

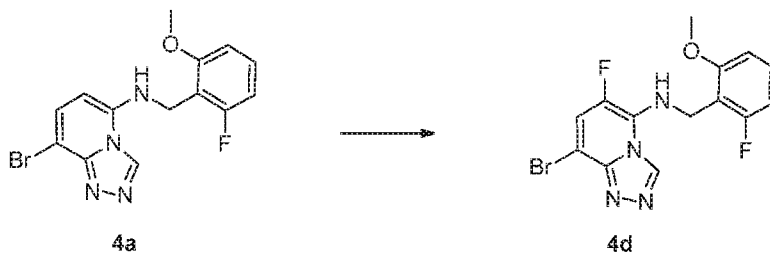
10 **[00212]** Intermediate **3b**: A mixture of **2b** (840 mg, 3.32 mmol) in trimethoxymethane (0.8 mL) was heated at 100 °C for 80 min. Then to the mixture was added a drop of TFA at 100 °C. After stirring at 100 °C for 10 min, The mixture was concentrated to remove the trimethoxymethane and TFA to give the title compound (830 mg, 95%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 6.74 (dd, 1H), 7.97 (dd, 1H), 9.65 (s, 1H). LC-MS: [MH]⁺ = 264.



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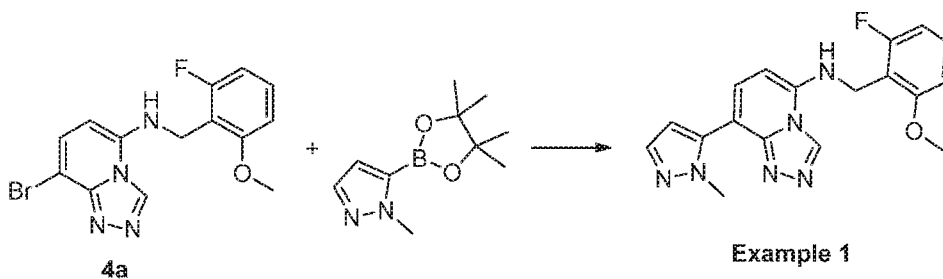
Preparation of 6-fluoronated Intermediate **4d**: 8-Bromo-6-fluoro-*N*-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine (**4d**)



[00213] A mixture of **4a** (540 mg, 1.6 mmol) in MeOH (24 mL) and MeCN (36 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate (544 mg, 1.6 mmol) slowly within 5 min. Then the mixture was stirred at rt for 10 min. The solvent was removed and the residue was purified by Prep-TLC (DCM / MeOH = 10/1) to give the title compound as a yellow solid (150 mg, 26%). ¹H-NMR (500 MHz, DMSO-*d*₆) δ ppm 3.68 (s, 3H), 4.62 (d, 2H), 6.78 - 6.86 (m, 3H), 7.31 (dd, 1H), 7.92 (d, 1H), 9.55 (s, 1H). LC-MS: [MH]⁺ = 369.1.

Example 1

N-(2-Fluoro-6-methoxybenzyl)-8-(1-methyl-1H-pyrazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



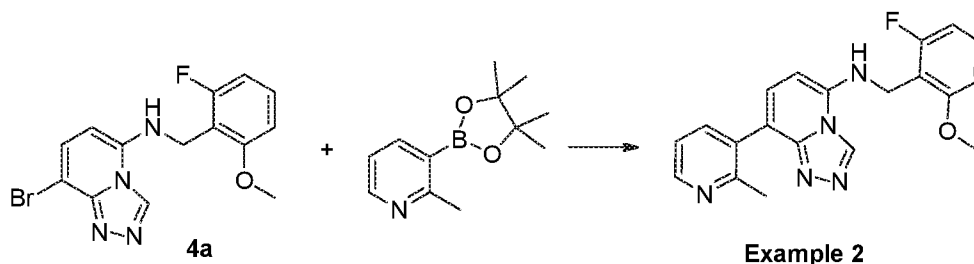
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[00214] To a solution of **4a** (50 mg, 0.142 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (59.2 mg, 0.285 mmol) and NaHCO₃ (35.9 mg, 0.427 mmol) in dioxane (2 mL) and H₂O (1 mL) was added PdCl₂(dppf) (15.63 mg, 0.021 mmol) under N₂. The reaction mixture was heated at 90 °C for 1 h. The reaction mixture was concentrated and purified by prep-HPLC to afford the title compound (22 mg, 35%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 3.79 (s, 3H), 3.90 (s, 3H), 4.55 (d, 2H), 6.34 - 6.36 (m, 1H), 6.50 (s, 1H), 6.88 - 6.93 (t, 1H), 6.98 (d, 1H), 7.41 (dd, 1H), 7.53 (s, 1H), 7.62 - 7.64 (m, 1H), 8.02 (s, 1H), 9.62 (s, 1H). LC-MS: [MH]⁺ = 353.1.

20

Example 2

N-(2-Fluoro-6-methoxybenzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



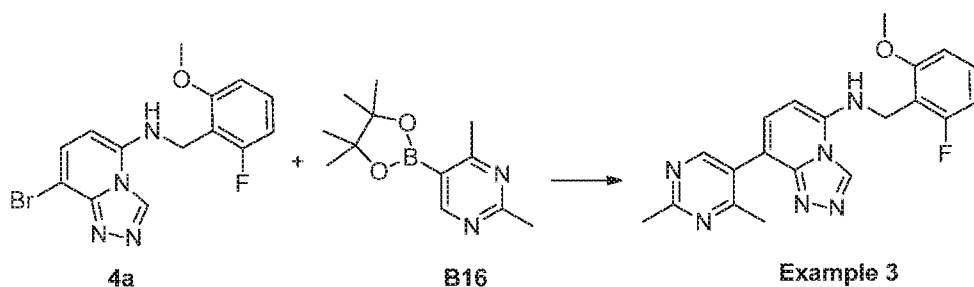
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[00215] A mixture of **4a** (8 g, 22.78 mmol), 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.99 g, 31.9 mmol), PdCl₂(dppf) (1.667 g, 2.278 mmol) and Na₂CO₃ (7.24 g, 68.3 mmol) in dioxane (100 mL) and H₂O (50 mL) was placed under N₂, sealed and heated at 120 °C for 5 h with oil-bath. The reaction mixture was cooled to rt, extracted with EA (100mL×3). The organic extracts were combined, dried over Na₂SO₄. The residue was purified by column chromatography (eluted with DCM:MeOH, 100:3 to 100:10, column: 120g silica gel) to give the title compound (5.8 g, 70%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3H), 3.89 (s, 3H), 4.50 (s, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.27 - 7.33 (m, 2H), 7.38 - 7.44 (m, 1H), 7.52 (s, 1H), 7.73 (dd, 1H), 8.48 (dd, 1H), 9.50 (s, 1H). LC-MS: [MH]⁺ = 364.1.

15

Example 3

8-(2,4-Dimethylpyrimidin-5-yl)-*N*-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



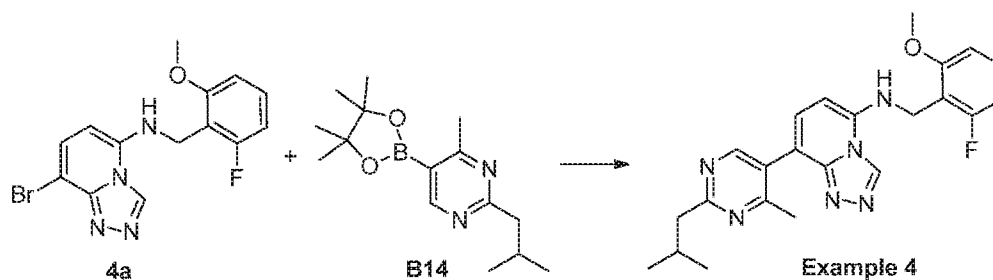
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[00216] To a stirred suspension of **B16** (42 g, 120 mmol), **4a** (56.2 g, 240 mmol) and NaHCO₃ (30.2 g, 360 mmol) in a mixed solution of 1,4-dioxane (500 mL) and H₂O (250

mL) was added Pd(dppf)Cl₂ (8.8 g, 12 mmol) under N₂. After stirring at 110 °C for 1 h, the mixture was evaporated under vacuum to remove 1,4-dioxane, diluted with DCM/MeOH (600 mL, v/v = 10/1) and filtered. The filter cake was slurried successively with water (600 mL) at rt, and MeOH (1000 mL) at 70 °C for 30 min. The resulting solid
 5 was dissolved in MeOH (2000 mL) under reflux, and filtered through celite and immediately, concentrated. The residue was diluted with acetone (200 mL), heated at 50 °C and stirred for 2 h. After cooling to rt, the mixture was filtered to give the title compound (19 g, 42%) as a white solid. ¹H NMR (500 MHz, DMSO) δ 2.35 (s, 3H), 2.63 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.15 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.30 - 7.45 (m, 2H),
 10 7.58 (t, 1H), 8.58 (s, 1H), 9.51 (s, 1H). LC-MS : [MH]⁺ = 379.1.

Example 4

N-(2-Fluoro-6-methoxybenzyl)-8-(2-isobutyl-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3a]-pyridin-5-amine



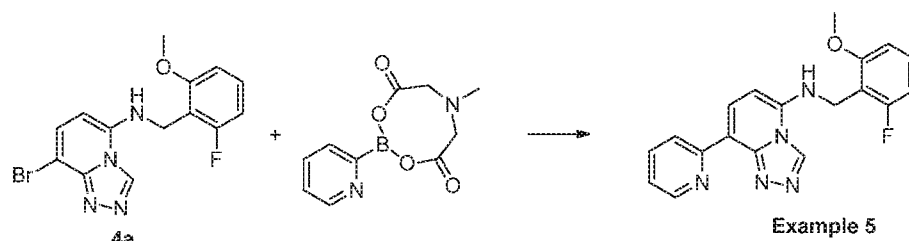
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[00217] A mixture of **4a** (381.5 mg, 1.09 mmol), **B14** (601.7 mg, 2.18 mmol), PdCl₂(dppf)·CH₂Cl₂ (100 mg, 0.11 mmol) and NaHCO₃ (275 mg, 3.27 mmol) in dioxane/H₂O (30 mL/15 mL) was purged with N₂, warmed to 100 °C and stirred for 2 h.
 20 The resulting mixture was cooled to rt and filtered. The filtrate was purified by prep-HPLC to afford the title compound (230 mg, 50.2%) as an off-yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.95 (d, 2H), 2.24 - 2.29 (m, 1H), 2.37 (s, 3H), 2.75 (d, 2H), 3.89 (s, 3H), 4.50 (s, 2H), 6.15 (d, 1H), 6.87 - 6.98 (m, 2H), 7.37 - 7.42 (m, 2H), 7.59 (s, 1H), 8.61 (s, 1H), 9.52 (s, 1H). LC-MS: [MH]⁺ = 421.3.

25

Example 5

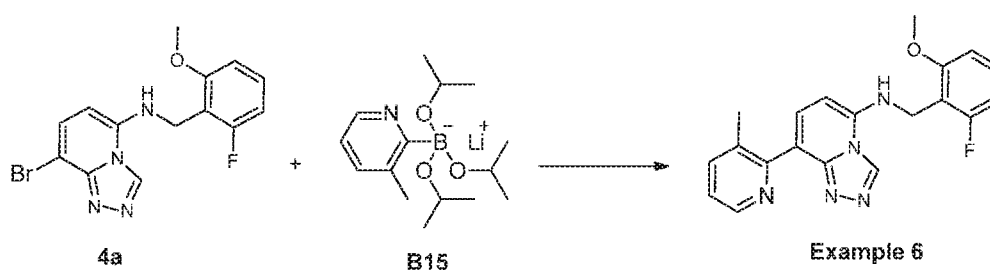
N-(2-Fluoro-6-methoxybenzyl)-8-(pyridin-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



- [00218]** To a mixture of **4a** (30 mg, 0.085 mmol), 6-methyl-2-(pyridin-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (40.0 mg, 0.171 mmol), 2,2'-azanedioldiethanol (13.47 mg, 0.128 mmol) and X-Phos Precatalyst (Chloro(2-dicyclohexylphosphino-2',4',6'-tri-
 5 propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct) (3.16 mg, 4.27 μ mol) in DMF (1.5 mL) was added K_3PO_4 (109 mg, 0.513 mmol) and $Cu(OAc)_2$ (11.64 mg, 0.064 mmol) quickly. Then the mixture was purged with N_2 for 30 s. The reaction mixture was heated at 120 $^{\circ}C$ for 3 h. After cooling to rt, The mixture was diluted with H_2O (10 mL), extracted with EA (20 mL \times 3), and EA layer was
 10 concentrated. The residue was purified with acidic Prep-HPLC to give the title compound (4.2 mg, 10%) as a trifluoroacetate. 1H -NMR (400 MHz, $DMSO-d_6$) δ ppm 3.90 (s, 3H), 4.61 (d, 2H), 6.49 (d, 1H), 6.89 - 6.95 (m, 1H), 6.99 (d, 1H), 7.39 - 7.47 (m, 2H), 8.03 (s, 1H), 8.59 (d, 1H), 8.72 (s, 2H), 9.69 (s, 1H). LC-MS: $[MH]^+ = 350.0$.

15 Example 6

N-(2-Fluoro-6-methoxybenzyl)-8-(3-methylpyridin-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine

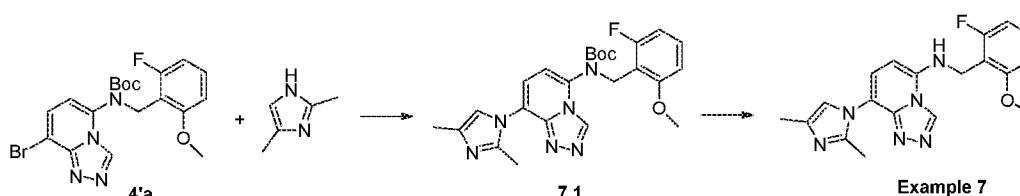


- [00219]** To DMF (2 mL), **B15** (65.4 mg, 0.228 mmol), $CuCl$ (3.38 mg, 0.034 mmol) and $ZnCl_2$ (15.52 mg, 0.114 mmol) were added in this order and degassed for 5 min. Cs_2CO_3 (74.2 mg, 0.228 mmol) and **4a** (40 mg, 0.114 mmol) were added sequentially and the solution was degassed for an additional 5 min. $PdCl_2(dppf)$ (4.17 mg, 5.70

μmol) was then added. The reaction mixture was heated at 120 °C for 3 h. The reaction mixture was cooled to rt, brine (10 mL) and EA (10 mL) were added, and filtered. The resulting mixture was extracted with EA (20 mL × 3). The organic layers were combined, dried (Na₂SO₄), filtered and concentrated. The residue was purified by basic prep-HPLC to give the title compound (2.5 mg, 6%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 (s, 3H) 3.90 (s, 3H), 4.52 (s, 2H), 6.17 (d, 1H), 6.91 (t, 1H), 6.98 (d, 1H), 7.32 - 7.45 (m, 3H), 7.72 (d, 1H), 8.48 (d, 1H), 9.50 (s, 1H). LCMS: [MH]⁺ = 364.1.

Example 7

8-(2,4-Dimethyl-1H-imidazol-1-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine

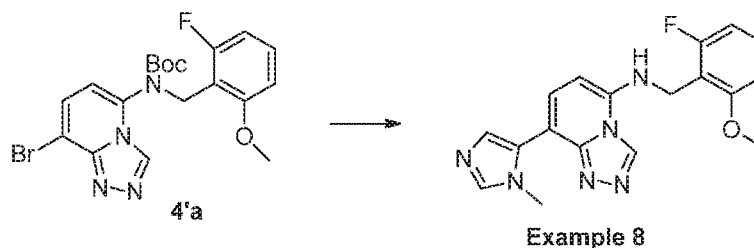


[00220] *tert*-butyl 8-(2,4-Dimethyl-1H-imidazol-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-yl(2-fluoro-6-methoxybenzyl)carbamate (**7.1**): A suspension of Pd₂(dba)₃ (18 mg, 0.02 mmol) and Me₄-*t*-BuXPhos (di-*tert*-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphane) (19.2 mg, 0.04 mmol) in 1.0 mL anhydrous dioxane was heated at 120 °C for 10 min under N₂. Then it was transferred into a stirred suspension of **4'a** (90 mg, 0.2 mmol), 2,4-dimethyl-1H-imidazole (85 mg, 0.88 mmol) and K₃PO₄ (110 mg, 0.52 mmol) in 2.0 mL anhydrous Dioxane. The reaction mixture was stirred at 120 °C overnight, then evaporated under reduced pressure to give a black residue, which was purified by flash chromatography (silica gel, DCM:CH₃OH=0-25%, UV214&UV254) to give the title compound (27 mg, 15%) as a yellow oil. LC-MS: [MH]⁺ = 467.2.

[00221] **Example 7**: A solution of **7.1** (27 mg, 0.06 mmol) in 6 mL 1,1,1,3,3,3-hexafluoropropan-2-ol was heated in a Biotage microwave reactor at 120 °C for 1 h. The mixture was evaporated under vacuum to give a yellow oil, which was purified by Pre-HPLC to give the title compound (9 mg, 42%) as a white solid. ¹H NMR (500 MHz, DMSO) δ ppm 2.06 – 2.16 (m, 6H), 3.88 (s, 3H), 4.49 (d, 2H), 6.05 (d, 1H), 6.90 (dd, 2H), 6.96 (d, 1H), 7.40 (dd, 2H), 7.65 (t, 1H), 9.54 (s, 1H). LC-MS: [MH]⁺ = 367.2.

Example 8

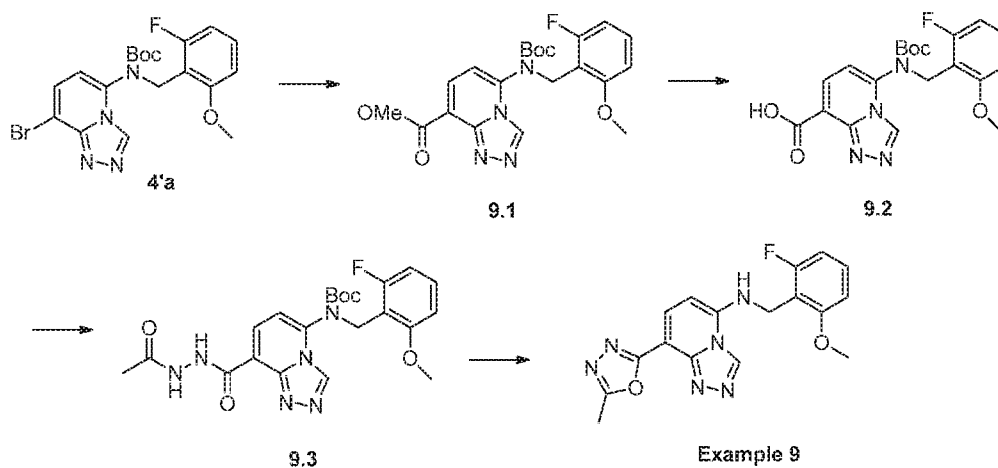
(*N*-(2-Fluoro-6-methoxybenzyl)-8-(1-methyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



- 5 **[00222]** A mixture of **4'a** (90 mg, 0.2 mmol), 1-methyl-1*H*-imidazole (38 mg, 0.4 mmol), KOAc (60 mg, 0.6 mmol) and Pd (OAc)₂ (15 mg, 0.062 mmol) in DMAc (0.5 mL) was purged with N₂ for 1 min. Then the sealed reaction vial was stirred at 150 °C for 5 h. The mixture was purified successively with prep-TLC (DCM/MeOH=10/1) and prep-HPLC (MeCN:H₂O: NH₄HCO₃=1/1/0.05) to yield the title compound (10 mg, 14%) as a white solid. ¹H-NMR (500 MHz, DMSO-*d*₆) δ ppm 3.64 (s, 3H), 3.88 (s, 3H), 4.49 (d, 2H), 6.10 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.13 (s, 1H), 7.35 (d, 1H), 7.40 (dd, 1H), 7.54 (t, 1H), 7.72 (s, 1H), 9.50 (s, 1H). LC-MS: [MH]⁺ = 352.8.
- 10

Example 9

- 15 *N*-(2-Fluoro-6-methoxybenzyl)-8-(5-methyl-1,3,4-oxadiazol-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



[00223] *Methyl 5-(tert-butoxycarbonyl(2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridine-8 carboxylate (9.1)*: A mixture of **4'a** (4.8 g, 10.6 mmol), TEA (7.09 g, 70.2 mmol), and PdCl₂(dppf) (288 mg, 1.06 mmol) in MeOH (20 mL) was placed under 15 atm CO and stirred at 85 °C for 12 h. The resulting mixture was cooled to rt and poured into saturated NaHCO₃ solution. The mixture was extracted with EtOAc (100 mL x 3), washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (PE : EA = 1 : 1) to give 4.0 g (87 %) of the title compound as a gray solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.20 (s, 9H), 3.38 (s, 3H), 3.93 (s, 3H), 4.88 (d, 1H), 5.08 (d, 1H), 6.69 – 6.72 (m, 2H), 7.00 (s, 1H), 7.21 -7.26 (dd, 1H), 8.05 (d, 1H), 8.96 (s, 1H). LC-MS: [MH]⁺ = 431.

[00224] *5-(tert-Butoxycarbonyl(2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridine-8-carboxylic acid (9.2)*: A mixture of **9.1** (3.0 g, 6.98 mmol) and LiOH·H₂O (1.17 g, 27.9 mmol) in a mixed solvent of MeOH/THF/H₂O (10 mL/10 mL/10 mL) was stirred at rt for 2 h. The resulting mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine, dried (Na₂SO₄) and filtered. The filtrate was concentrated to give the title compound (2.5 g, 86%) as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.30 (s, 9H), 3.41 (s, 3H), 4.82 (d, 1H), 5.07 (d, 1H), 6.69 – 6.72 (m, 2H), 6.97 (s, 1H), 7.22 -7.26 (dd, 1H), 7.99 (d, 1H), 8.92 (s, 1H). LC-MS: [MH]⁺ = 417.

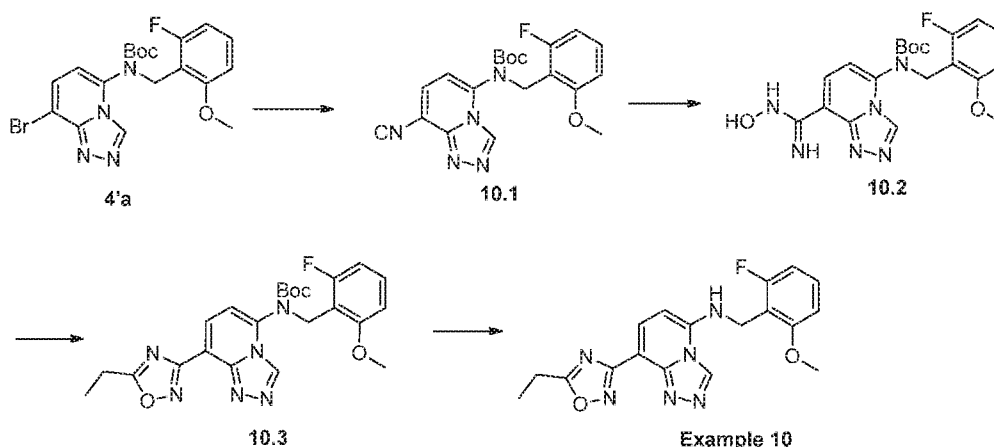
[00225] *tert-butyl 8-(2-Acetylhydrazinecarbonyl)-[1,2,4]triazolo[4,3-a]pyridin-5-yl(2-fluoro-6-methoxybenzyl)carbamate (9.3)*: To a solution of **9.2** (200 mg, 0.48 mmol) and DIEA (124 mg, 0.96 mmol) in DCM (10 mL) was added isopropyl carbonochloridate and stirred (72 mg, 0.53 mmol). The resulting mixture was stirred at rt for 1 h, followed by addition of acetohydrazide (53 mg, 0.72 mmol). The reaction mixture was then stirred at rt for 18 h, then poured into NaHCO₃ (Sat.) solution, and extracted with EtOAc (50 mL x 3). The organic extracts were combined and washed with brine, dried over Na₂SO₄, filtered and concentrated to give the title compound (220 mg, 92 %), which was used in next step without further purification. LC-MS: [MH]⁺ = 473.

[00226] **Example 9**: The solution of **13** (100 mg, 0.21 mmol) in POCl₃ (5 mL) was stirred at 110 °C for 3 h. After cooling to rt, the mixture was concentrated, poured in to ice, and neutralized with saturated NaHCO₃ solution with caution. The mixture was extracted with EA (50 mL x 3). The organic layers were combined and washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC (MeCN/H₂O (10 mM NH₄HCO₃)) to give the title compound (16 mg, 22%) as a white solid. ¹H NMR (500 MHz, DMSO) δ ppm 2.59 (s, 3H), 3.88 (s, 3H), 4.56 (s, 2H), 6.25 (d,

1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.41 (dd, 1H), 8.04 (d, 1H), 8.17 (s, 1H), 9.61 (s, 1H). LC-MS: $[MH]^+ = 355.1$.

Example 10

- 5 **8-(5-Ethyl-1,2,4-oxadiazol-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine**



[00227] *tert-Butyl 8-cyano-[1,2,4]triazolo[4,3-a]pyridin-5-yl(2-fluoro-6-methoxybenzyl) carbamate (10.1)*: A mixture of **4'a** (500 mg, 1.1 mmol), $ZnCN_2$ (1.28 g, 11.0 mmol) and
 10 $Pd(PPh_3)_4$ (254 mg, 0.22 mmol) in DMF (10 mL) was stirred at 120 °C for 3 h. The reaction mixture was filtered and purified by prep-HPLC (MeCN/H₂O (10 mM NH_4HCO_3)) to give the title compound (140 mg, 32%) as a white solid. LC-MS: $[MH]^+ = 398$.

[00228] *tert-Butyl 2-fluoro-6-methoxybenzyl(8-(N-hydroxycarbamimidoyl)-[1,2,4]triazolo[4,3-a]pyridin-5-yl)carbamate (10.2)*: A mixture of **10.1** (140 mg, 0.35 mmol),
 15 hydroxylamine hydrochloride (73 mg, 1.06 mmol) and DIEA (137 mg, 1.06 mmol) in EtOH (10 mL) was stirred at 90 °C for 18 h. The resulting mixture was cooled to RT, concentrated, added saturated $NaHCO_3$ solution, and then extracted with DCM (50 mL x 3). The organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the title compound (120 mg, 80%). LC-
 20 MS: $[MH]^+ = 431$.

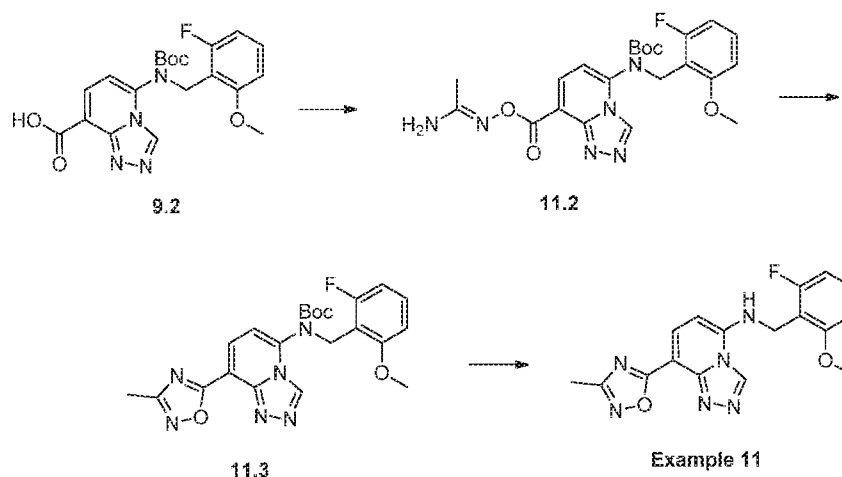
[00229] *tert-butyl 8-(5-Ethyl-1,2,4-oxadiazol-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-yl(2-fluoro-6-methoxybenzyl)carbamate (10.3)*: A mixture of **10.2** (100 mg, 0.23 mmol) and propionic anhydride (90 mg, 0.698 mmol) in toluene (2 mL) was stirred at 125 °C for 18 h. The resulting mixture was cooled to RT, poured into saturated $NaHCO_3$ solution, and
 25 extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with

brine, dried over Na₂SO₄ and concentrated to give the title compound (130 mg,) which is used in next step without further purification. LC-MS: [MH]⁺ = 469.

[00230] Example 10: A solution of **10.3** (130 mg, 0.28 mmol) in HCl/dioxane (10 mL, 4M) was stirred at rt for 4 h. The mixture was concentrated, quenched with saturated NaHCO₃ solution, then extracted with EA (50 mL x 3). The organic layers were combined and washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC (MeCN/H₂O (10 mM NH₄HCO₃)) to give the title compound (4 mg, 4%) as a white solid. ¹H NMR (500 MHz, DMSO) δ ppm 1.35 (t, 3H), 3.00 (q, 2H), 3.87 (d, 3H), , 4.55 (d, 2H), 6.24 (d, 1H 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 8.03 (t, , 1H), (d, 1H), 8.09 (d, 1H), 9.57 (s, 1H). LC-MS: [MH]⁺ = 369.

Example 11

N-(2-Fluoro-6-methoxybenzyl)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-amine



15

[00231] (E)-tert-Butyl 8-((1-aminoethylideneaminoxy)carbonyl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-yl(2-fluoro-6-methoxybenzyl)carbamate (11.2**):** A mixture of **9.2** (250 mg, 0.6 mmol) and CDI (116 mg, 0.72 mmol) in DCM (15mL) was stirred at rt for 2 h. (Z)-N'-hydroxyacetimidamide (133 mg, 1.80 mmol) was added and stirred at rt for 18 h. The reaction mixture was poured into saturated NaHCO₃ solution, and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated to give the title compound (260 mg, 93%) as a yellow oil, which was used in next without further purification. LC-MS: [MH]⁺ = 473.

[00232] tert-Butyl 2-fluoro-6-methoxybenzyl(8-(3-methyl-1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-5-yl)carbamate (11.3**):** A mixture of **11.2** (100 mg, 0.21 mmol)

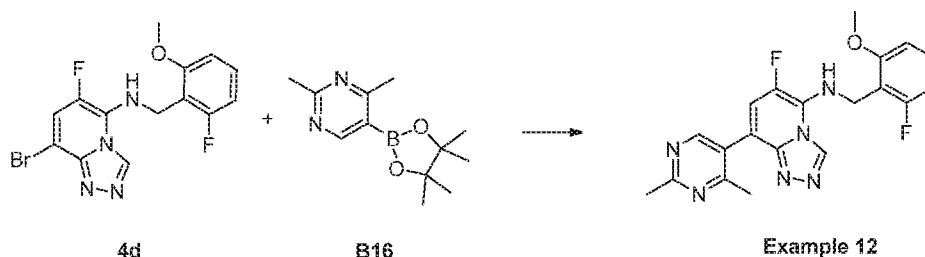
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and TBAF (0.21 mL, 0.21 mmol) in MeCN (5 mL) was stirred at rt for 2 h. The reaction mixture was poured into saturated NaHCO₃ solution and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (100 g) as a yellow oil which was used in next step without further purification. LC-MS: [MH]⁺ = 455.

[00233] Example 11: A solution of **11.3** (100 mg, 0.22 mmol) in HCl in dioxane (10 mL, 4M) was stirred in at rt for 4 h. The mixture was concentrated and quenched with saturated NaHCO₃ solution, and extracted with EA (50 mL x 3). The organic layers were combined, washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by prep-HPLC (MeCN/H₂O (10 mM NH₄HCO₃)) to give the title compound (25 mg, 32%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.39 (s, 3H), 3.88 (s, 3H), 4.59 (s, 2H), 6.30 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.41 (dd, 1H), 8.24 (d, 1H), 8.44 (s, 1H), 9.61 (s, 1H). LCMS: [MH]⁺ = 355.1.

Example 12

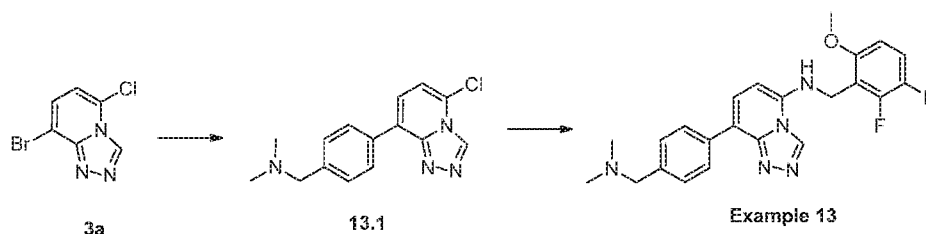
8-Bromo-6-fluoro-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine



[00234] PdCl₂(dppf) (15 mg, 0.021 mmol) was added to a stirred suspension of **B16** (41 mg, 0.18 mmol), **4d** (50 mg, 0.14 mmol) and NaHCO₃ (36 mg, 0.42 mmol) in a mixed solution of 1,4-dioxane (2 mL) and H₂O (1 mL). The mixture was stirred at 110°C for 40 min in a sealed tube under nitrogen, and cooled to rt. The resulting mixture was concentrated and purified by prep-HPLC (MeCN : H₂O : NH₄HCO₃ = 1/1/0.05) to give the title compound (27 mg, 49%) as white a solid. ¹H-NMR (500 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3H), 2.65 (s, 3H), 3.71 (s, 3H), 4.71 (d, 2H), 6.91 - 6.81 (m, 3H), 7.34 (dd, 1H), 7.62 (d, 1H), 8.63 (s, 1H), 9.52 (s, 1H). LC-MS [MH]⁺ = 397.1.

Example 13

N-(2,3-Difluoro-6-methoxybenzyl)-8-(4-((dimethylamino)methyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine



1-(4-(5-Chloro-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)-N,N-dimethylmethanamine (13.1)

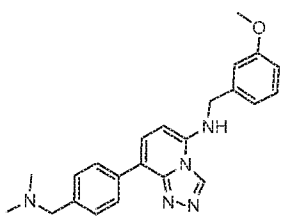
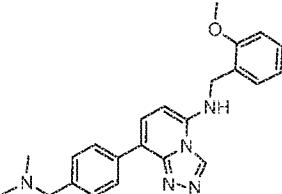
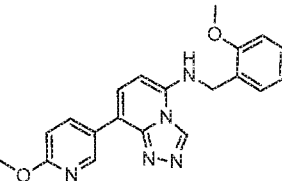
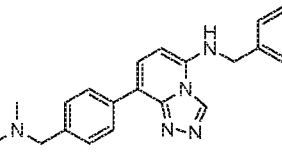
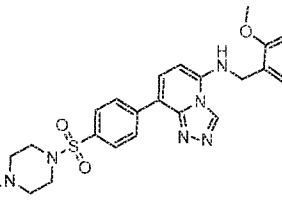
A mixture of **3a** (800 mg, 3.44 mmol), corresponding boronic acid (742 mg (hydrochloride), 3.44 mmol), PdCl₂(dppf) (20 mg, 0.027 mmol) and NaHCO₃ (1156 mg, 13.77 mmol) in dioxane (8 mL) and H₂O (4 mL) was purged with N₂, then heated at 95 °C for 6 h with oil bath. The mixture was concentrated to remove the solvent, the residue was purified by flash chromatograph to give the title compound (800 mg, 81%). LC-MS: [MH]⁺ = 286.9.

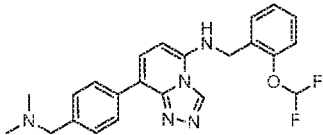
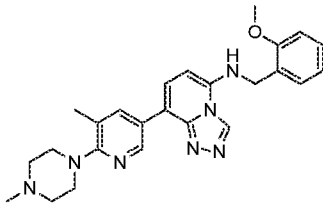
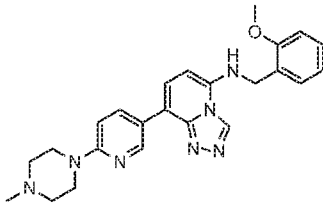
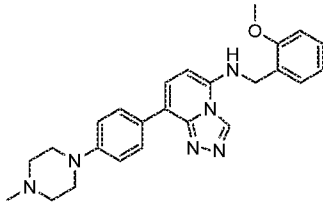
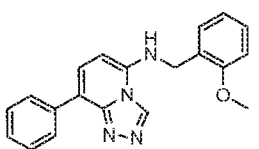
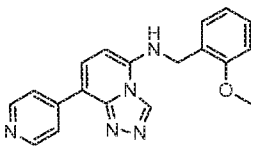
N-(2,3-Difluoro-6-methoxybenzyl)-8-(4-((dimethylamino)methyl)phenyl)-[1,2,4]triazolo

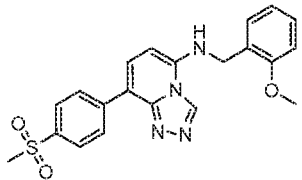
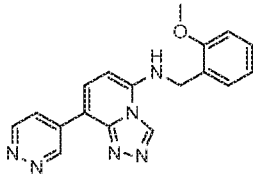
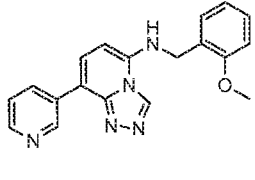
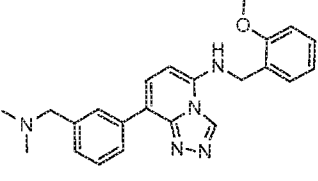
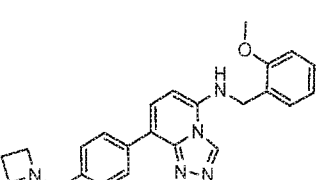
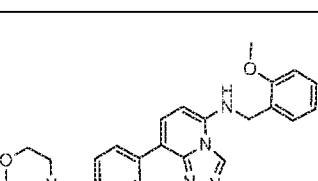
[4,3-a]pyridin-5-amine (13): To a solution of **13.1** (50 mg, 0.17 mmol), **A2** (61 mg, 0.28 mmol) and Cs₂CO₃ (165 mg, 0.51 mmol), Pd₂(dba)₃ (10 mg, 0.016 mmol), Mix-phos (20 mg, anotation: Mix-phos is a mixture of X-phos, S-phos, and Xant-phos with the mass ratio 1:1:1) in dioxane (2 mL) under N₂. The reaction mixture was heated at 120 °C for 2 h, concentrated and purified by Prep-HPLC to afford the title compound (10 mg, 14%) as a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 (s, 6H), 3.42(s, 2H), 3.87 (s, 3H), 4.54 (d, 2H), 6.14 (d, 1H), 6.92-6.96 (m, 1H), 7.36 (d, 2H), 7.43 - 7.45 (m, 1H), 7.49 - 7.52 (m, 1H), 7.66 (d, 1H), 8.09(d, 2H), 9.47 (s, 1H). LCMS: [MH]⁺ = 424.7.

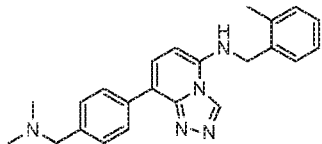
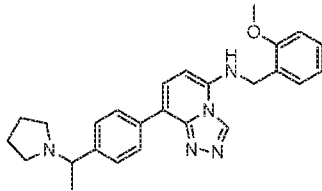
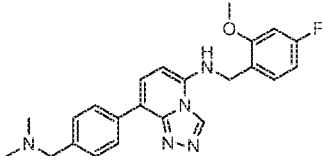
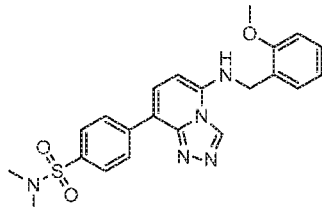
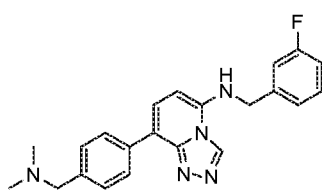
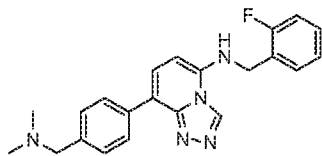
[00235] The following compounds, as identified in Table 2, were prepared using the general procedures as well as the procedures from the examples described above with the appropriate starting materials and reagents.

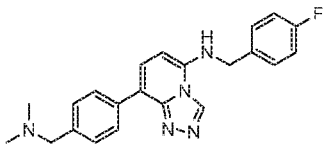
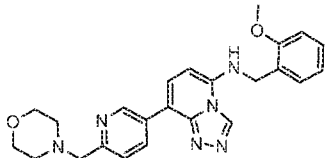
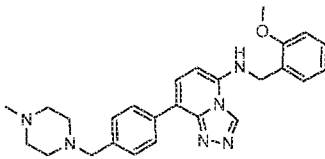
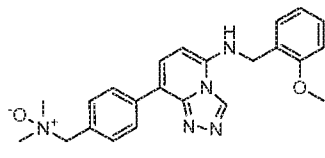
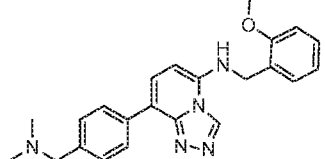
Table 2

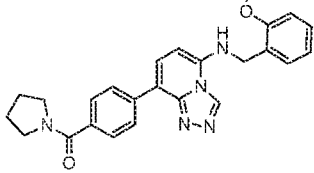
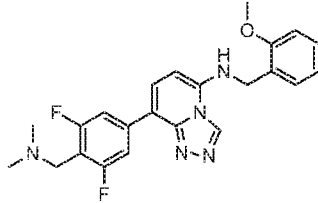
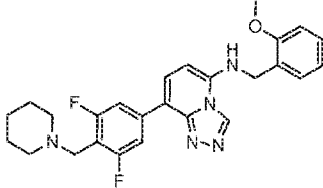
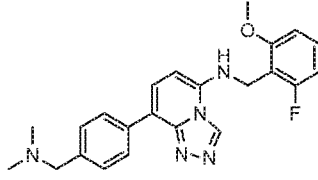
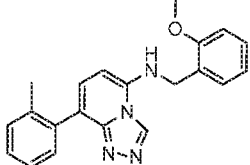
Ex #	Structure	¹ H-NMR (400 MHz, DMSO-d ₆) or otherwise indicated / LC-MS Data
14		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.22 (s, 6H), 3.45 (s, 2H), 3.80 (s, 3H), 4.67 (s, 2H), 6.04 (d, 1H), 6.88 (d, 1H), 7.07 - 7.12 (m, 2H), 7.30 (t, 1H), 7.40 (d, 2H), 7.59 (d, 1H), 8.18 (d, 2H), 9.31 (s, 1H). / [MH] ⁺ = 388
15		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.22 (s, 6H), 3.45 (s, 2H), 3.93 (s, 3H), 4.65 (s, 2H), 6.04 (d, 1H), 6.93 (t, 1H), 7.06 (d, 1H), 7.30 (d, 1H), 7.43 (d, 1H), 7.40 (d, 2H), 7.60 (d, 1H), 8.18 (d, 2H), 9.32 (s, 1H). / [MH] ⁺ = 388
16		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 3.93 (s, 3H), 3.95 (s, 3H), 4.65 (s, 2H), 6.04 (d, 1H), 6.86 (d, 1H), 6.92 - 6.97 (m, 1H), 7.07 (d, 1H), 7.31 (t, 1H), 7.43 (d, 1H), 7.58 (d, 1H), 8.50 (dd, 1H), 8.99 (d, 1H), 9.31 (s, 1H). / [MH] ⁺ = 362
17		δ ppm 2.17 (s, 6H), 3.41 (s, 2H), 4.61 (s, 2H), 5.94 (d, 1H), 7.29 - 7.39 (m, 5H), 7.46 (d, 2H), 7.58 (d, 1H), 8.00 (s, 1H), 8.08 (d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 358
18		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.20 (s, 3H), 2.44 (t, 4H), 3.04 (s, 4H), 3.93 (s, 3H), 4.68 (s, 2H), 6.12 (d, 1H), 6.94 (t, 1H), 7.07 (d, 1H), 7.32 (t, 1H), 7.44 (d, 1H), 7.80 - 7.86 (m, 3H), 8.56 (d, 2H), 9.36 (s, 1H). / [MH] ⁺ = 493

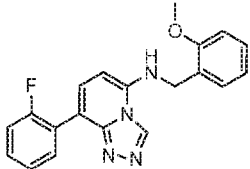
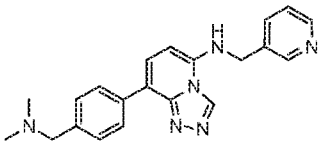
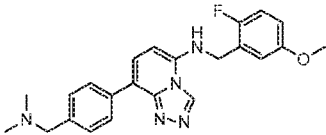
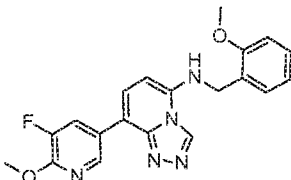
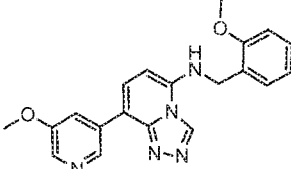
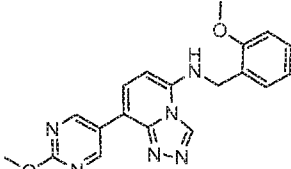
19		δ ppm 2.17 (s, 6H), 3.41 (s, 2H), 4.61 (d, 2H), 5.88 (d, 1H), 7.24 - 7.39 (m, 5H), 7.48 (d, 2H), 7.59 (d, 1H), 7.93 (t, 1H), 8.08 (d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 424
20		δ ppm 2.25 (s, 3H), 2.31 (s, 3H), 2.51 (s, 4H), 3.11 (s, 4H), 3.88 (s, 3H), 4.54 (d, 2H), 5.86 (d, 1H), 6.91 - 6.94 (m, 1H), 7.07 (d, 1H), 7.27 - 7.33 (m, 2H), 7.56 (d, 1H), 7.81 (s, 1H), 8.24 (d, 1H), 8.79 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 444
21		δ ppm 2.23 (s, 3H), 2.40 - 2.43 (m, 4H), 3.52 - 3.54 (m, 4H), 3.88 (s, 3H), 4.53 (d, 2H), 5.84 (s, 1H), 6.91 - 6.94 (m, 2H), 7.07 (d, 1H), 7.29 - 7.32 (m, 2H), 7.51 (d, 1H), 7.73 (t, 1H), 8.30 (dd, 1H), 8.85 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 430
22		δ ppm 2.23 (s, 3H), 2.46 - 2.48 (m, 4H), 3.18 - 3.20 (m, 4H), 3.88 (s, 3H), 4.52 (s, 2H), 5.84 (d, 1H), 6.90 - 7.08 (m, 4H), 7.27 - 7.32 (m, 2H), 7.47 (d, 1H), 7.66 (t, 1H), 8.02 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 429
23		δ ppm 3.88 (s, 3H), 4.54 (d, 2H), 5.89 (d, 1H), 6.91 - 6.95 (m, 1H), 7.07 (d, 1H), 7.30 - 7.33 (m, 3H), 7.43 - 7.46 (m, 2H), 7.60 (d, 1H), 7.83 (t, 1H), 8.12 (d, 2H), 9.51 (s, 1H). / [MH] ⁺ = 331
24		δ ppm 3.88 (s, 3H), 4.58 (s, 2H), 5.95 (d, 1H), 6.93 - 7.31 (m, 4H), 7.94 (d, 1H), 8.18 (s, 1H), 8.25 (d, 2H), 8.59 (d, 2H), 9.56 (s, 1H). / [MH] ⁺ = 332

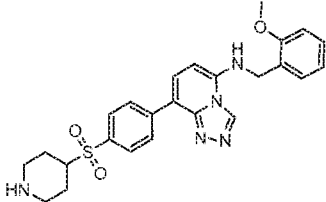
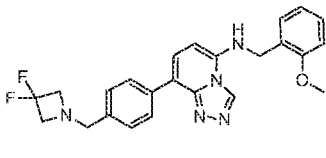
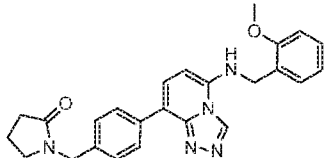
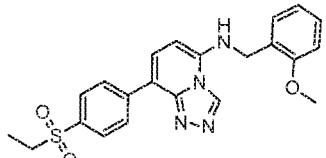
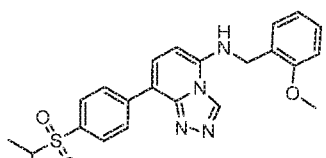
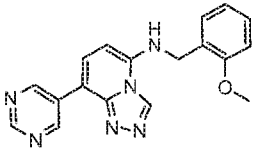
25		δ ppm 3.25 (s, 3H), 3.88 (s, 3H), 4.57 (d, 2H), 5.96 (d, 1H), 6.92 - 6.95 (m, 1H), 7.08 (d, 1H), 7.30-7.34 (m, 2H), 7.83 (d, 1H), 7.97 (d, 2H), 8.11 (t, 1H), 8.47 (d, 2H), 9.56 (s, 1H). / [MH] ⁺ = 409
26		δ ppm 3.88 (s, 3H), 4.60 (s, 2H), 6.01 (d, 1H), 6.93 - 6.97 (m, 1H), 7.08 (d, 1H), 7.31 - 7.34 (m, 2H), 8.16 (d, 1H), 8.61 (dd, 1H), 9.18 - 9.30 (m, 1H), 9.59 (s, 1H), 10.06 (dd, 1H). / [MH] ⁺ = 333
27		δ ppm 3.89 (s, 3H), 4.56 (d, 2H), 5.92 (d, 1H), 6.91 - 6.95 (m, 1H), 7.08 (d, 1H), 7.30 - 7.33 (m, 2H), 7.47 (dd, 1H), 7.73 (d, 1H), 7.97 (s, 1H), 8.49 - 8.55 (m, 2H), 9.30 (d, 1H), 9.54 (s, 1H). / [MH] ⁺ = 332
28		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.23 (s, 6H), 3.48 (s, 2H), 3.93 (s, 3H), 4.65 (s, 2H), 6.05 (d, 1H), 6.94 (t, 1H), 7.07 (d, 1H), 7.30 (q, 2H), 7.38 - 7.45 (m, 2H), 7.59 (d, 1H), 8.10 - 8.17 (m, 2H), 9.31 (s, 1H). / [MH] ⁺ = 388
29		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.11 - 2.18 (m, 2H) 3.18 (t, 4H) 3.57 (s, 2H) 3.93 (s, 3H) 4.64 (s, 2H) 6.04 (d, 1H) 6.94 (t, 1H) 7.06 (d, 1H) 7.31 (t, 1H) 7.37 (d, 2H) 7.43 (d, 1H) 7.58 (d, 1H) 8.16 (d, 2H) 9.30 (s, 1H). / [MH] ⁺ = 400
30		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.44 (s, 4H) 3.53 (s, 2H) 3.64 (t, 4H) 3.93 (s, 3H) 4.65 (s, 2H) 6.04 (d, 1H) 6.94 (t, 1H) 7.07 (d, 1H) 7.26 - 7.34 (m, 1H) 7.42 (d, 3H) 7.60 (d, 1H) 8.19 (d, 2H) 9.31 (s, 1H). / [MH] ⁺ = 430

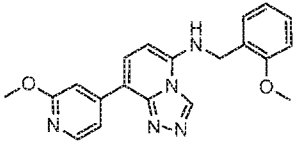
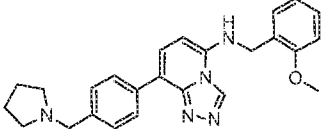
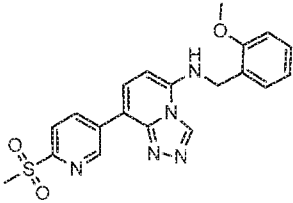
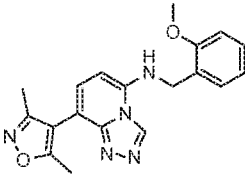
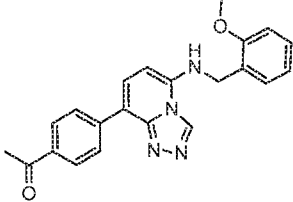
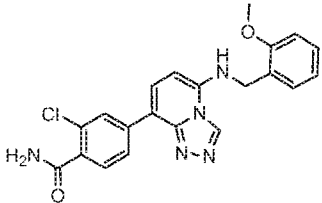
31		δ ppm 2.17 (s, 6H), 2.39 (s, 3H), 3.42 (s, 2H), 4.56 (d, 2H), 5.94 (d, 1H), 7.17-7.24 (m, 3H), 7.32-7.37 (m, 3H), 7.60 (d, 1H), 7.78 (t, 1H), 8.09 (d, 2H), 9.52 (s, 1H). / [MH] ⁺ = 372
32		δ ppm 1.33 (d, 3H), 1.63 - 1.69 (m, 4H), 2.32 - 2.34 (m, 3H), 3.23 (q, 1H), 3.88 (s, 3H), 4.54 (d, 2H), 5.88 (d, 1H), 6.91 - 6.95 (m, 1H), 7.07 (d, 1H), 7.28 - 7.38 (m, 4H), 7.56 (d, 1H), 7.79 (t, 1H), 8.04 (d, 2H), 9.50 (s, 1H). / [MH] ⁺ = 428
33		δ ppm 2.18 (s, 6H), 3.42 (s, 2H), 3.89 (s, 3H), 4.49 (d, 2H), 5.89 (d, 1H), 6.72 - 6.77 (m, 1H), 6.99 (dd, 1H), 7.32 - 7.36 (m, 3H), 7.59 (d, 1H), 7.76 (t, 1H), 8.09 (d, 2H), 9.49 (s, 1H). / [MH] ⁺ = 406
34		δ ppm 2.66 (s, 6H), 3.89 (s, 3H), 4.59 (d, 2H), 6.00 - 6.10 (s, 1H), 6.92 - 6.96 (m, 1H), 7.09 (d, 1H), 7.29 - 7.38 (m, 2H), 7.80 - 7.87 (m, 3H), 8.17 - 8.23 (m, 1H), 8.38 - 8.42 (m, 2H), 9.60 (s, 1H). / [MH] ⁺ = 438
35		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 4.63 (d, 2H), 5.93 (d, 1H), 7.10 - 7.15 (m, 1H), 7.30 - 7.43 (m, 5H), 7.59 (d, 1H), 8.00 (t, 1H), 8.08 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 376
36		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 4.65 (s, 2H), 5.98 (d, 1H), 7.18 - 7.62 (m, 7H), 7.90 (s, 1H), 8.09 (d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 376

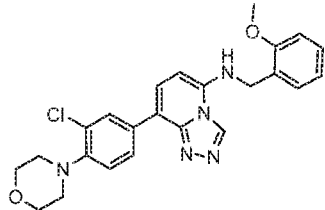
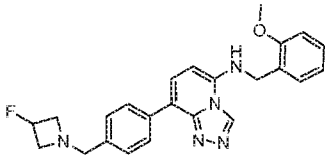
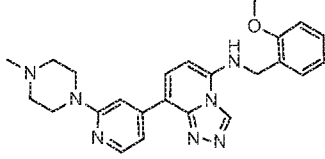
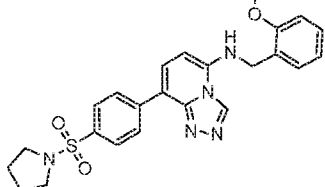
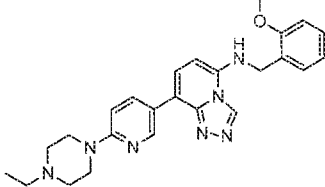
37		δ ppm 2.17 (s, 6H), 3.41 (s, 2H), 4.59 (d, 2H), 5.95 (d, 1H), 7.18 - 7.22 (m, 2H), 7.35 (d, 2H), 7.49 - 7.59 (m, 3H), 7.96 (t, 1H), 8.08 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 376
38		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.51 (s, 4H), 3.65 - 3.69 (m, 6H), 3.93 (s, 3H), 4.66 (s, 2H), 6.08 (d, 1H), 6.91 - 6.97 (m, 1H), 7.07 (d, 1H), 7.32 (t, 1H), 7.44 (d, 1H), 7.58 (d, 1H), 7.69 (d, 1H), 8.60 (dd, 1H), 9.28 (s, 1H), 9.34 (s, 1H). / [MH] ⁺ = 431
39		¹ H-NMR (400 MHz, Acetone-d ₆) δ ppm 2.13 (s, 5H), 2.19 (s, 3H), 2.38 (s, 2H), 2.45 (s, 1H), 3.52 (s, 2H), 3.93 (s, 3H), 4.64 (s, 2H), 6.04 (d, 1H), 6.94 (t, 1H), 7.07 (d, 1H), 7.31 (t, 1H), 7.39 - 7.45 (m, 3H), 7.59 (d, 1H), 8.18 (d, 2H), 9.31 (s, 1H). / [MH] ⁺ = 443
40		δ ppm 2.53 (s, 6H), 3.88 (s, 3H), 4.54 (d, 2H), 4.64 (s, 2H), 5.89 (d, 1H), 6.90 - 6.94 (m, 1H), 7.07 (d, 1H), 7.27 - 7.33 (m, 2H), 7.39 (d, 2H), 7.60 (d, 1H), 7.83 (t, 1H), 8.11 (d, 2H), 9.51 (s, 1H). / [MH] ⁺ = 404
41		δ ppm 2.99 (s, 6H), 3.88 (s, 3H), 4.55 (d, 2H), 5.91 (d, 1H), 6.90 - 6.94 (m, 1H), 7.07 (d, 1H), 7.27 - 7.33 (m, 2H), 7.48 (d, 2H), 7.69 (d, 1H), 7.92 (t, 1H), 8.22 (d, 2H), 9.52 (s, 1H). / [MH] ⁺ = 402

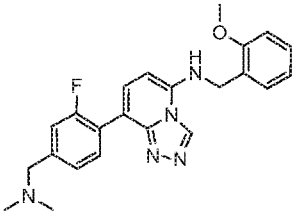
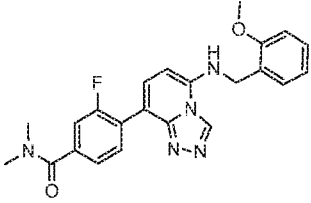
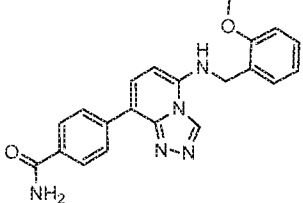
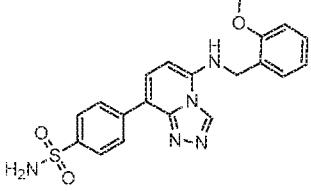
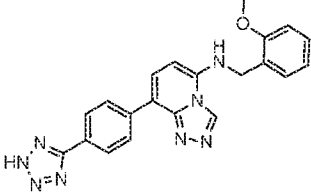
42		δ ppm 1.81 - 1.90 (m, 4H), 3.45 - 3.05 (m, 4H), 3.88 (s, 3H), 4.55 (d, 2H), 5.91 (d, 1H), 6.91 - 6.94 (m, 1H), 7.07 (d, 1H), 7.27 - 7.33 (m, 2H), 7.59 (d, 2H), 7.70 (d, 1H), 7.92 (t, 1H), 8.22 (d, 2H), 9.52 (s, 1H). / [MH] ⁺ = 428
43		δ ppm 2.18 (s, 6H), 3.52 (s, 2H), 3.88 (s, 3H), 4.56 (d, 2H), 5.91 (d, 1H), 6.91 - 6.95 (m, 1H), 7.08 (d, 1H), 7.30 - 7.33 (m, 2H), 7.86 (d, 1H), 8.00 - 8.09 (m, 3H), 9.55 (s, 1H). / [MH] ⁺ = 424
44		δ ppm 1.32 - 1.49 (m, 6H), 2.39 (s, 4H), 3.55 (s, 2H), 3.88 (s, 3H), 4.56 (d, 2H), 5.91 (d, 1H), 6.91 - 6.95 (m, 1H), 7.08 (d, 1H), 7.28 - 7.33 (m, 2H), 7.84 (d, 1H), 8.01 - 8.08 (m, 3H), 9.55 (s, 1H). / [MH] ⁺ = 464
45		δ ppm 2.18 (s, 6H), 3.42 (s, 2H), 3.89 (s, 3H), 4.51 (d, 2H), 6.16 (d, 1H), 6.89 - 6.97 (m, 2H), 7.35 - 7.48 (m, 4H), 7.66 (d, 1H), 8.10 (d, 2H), 9.51 (s, 1H). / [MH] ⁺ = 406
46		δ ppm 2.15 (s, 3H), 3.87 (s, 3H), 4.52 (d, 2H), 5.83 (d, 1H), 6.92 - 6.95 (m, 1H), 7.05 - 7.12 (m, 2H), 7.24 - 7.36 (m, 6H), 7.70 (t, 1H), 9.46 (s, 1H). / [MH] ⁺ = 345

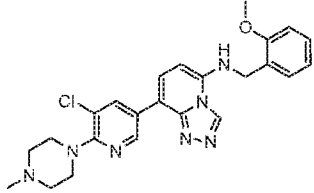
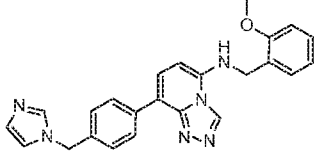
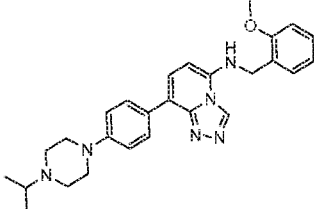
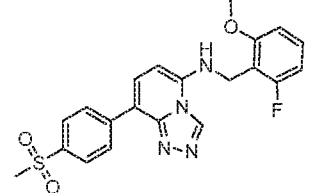
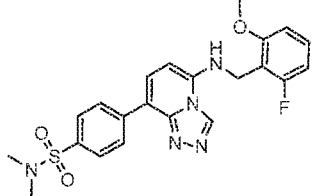
47		δ ppm 3.87 (s, 3H), 4.54 (d, 2H), 5.87 (d, 1H), 6.91 - 6.94 (m, 1H), 7.07 (d, 1H), 7.26 - 7.39 (m, 6H), 7.86 - 7.89 (m, 2H), 9.49 (s, 1H). / [MH] ⁺ = 349
48		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 4.65 (d, 2H), 6.00 (d, 1H), 7.34 - 7.40 (m, 3H), 7.59 (d, 1H), 7.86 (dd, 1H), 7.96 (t, 1H), 8.08 (d, 2H), 8.51 (dd, 1H), 8.70 (d, 1H), 9.46 (s, 1H). / [MH] ⁺ = 359
49		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 3.71 (s, 3H), 4.59 (s, 2H), 5.99 (d, 1H), 6.89 - 6.93 (m, 1H), 7.04 - 7.06 (m, 1H), 7.17 - 7.22 (m, 1H), 7.36 (d, 2H), 7.62 (d, 1H), 7.87 (s, 1H), 8.09 (d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 406
50		δ ppm 3.87 (s, 3H), 3.98 (s, 3H), 4.54 (s, 2H), 5.87 (d, 1H), 6.89 - 6.94 (m, 1H), 7.06 (d, 1H), 7.26 - 7.32 (m, 2H), 7.69 (d, 1H), 7.93 (s, 1H), 8.47 (dd, 1H), 8.79 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 380
51		δ ppm 3.89 (s, 3H), 3.87 (s, 3H), 4.54 (s, 2H), 5.88 (d, 1H), 6.91 (t, 1H), 7.06 (d, 1H), 7.25 - 7.34 (m, 2H), 7.76 (d, 1H), 7.98 (s, 1H), 8.16 - 8.22 (m, 2H), 8.91 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 362
52		δ ppm 3.87 (s, 3H), 3.96 (s, 3H), 4.54 (s, 2H), 5.89 (d, 1H), 6.89 - 6.95 (m, 1H), 7.06 (d, 1H), 7.22 - 7.42 (m, 3H), 7.70 (d, 1H), 7.94 (s, 1H), 9.31 (s, 2H), 9.52 (s, 1H). / [MH] ⁺ = 363

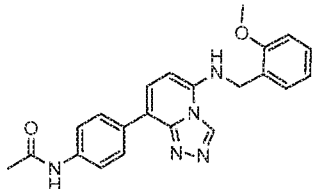
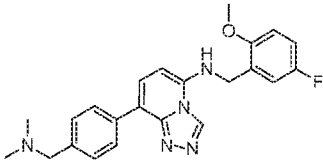
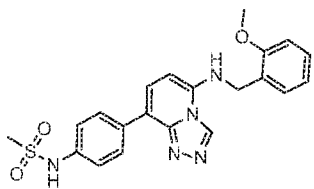
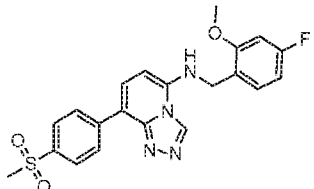
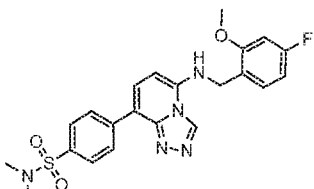
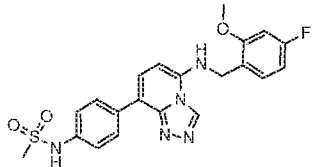
53		$^1\text{H-NMR}$ (400 MHz, Acetone- d_6) δ ppm 1.49 - 1.59 (m, 2H), 1.91 (d, 2H), 2.51 - 2.59 (m, 2H), 3.07 - 3.23 (m, 3H), 3.93 (s, 3H), 4.67 - 4.71 (m, 2H), 6.12 (d, 1H), 6.94 (t, 1H), 7.07 (d, 1H), 7.19 (s, 1H), 7.32 (t, 1H), 7.44 (d, 1H), 7.84 (d, 1H), 7.92 (m, 2H), 8.57 (m, 2H), 9.37 (s, 1H). / $[\text{MH}]^+ = 478$
54		δ ppm 3.59 - 3.65 (m, 4H), 3.76 (s, 2H), 3.88 (s, 3H), 4.54 (d, 2H), 5.88 (d, 1H), 6.92 - 6.05 (m, 1H), 7.07 (d, 1H), 7.30 - 7.38 (m, 4H), 7.59 (d, 1H), 7.82 (t, 1H), 8.09 (d, 2H), 9.50 (s, 1H). / $[\text{MH}]^+ = 436$
55		δ ppm 1.91 - 1.97 (m, 2H), 2.31 (t, 2H), 3.27 (t, 2H), 3.88 (s, 3H), 4.40 (s, 2H), 4.54 (d, 2H), 5.88 (d, 1H), 6.90 - 6.94 (m, 1H), 7.07 (d, 1H), 7.27 - 7.32 (m, 4H), 7.58 (d, 1H), 7.83 (t, 1H), 8.09 (d, 2H), 9.50 (s, 1H). / $[\text{MH}]^+ = 428$
56		δ ppm 1.14 (t, 3H), 3.32 (q, 2H), 3.89 (s, 3H), 4.58 (s, 2H), 5.96 (d, 1H), 6.91 - 6.95 (m, 1H), 7.08 (d, 1H), 7.29 - 7.35 (m, 2H), 7.84 (d, 1H), 7.93 (d, 2H), 8.49 (d, 2H), 9.56 (s, 1H). / $[\text{MH}]^+ = 423$
57		δ ppm 1.19 (d, 6H), 3.43 - 3.45 (m, 1H), 3.89 (s, 3H), 4.58 (d, 2H), 5.97 (d, 1H), 6.91 - 6.94 (m, 1H), 7.08 (d, 1H), 7.20 - 7.34 (m, 2H), 7.84 - 7.91 (m, 3H), 8.11 (t, 1H), 8.49 (d, 2H), 9.56 (s, 1H). / $[\text{MH}]^+ = 437$
58		δ ppm 3.88 (s, 3H), 4.58 (s, 2H), 5.95 (d, 1H), 6.91 - 6.95 (m, 1H), 7.08 (d, 1H), 7.28 - 7.33 (m, 2H), 7.88 (d, 1H), 9.09 (s, 1H), 9.57 (s, 3H). / $[\text{MH}]^+ = 333$

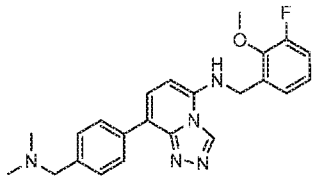
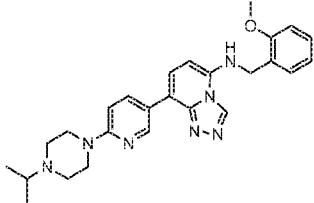
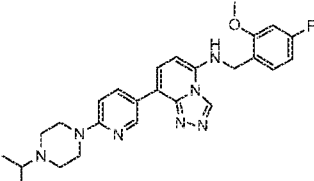
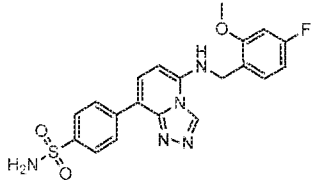
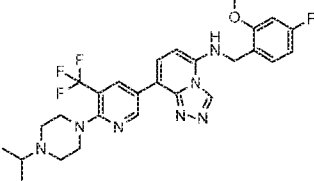
59		δ ppm 3.88 (s, 3H), 3.93 (s, 3H), 4.60 (d, 2H), 6.03 (d, 1H), 6.90 - 6.95 (m, 1H), 7.08 (d, 1H), 7.28 - 7.34 (m, 2H), 7.74 - 7.80 (m, 2H), 7.99 (d, 1H), 8.21 (d, 1H), 8.34 (t, 1H), 9.60 (s, 1H). / [MH] ⁺ = 362
60		δ ppm 1.68 - 1.71 (m, 4H), 2.45 (s, 4H), 3.60 (s, 2H), 3.88 (s, 3H), 4.54 (d, 2H), 5.88 (d, 1H), 6.90 - 6.95 (m, 1H), 7.07 (d, 1H), 7.27 - 7.38 (m, 4H), 7.58 (d, 1H), 7.78 - 7.81 (m, 1H), 8.06 (d, 2H), 9.50 (s, 1H). / [MH] ⁺ = 414
61		δ ppm 3.29 (s, 4H), 4.58 (s, 2H), 5.97 (d, 1H), 6.92 (t, 1H), 7.06 (d, 1H), 7.26 - 7.35 (m, 2H), 7.95 (d, 1H), 8.09 (d, 1H), 8.24 (s, 1H), 8.98 (dd, 1H), 9.51 (d, 1H), 9.56 (s, 1H). / [MH] ⁺ = 410
62		δ ppm 2.16 (s, 3H), 2.33 (s, 3H), 3.87 (s, 3H), 4.52 (d, 2H), 5.84 (d, 1H), 6.92 - 6.96 (m, 1H), 7.07 (d, 1H), 7.21 - 7.35 (m, 3H), 7.82 (t, 1H), 9.47 (s, 1H). / [MH] ⁺ = 350
63		δ ppm 2.59 (s, 3H), 4.56 (d, 2H), 5.93 (d, 1H), 6.91 (t, 1H), 7.06 (d, 1H), 7.26 - 7.33 (m, 2H), 7.79 (d, 1H), 7.99 - 8.04 (m, 3H), 8.35 (d, 2H), 9.53 (s, 1H). / [MH] ⁺ = 373
64		δ ppm 3.87 (s, 3H), 4.54 (s, 2H), 5.88 (d, 1H), 6.91 (t, 1H), 7.06 (d, 1H), 7.26 - 7.34 (m, 2H), 7.49 (d, 1H), 7.55 (s, 1H), 7.76 (d, 1H), 7.85 (s, 1H), 8.12 (d, 1H), 8.43 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 408

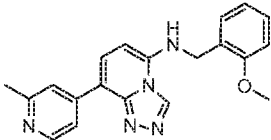
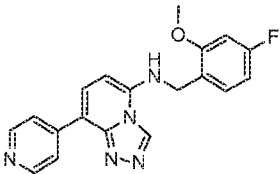
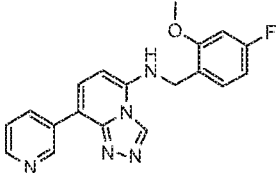
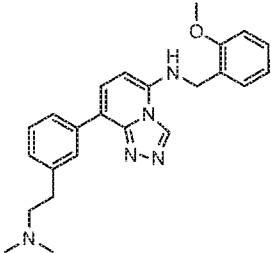
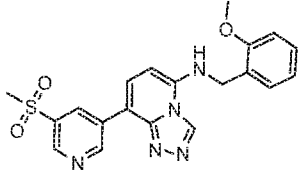
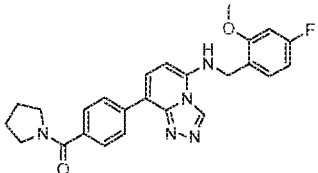
65		δ ppm 2.99 - 3.05 (m, 4H), 3.74 - 3.79 (m, 4H), 3.87 (s, 3H), 4.53 (s, 2H), 5.86 (d, 1H), 6.87 - 6.95 (m, 1H), 7.06 (d, 1H), 7.22 (d, 1H), 7.26 - 7.34 (m, 2H), 7.62 (d, 1H), 7.85 (s, 1H), 8.03 (dd, 1H), 8.33 - 8.38 (m, 1H), 9.50 (s, 1H). / [MH] ⁺ = 450
66		δ ppm 3.11 - 3.20 (m, 2H), 3.53 - 3.61 (m, 2H), 3.66 (s, 2H), 3.88 (s, 3H), 4.54 (d, 2H), 5.10 - 5.28 (m, 1H), 5.88 (d, 1H), 6.90 - 6.95 (m, 1H), 7.08 (d, 1H), 7.39 - 7.35 (m, 4H), 7.58 (d, 1H), 7.79 (t, 1H), 8.07 (d, 2H), 9.50 (s, 1H). / [MH] ⁺ = 418
67		δ ppm 2.23 (s, 3H), 2.42 - 2.45 (m, 4H), 3.51 - 3.54 (m, 4H), 3.88 (s, 3H), 4.57 (d, 2H), 5.91 (d, 1H), 6.91 - 6.94 (m, 1H), 7.07 (d, 1H), 7.30 - 7.40 (m, 3H), 7.84 - 7.87 (m, 2H), 8.06 - 8.13 (m, 2H), 9.53 (s, 1H). / [MH] ⁺ = 430
68		δ ppm 1.65 - 1.69 (m, 4H), 3.17 - 3.21 (m, 4H), 3.88 (s, 3H), 4.58 (d, 2H), 6.04 (d, 1H), 6.95 - 7.10 (m, 2H), 7.28 - 7.35 (m, 2H), 7.83 - 7.88 (m, 3H), 8.18 (t, 1H), 8.38 (d, 2H), 9.60 (s, 1H). / [MH] ⁺ = 464
69		δ ppm 1.05 (t, 3H), 2.35 - 2.51 (m, 6H), 3.50 - 3.54 (m, 4H), 3.88 (s, 3H), 4.53 (d, 2H), 5.83(d, 1H), 6.90 - 6.94 (m, 2H), 7.07 (d, 1H), 7.26 - 7.32 (m, 2H), 7.51 (d, 1H), 7.74 (t, 1H), 8.29 (q, 1H), 8.85(d, 1H), 9.49 (s, 1H). / [MH] ⁺ = 444

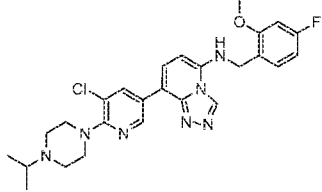
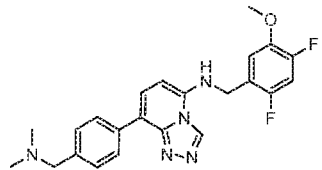
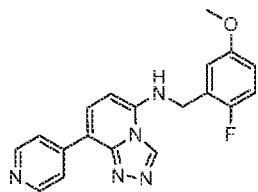
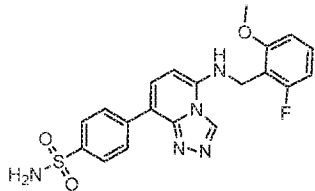
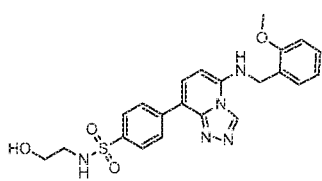
70		δ ppm 2.20 (d, 6H), 3.45 (s, 2H), 3.88 (s, 3H), 4.54 (d, 2H), 5.87 (d, 1H), 6.91 - 6.95 (m, 1H), 7.07 (d, 1H), 7.18 - 7.39 (m, 5H), 7.83 - 7.87 (m, 2H), 9.49 (s, 1H). / [MH] ⁺ = 406
71		δ ppm 4.57 (d, 2H), 6.05 (d, 1H), 6.90 - 6.97 (m, 1H), 7.07 (d, 1H), 7.28 - 7.40 (m, 4H), 7.58 (d, 1H), 7.90 (t, 1H), 9.57 (s, 1H). / [MH] ⁺ = 420
72		δ ppm 3.87 (s, 3H), 4.55 (s, 2H), 5.90 (d, 1H), 6.91 (t, 1H), 7.06 (d, 1H), 7.26 - 7.35 (m, 3H), 7.72 (d, 1H), 7.90 - 8.00 (m, 3H), 8.25 (d, 2H), 9.52 (s, 1H). / [MH] ⁺ = 374
73		δ ppm 3.87 (s, 3H), 4.55 (d, 2H), 5.93 (d, 1H), 6.91 (t, 1H), 7.06 (d, 1H), 7.26 - 7.36 (m, 4H), 7.76 (d, 1H), 7.86 (m, 2H), 8.02 (t, 1H), 8.36 (m, 2H), 9.53 (s, 1H). / [MH] ⁺ = 410
74		δ ppm 4.56 (d, 2H) 5.94 (d, 1H) 6.93 (q, 1H) 7.07 (d, 1H) 7.27 - 7.35 (m, 2H) 7.80 (d, 1H) 8.01 (s, 1H) 8.10 (d, 2H) 8.44 (d, 2H) 9.54 (s, 1H). / [MH] ⁺ = 399

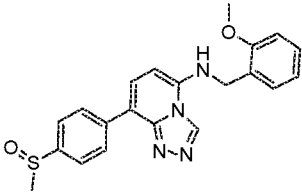
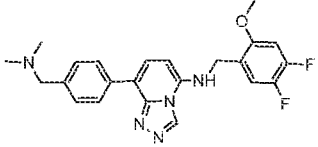
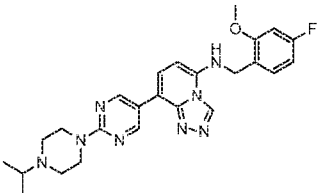
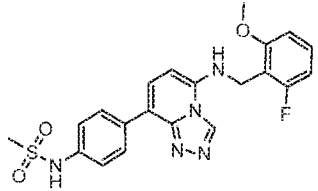
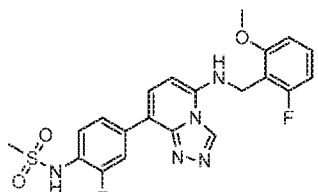
75		$^1\text{H-NMR}$ (400MHz, Acetone- d_6) δ ppm 2.41 (s, 3H), 2.51 - 2.64 (m, 4H), 3.46 - 3.55 (m, 4H), 3.93 (s, 3H), 4.63 - 4.67 (m, 2H), 6.06 (d, 1H), 6.92 - 6.96 (m, 2H), 7.07 (d, 1H), 7.29 - 7.34 (m, 1H), 7.43 (d, 1H), 7.70 (d, 1H), 8.74 (d, 1H), 9.01 (d, 1H), 9.36 (s, 1H). / $[\text{MH}]^+ = 464$
76		δ ppm 3.88 (s, 3H), 4.54 (s, 2H), 5.23 (s, 2H), 5.86 (s, 1H), 6.91 - 7.08 (m, 3H), 7.22 - 7.33 (m, 5H), 7.59 (s, 1H), 7.78 - 7.88 (m, 2H), 8.10 - 8.30 (m, 2H), 9.52 (s, 1H). / $[\text{MH}]^+ = 411$
77		δ ppm 1.30 (d, 6H), 2.98 - 3.53 (m, 7H), 3.88 (s, 3H), 3.97 (d, 2H), 4.53 (d, 2H), 5.88 (d, 1H), 6.91 - 6.95 (m, 1H), 7.06 - 7.13 (m, 3H), 7.27 - 7.32 (m, 2H), 7.53 (d, 1H), 7.78 - 7.80 (m, 1H), 8.04 (d, 2H), 9.50 (s, 1H). / $[\text{MH}]^+ = 457$
78		δ ppm 3.26 (s, 3H), 3.90 (s, 3H), 4.56 (d, 2H), 6.29 (d, 1H), 6.87 - 6.98 (m, 2H), 7.37 - 7.44 (m, 1H), 7.87 - 8.00 (m, 4H), 8.42 - 8.45 (m, 2H), 9.60 (s, 1H). / $[\text{MH}]^+ = 427$
79		δ ppm 2.66 (s, 6H), 3.90 (s, 3H), 4.56 (d, 2H), 6.28 (d, 1H), 6.87 - 6.98 (m, 2H), 7.38 - 7.44 (m, 1H), 7.80 - 7.94 (m, 4H), 8.45 (d, 2H), 9.60 (s, 1H). / $[\text{MH}]^+ = 456$

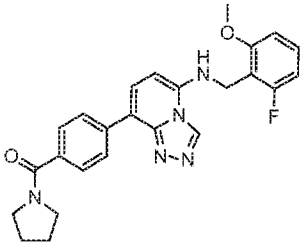
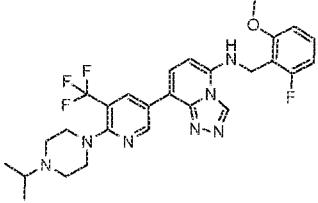
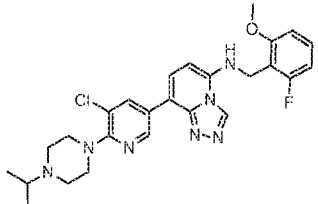
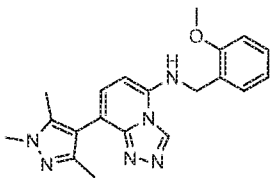
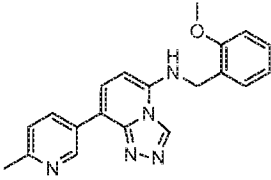
80		δ ppm 2.05 (s, 3H), 3.87 (s, 3H), 4.52 (s, 2H), 5.85 (d, 1H), 6.88 - 6.95 (m, 1H), 7.06 (d, 1H), 7.25 - 7.33 (m, 2H), 7.53 (d, 1H), 7.63 (d, 2H), 7.74 (s, 1H), 8.06 (d, 2H), 9.48 (s, 1H), 9.98 (s, 1H). / [MH] ⁺ = 388
81		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 3.88 (s, 3H), 4.53 (s, 2H), 5.86 (d, 1H), 7.05 - 7.20 (m, 3H), 7.35 (d, 2H), 7.59 (d, 1H), 7.82 (s, 1H), 8.09 (d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 406
82		δ ppm 2.73 (s, 3H), 3.88 (s, 3H), 4.51 (s, 2H), 5.83 (d, 1H), 6.92 (t, 1H), 7.01 (m, 2H), 7.06 (d, 1H), 7.26 - 7.34 (m, 2H), 7.42 (d, 1H), 7.88 (m, 2H), 8.64 (s, 2H), 9.45 (s, 1H). / [MH] ⁺ = 424
83		δ ppm 3.25 (s, 3H), 3.89 (s, 3H), 4.53 (s, 2H), 5.97 (d, 1H), 6.73 - 6.78 (m, 1H), 6.98 - 7.02 (m, 1H), 7.36 (t, 1H), 7.84 (d, 1H), 7.97 (d, 2H), 8.07 (s, 1H), 8.48 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 427
84		δ ppm 2.65 (s, 6H), 3.89 (s, 3H), 4.52 (s, 2H), 5.97 (d, 1H), 6.73 - 6.77 (m, 1H), 7.00 (d, 1H), 7.34 - 7.38 (m, 1H), 7.79 - 7.84 (m, 3H), 8.06 (s, 1H), 8.47 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 456
85		δ ppm 3.03 (s, 3H), 3.89 (s, 3H), 4.49 (d, 2H), 5.88 (d, 1H), 6.72 - 6.77 (m, 1H), 6.97 - 7.00 (m, 1H), 7.27 - 7.36 (m, 3H), 7.56 (d, 1H), 7.77 (t, 1H), 8.11 (d, 2H), 9.49 (s, 1H), 9.80 (s, 1H). / [MH] ⁺ = 442

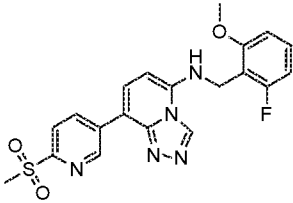
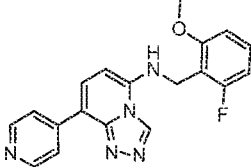
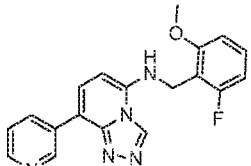
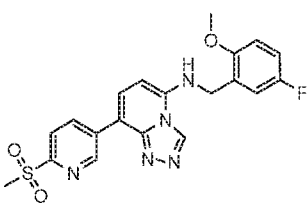
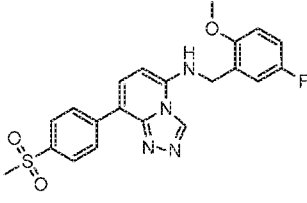
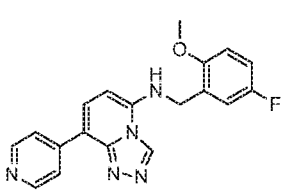
86		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 3.94 (s, 3H), 4.61 (s, 2H), 5.95 (d, 1H), 7.06 - 7.12 (m, 1H), 7.20 - 7.23 (m, 2H), 7.35 (d, 2H), 7.61 (d, 1H), 7.88 (s, 1H), 8.08 (d, 2H), 9.49 (s, 1H). / $[MH]^+ = 406$
87		δ ppm 1.01 (d, 6H), 2.53 - 2.55 (m, 4H), 2.65 - 2.72 (m, 1H), 3.50 - 3.53 (m, 4H), 3.88 (s, 3H), 4.52 (d, 2H), 5.83 (d, 1H), 6.90 - 6.93 (m, 2H), 7.07 (d, 1H), 7.27 - 7.32 (m, 2H), 7.51 (d, 1H), 7.74 (t, 1H), 8.29 (dd, 1H), 8.84 (d, 1H), 9.48 (s, 1H). / $[M+H]^+ = 458$
88		δ ppm 1.09 (d, 6H), 2.75 (s, 4H), 2.92 (t, 1H), 3.61 (s, 4H), 3.89 (s, 3H), 4.48 (d, 2H), 5.84 (d, 1H), 6.71 - 6.76 (m, 1H), 6.94 - 7.00 (m, 2H), 7.31 - 7.35 (m, 1H), 7.52 (d, 1H), 7.75 (t, 1H), 8.31 (dd, 1H), 8.87 (d, 1H), 9.49 (s, 1H). / $[MH]^+ = 476$
89		δ ppm 3.89 (s, 3H), 4.52 (s, 2H), 5.95 (d, 1H), 6.08 (d, 2H), 6.73 - 6.77 (m, 1H), 7.00 (dd, 1H), 7.35 (t, 1H), 7.78 (d, 1H), 7.87 (d, 2H), 8.38 (d, 2H), 9.53 (s, 1H). / $[MH]^+ = 428$
90		δ ppm 1.03 (d, 6H), 2.60 - 2.64 (m, 4H), 2.66 - 2.74 (m, 1H), 3.24 - 3.29 (m, 4H), 3.89 (s, 3H), 4.51 (d, 2H), 5.91 (d, 1H), 6.72 - 6.77 (m, 1H), 6.99 (dd, 1H), 7.33 - 7.37 (m, 1H), 7.80 (d, 1H), 7.98 (t, 1H), 8.99 (d, 1H), 9.17 (d, 1H), 9.53 (s, 1H). / $[MH]^+ = 544$

91		δ ppm 2.52 (s, 3H), 3.88 (s, 3H), 4.57 (s, 2H), 5.94 (d, 1H), 6.91 - 7.00 (m, 1H), 7.08 (d, 1H), 7.20 - 7.33 (m, 2H), 7.90 (d, 1H), 8.02 (d, 1H), 8.14 (s, 2H), 8.45 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 346
92		δ ppm 3.89 (s, 3H), 4.53 (s, 2H), 5.96 (d, 1H), 6.72 - 6.77 (m, 1H), 6.99 (dd, 1H), 7.33 - 7.37 (m, 1H), 7.94 (d, 1H), 8.26 (dd, 2H), 8.59 (dd, 2H), 9.55 (s, 1H). / [MH] ⁺ = 350
93		δ ppm 3.89 (s, 3H), 4.51 (s, 2H), 5.92 (d, 1H), 6.72 - 6.77 (m, 1H), 6.99 (dd, 1H), 7.32 - 7.37 (m, 1H), 7.47 (dd, 1H), 7.72 (d, 1H), 7.92 (s, 1H), 8.48 - 8.55 (m, 2H), 9.30 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 350
94		δ ppm 2.19 (s, 6H), 2.48 - 2.79 (m, 4H), 3.88 (s, 3H), 4.54 (s, 2H), 5.88 (d, 1H), 6.91 - 6.95 (m, 1H), 7.07 (d, 1H), 7.16 (d, 1H), 7.28 - 7.36 (m, 3H), 7.58 (d, 1H), 7.82 (s, 1H), 7.92 - 7.95 (m, 2H), 9.50 (s, 1H). / [MH] ⁺ = 402
95		δ ppm 3.38 (s, 3H), 3.88 (s, 3H), 4.58 (s, 2H), 5.98 (d, 1H), 6.93 (t, 1H), 7.08 (d, 1H), 7.28 - 7.37 (m, 2H), 7.98 (d, 1H), 8.95 (d, 1H), 9.18 (t, 1H), 9.58 (s, 1H), 9.64 (d, 1H). / [MH] ⁺ = 410
96		δ ppm 1.82 - 1.90 (m, 4H), 3.46 - 3.50 (m, 4H), 3.89 (s, 3H), 4.50 (d, 2H), 5.91 (d, 1H), 6.73 - 6.77 (m, 1H), 6.99 (dd, 1H), 7.35 (t, 1H), 7.60 (d, 2H), 7.70 (d, 1H), 7.98 (s, 1H), 8.23 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 446

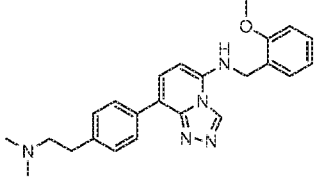
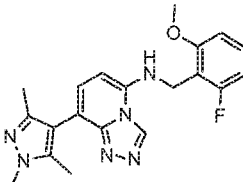
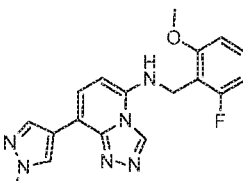
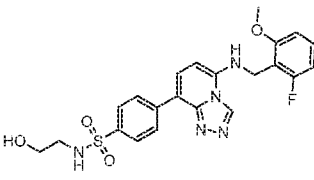
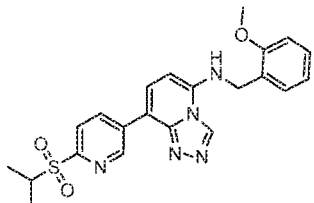
97		δ ppm 1.02 (d, 6H), 2.40 - 2.63 (m, 4H), 2.66 - 2.72 (m, 1H), 3.31 - 2.32 (m, 4H), 3.88 (s, 3H), 4.49 (d, 2H), 5.88 (d, 1H), 6.72 - 6.76 (m, 1H), 6.99 (dd, 1H), 7.32 - 7.35 (m, 1H), 7.71 (d, 1H), 7.91 (t, 1H), 8.66 (d, 1H), 8.92 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 510
98		δ ppm 2.17 (s, 6H), 3.42 (s, 2H), 3.80 (s, 3H), 4.57 (s, 2H), 6.04 - 6.09 (m, 2H), 7.35 - 7.40 (m, 4H), 7.64 (d, 1H), 8.10 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 424
99		δ ppm 3.71 (s, 3H), 4.63 (s, 2H), 6.06 (d, 1H), 6.90 - 6.93 (m, 1H), 7.06 (dd, 1H), 7.20 (t, 1H), 7.96 (d, 1H), 8.25 - 8.27 (m, 3H), 8.60 (dd, 2H), 9.54 (s, 1H). / [MH] ⁺ = 350
100		δ ppm 3.89 (s, 3H), 4.54 (s, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (q, 1H), 7.50 (s, 2H), 7.83 - 7.91 (m, 3H), 8.40 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 428
101		δ ppm 2.82 (t, 2H), 3.37 - 3.41 (m, 2H), 3.88 (s, 3H), 4.55 (s, 2H), 5.89 (d, 1H), 6.93 (t, 1H), 7.07 (d, 1H), 7.29 (t, 1H), 7.35 (d, 1H), 7.77 (d, 1H), 7.82 (d, 2H), 8.39 (d, 2H), 9.51 (s, 1H). / [MH] ⁺ = 454

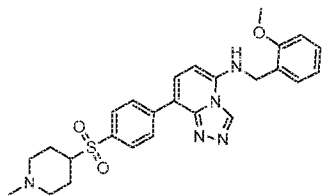
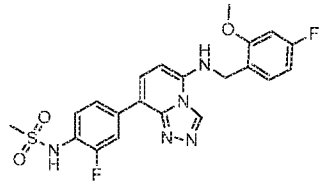
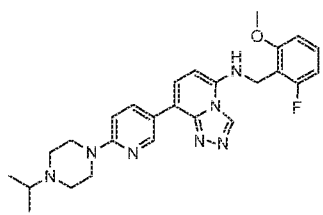
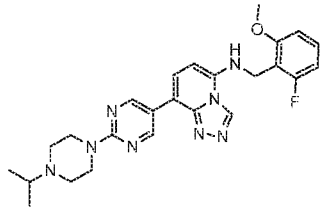
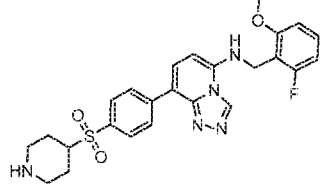
102		δ ppm 2.78 (s, 3H), 3.88 (s, 3H), 4.55 (s, 2H), 5.88 (d, 1H), 6.93 (t, 1H), 7.07 (d, 1H), 7.30 (t, 1H), 7.34 (d, 1H), 7.74 (d, 3H), 8.37 (d, 2H), 9.52 (s, 1H). / [MH] ⁺ = 393
103		δ ppm 2.17 (s, 6H), 3.41 (s, 2H), 3.88 (s, 3H), 4.48 (d, 2H), 5.86 (d, 1H), 7.23 - 7.27 (m, 1H), 7.35 (d, 2H), 7.42 - 7.46 (m, 1H), 7.59 (d, 1H), 7.81 (t, 1H), 8.08 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 424
104		δ ppm 0.99 (d, 6H), 2.50 (t, 4H), 2.66 - 2.71 (m, 1H), 3.77 (t, 4H), 3.88 (s, 3H), 4.48 (d, 2H), 5.85 (d, 1H), 6.72 - 6.76 (m, 1H), 6.98 (dd, 1H), 7.33 (t, 1H), 7.56 (d, 1H), 7.78 (t, 1H), 9.08 (s, 2H), 9.48 (s, 1H). / [MH] ⁺ = 477
105		δ ppm 3.03 (s, 3H), 3.87 (s, 3H), 4.50 (d, 2H), 6.15 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.29 (d, 2H), 7.37 - 7.42 (m, 1H), 7.48 (t, 1H), 7.63 (d, 1H), 8.13 (d, 2H), 9.51 (s, 1H), 9.71 (s, 1H). / [MH] ⁺ = 442
106		δ ppm 2.95 (s, 3H), 3.88 (s, 3H), 4.51 (s, 2H), 6.15 (d, 1H), 6.72 - 6.97 (m, 3H), 7.37 - 7.43 (m, 2H), 7.55 (s, 1H), 7.73 (d, 1H), 7.91 (dd, 1H), 8.16 (dd, 1H), 9.52 (s, 1H). / [MH] ⁺ = 460

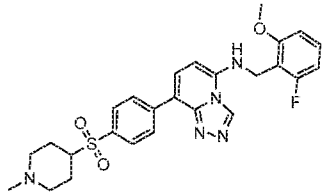
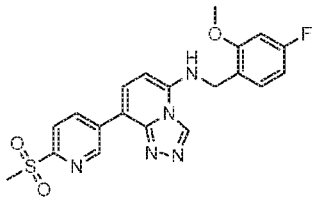
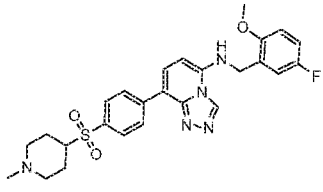
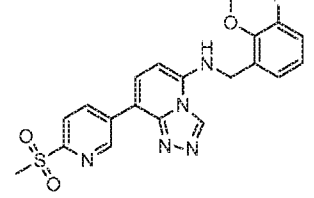
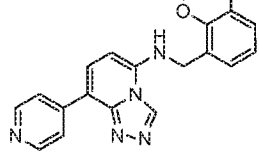
107		δ ppm 1.82 - 1.90 (m, 4H), 3.46 - 3.50 (m, 4H), 3.89 (s, 3H), 4.52 (d, 2H), 6.19 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.43 (m, 1H), 7.58 - 7.62 (m, 3H), 7.78 (d, 1H), 8.25 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 446
108		δ ppm 1.02 (d, 6H), 2.60 - 2.71 (m, 5H), 3.24 - 3.26 (m, 4H), 3.89 (s, 3H), 4.52 (d, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.42 (m, 1H), 7.68 (s, 1H), 7.88 (d, 1H), 9.00 (s, 1H), 9.20 (s, 1H), 9.55 (s, 1H). / [MH] ⁺ = 544
109		δ ppm 1.02 (d, 6H), 2.62 - 2.70 (m, 5H), 3.24 - 3.26 (m, 4H), 3.89 (s, 3H), 4.52 (d, 2H), 6.15 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.42 (m, 1H), 7.63 (s, 1H), 7.79 (d, 1H), 8.68 (s, 1H), 8.96 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 510
110		δ ppm 2.03 (s, 3H), 2.11 (s, 3H), 3.71 (s, 3H), 3.87 (s, 3H), 4.50 (d, 2H), 5.80 (d, 1H), 6.93 (t, 1H), 7.00 (d, 1H), 7.06 (d, 1H), 7.28 - 7.32 (m, 1H), 7.34 (d, 1H), 7.62 (t, 1H), 9.43 (s, 1H). / [M+H] ⁺ = 363
111		δ ppm 2.50 (s, 3H), 3.88 (s, 3H), 4.54 (d, 2H), 5.88 (d, 1H), 6.92 (t, 1H), 7.07 (d, 1H), 7.28 - 7.34 (m, 3H), 7.67 (d, 1H), 7.93 (s, 1H), 8.42 (dd, 1H), 9.16 (d, 1H), 9.53 (s, 1H). / [M+H] ⁺ = 346

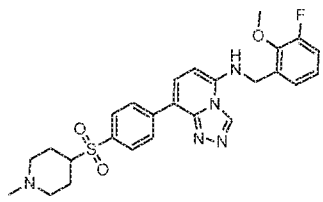
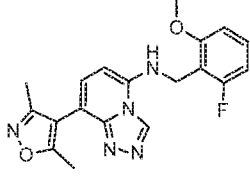
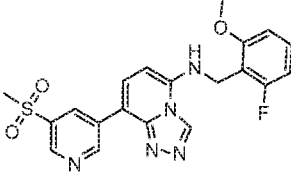
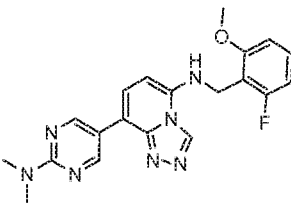
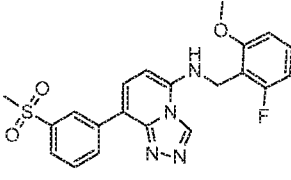
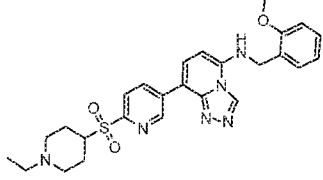
112		δ ppm 3.31 (s, 3H), 3.89 (s, 3H), 4.56 (s, 2H), 6.25 (d, 1H), 6.87 - 6.98 (m, 2H), 7.37 - 7.42 (m, 1H), 8.06 (d, 2H), 8.12 (d, 1H), 9.02 (dd, 1H), 9.54 (d, 1H), 9.59 (s, 1H). / [MH] ⁺ = 428
113		δ ppm 3.89 (s, 3H), 4.55 (d, 2H), 6.21 (d, 1H), 6.90 (t, 1H), 6.96 (d, 1H), 7.38 - 7.41 (m, 1H), 7.87 (s, 1H), 8.01 (s, 1H), 8.28 (d, 2H), 8.59 (d, 2H), 9.58 (s, 1H). / [MH] ⁺ = 350
114		δ ppm 3.89 (s, 3H), 4.52 (d, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.48 (m, 2H), 7.66 (s, 1H), 7.81 (d, 1H), 8.50 (s, 1H), 8.56 (d, 1H), 9.32 (s, 1H), 9.55 (d, 1H). / [MH] ⁺ = 350
115		δ ppm 3.31 (s, 3H), 3.87 (s, 3H), 4.58 (d, 2H), 5.96 (d, 1H), 7.06 - 7.23 (m, 3H), 7.97 (d, 1H), 8.12 (d, 1H), 8.25 (s, 1H), 9.00 (dd, 1H), 9.53 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 428
116		δ ppm 3.25 (s, 3H), 3.87 (s, 3H), 4.56 (d, 2H), 5.92 (d, 1H), 7.06 - 7.22 (m, 3H), 7.83 (d, 1H), 7.97 (d, 2H), 8.12 (s, 1H), 8.48 (d, 2H), 9.53 (s, 1H). [MH] ⁺ = 427
117		δ ppm 3.87 (s, 3H), 4.56 (d, 2H), 5.92 (d, 1H), 7.06 - 7.21 (m, 3H), 7.93 (d, 1H), 8.19 (t, 1H), 8.25 (d, 2H), 8.59 (d, 2H), 9.53 (s, 1H). / [MH] ⁺ = 350

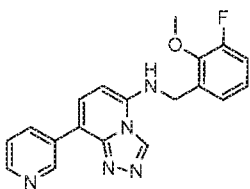
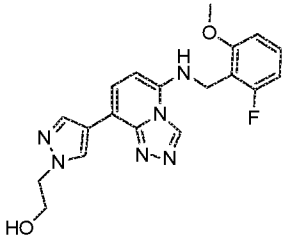
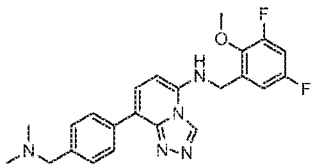
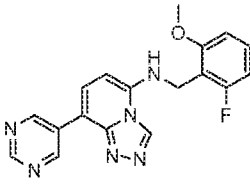
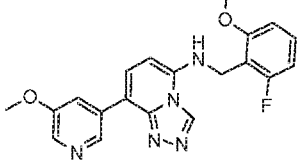
118		δ ppm 3.87 (s, 3H), 4.55 (d, 2H), 5.88 (d, 1H), 7.06 - 7.21 (m, 3H), 7.46 - 7.48 (m, 1H), 7.73 (d, 1H), 8.00 (t, 1H), 8.49 - 8.55 (m, 2H), 9.29 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 350
119		δ ppm 3.25 (s, 3H), 3.94 (s, 3H), 4.65 (s, 2H), 6.02 (d, 1H), 7.07 - 7.25 (m, 3H), 7.85 (d, 1H), 7.97 (d, 2H), 8.18 (s, 1H), 8.48 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 427
120		δ ppm 3.25 (s, 3H), 3.71 (s, 3H), , 4.63 (s, 2H), 6.06 (d, 1H), 6.90 - 6.92 (m, 1H), 7.06 (d, 1H), 7.20 (t, 1H), 7.86 (d, 1H), 7.98 (d, 2H), 8.17 (t, 1H), 8.49 (m, 2H), 9.53 (s, 1H). / [MH] ⁺ = 427
121		δ ppm 3.71 (s, 3H), 4.62 (s, 2H), 6.03 (d, 1H), 6.89 - 6.92 (m, 1H), 7.05 (dd, 1H), 7.20 (t, 1H), 7.48 (dd, 1H), 7.76 (d, 1H), 8.04 (t, 1H), 8.49 - 8.56 (m, 2H), 9.30 (s, 1H), 9.52 (s, 1H). / [MH] ⁺ = 350
122		δ ppm 3.31 (s, 3H), 3.70 (s, 3H), 4.65 (d, 2H), 6.12 (d, 1H), 6.91 - 6.93 (m, 1H), 7.06 (dd, 1H), 7.20 (t, 1H), 8.01 (d, 1H), 8.12 (d, 1H), 8.33 (t, 1H), 8.99 (dd, 1H), 9.51 (d, 1H), 9.56 (s, 1H). / [MH] ⁺ = 428

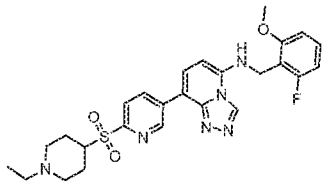
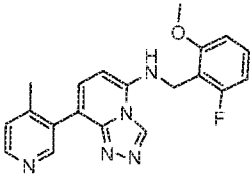
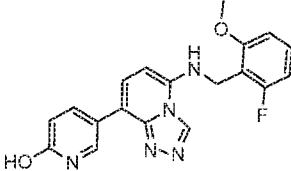
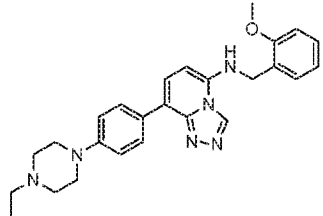
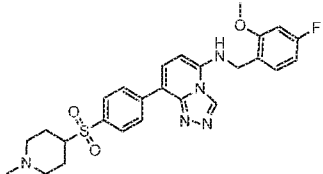
123		δ ppm 2.22 (s, 6H), 2.50 - 2.77 (m, 4H), 3.88 (s, 3H), 4.53 (d, 2H), 5.86 (d, 1H), 6.92 (t, 1H), 7.07 (d, 1H), 7.28 - 7.33 (m, 4H), 7.55 (d, 1H), 7.82 (t, 1H), 8.02 (d, 2H), 9.51 (s, 1H). / [MH] ⁺ = 402
124		δ ppm 2.04 (s, 3H), 2.12 (s, 3H), 3.72 (s, 3H), 3.87 (s, 3H), 4.46 (d, 2H), 6.08 (d, 1H), 6.90 (t, 1H), 6.96 (d, 1H), 7.09 (d, 1H), 7.27 (t, 1H), 7.40 (dd, 1H), 9.43 (s, 1H). / [MH] ⁺ = 381
125		δ ppm 3.88 (s, 3H), 3.91 (s, 3H), 4.49 (d, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.95 (d, 1H), 7.37 - 7.43 (m, 1H), 7.48 (s, 1H), 7.71 (d, 1H), 8.08 (s, 1H), 8.44 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 353
126		δ ppm 2.82 (t, 2H), 3.39 (d, 2H), 3.89 (s, 3H), 4.54 (s, 2H), 4.72 (s, 1H), 6.21 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.37 - 7.44 (m, 1H), 7.71 (s, 1H), 7.83 - 7.91 (m, 3H), 8.42 (d, 2H), 9.56 (s, 1H). / [MH] ⁺ = 472
127		δ ppm 1.22 (d, 6H), 3.74 (dt, 1H), 3.88 (s, 3H), 4.60 (s, 2H), 6.00 (d, 1H), 6.93 (t, 1H), 7.08 (d, 1H), 7.26 - 7.38 (m, 2H), 7.99 (d, 1H), 8.12 (d, 1H), 8.27 (s, 1H), 9.01 (dd, 1H), 9.54 - 9.57 (m, 1H), 9.59 (s, 1H). / [MH] ⁺ = 438

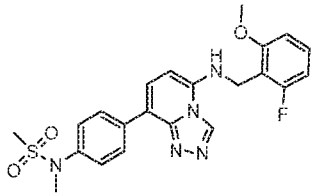
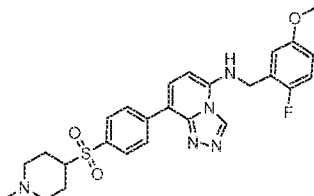
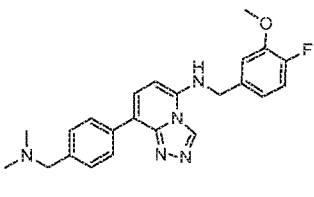
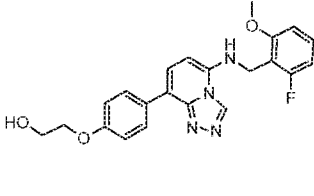
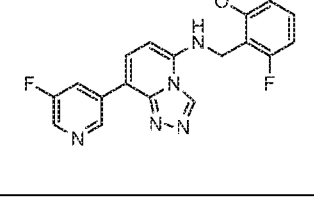
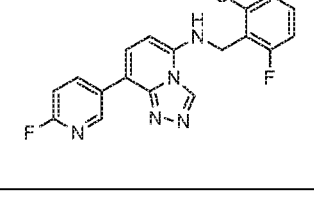
128		δ ppm 1.52 - 1.55 (m, 2H), 1.80 - 1.84 (m, 4H), 2.11 (s, 3H), 2.79 - 2.81 (m, 2H), 3.17 - 3.21 (m, 1H), 3.88 (s, 3H), 4.57 (s, 2H), 5.96 (d, 1H), 6.91 - 6.94 (m, 1H), 7.07 (d, 1H), 7.28 - 7.33 (m, 2H), 7.83 - 7.88 (m, 3H), 8.48 (d, 2H), 9.56 (s, 1H). / [MH] ⁺ = 492
129		δ ppm 3.00 (s, 3H), 3.89 (s, 3H), 4.50 (s, 2H), 5.90 (d, 1H), 6.73 - 6.77 (d, 1H), 7.00 (dd, 1H), 7.33 - 7.45 (m, 2H), 7.70 (d, 1H), 7.92 - 7.95 (m, 2H), 8.19 (dd, 1H), 9.51 (s, 1H). / [MH] ⁺ = 460
130		δ ppm 1.01 (d, 6H), 2.55 (s, 4H), 2.68 - 2.71 (m, 1H), 3.52 (s, 4H), 3.89 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.86 - 6.97 (m, 3H), 7.36 - 7.42 (m, 2H), 7.58 (d, 1H), 8.31 (dd, 1H), 8.87 (d, 1H), 9.49 (s, 1H). / [MH] ⁺ = 476
131		δ ppm 1.00 (d, 6H), 2.51 - 2.53 (m, 4H), 2.68 - 2.72 (m, 1H), 3.75 - 3.79 (m, 4H), 3.88 (s, 3H), 4.50 (d, 2H), 6.12 (d, 1H), 6.86 - 6.90 (m, 1H), 6.96 (d, 1H), 7.36 - 7.42 (m, 1H), 7.48 (t, 1H), 7.63 (d, 1H), 9.10 (s, 2H), 9.51 (s, 1H). / [MH] ⁺ = 477
132		δ ppm 1.36 - 1.40 (m, 2H), 1.76 - 1.78 (m, 2H), 2.38 - 2.43 (m, 2H), 2.95 - 2.97 (m, 2H), 3.28 - 3.34 (m, 1H), 3.89 (s, 3H), 4.54 (d, 2H), 6.22 (d, 1H), 6.87 - 6.91 (m, 1H), 6.96 (d, 1H), 7.38 - 7.42 (d, 1H), 7.81 - 7.92 (m, 4H), 8.51 (d, 2H), 9.58 (s, 1H). / [MH] ⁺ = 496

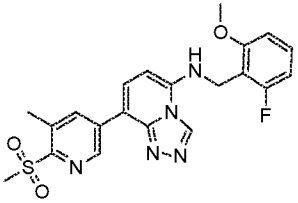
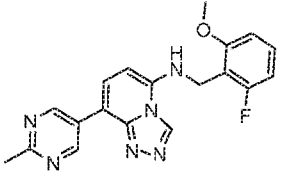
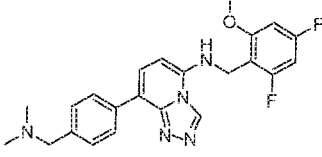
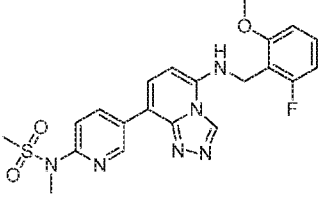
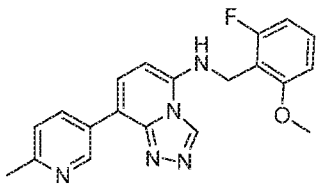
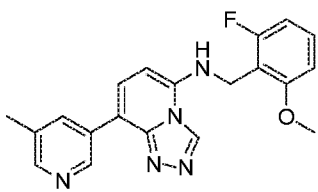
133		δ ppm 1.50 - 1.58 (m, 2H), 1.79 - 1.86 (m, 4H), 2.11 (s, 3H), 2.80 - 2.83 (d, 2H), 3.17 - 3.22 (m, 1H), 3.89 (s, 3H), 4.54 (s, 2H), 6.23 (d, 1H), 6.87 - 6.91 (m, 1H), 6.97 (d, 1H), 7.37 - 7.42 (m, 1H), 7.81 - 7.92 (m, 4H), 8.51 (d, 2H), 9.57 (s, 1H). / [MH] ⁺ = 510
134		δ ppm 3.31 (s, 3H), 3.89 (s, 3H), 4.55 (s, 2H), 6.00 (d, 1H), 6.74 - 6.77 (m, 1H), 7.00 (dd, 1H), 7.35 - 7.39 (m, 1H), 7.98 (d, 1H), 8.12 (d, 1H), 8.22 (s, 1H), 9.00 (dd, 1H), 9.53 (d, 1H), 9.57 (s, 1H). / [MH] ⁺ = 428
135		δ ppm 1.51 - 1.57 (m, 2H), 1.80 - 1.85 (m, 4H), 2.11 (s, 3H), 2.79 - 2.82 (d, 2H), 3.18 - 3.22 (m, 1H), 3.87 (s, 3H), 4.56 (s, 2H), 5.93 (d, 1H), 7.07 - 7.22 (m, 3H), 7.83 - 7.89 (m, 3H), 8.15 (s, 1H), 8.49 (d, 2H), 9.53 (s, 1H). / [MH] ⁺ = 510
136		δ ppm 3.31 (s, 3H), 3.94 (s, 3H), 4.66 (d, 2H), 6.06 (d, 1H), 7.08 - 7.12 (m, 1H), 7.22 - 7.26 (m, 2H), 8.00 (d, 1H), 8.12 (d, 1H), 8.34 (s, 1H), 9.01 (dd, 1H), 9.53 (d, 1H), 9.58 (s, 1H). / [MH] ⁺ = 428
137		δ ppm 3.94 (s, 3H), 4.65 (s, 2H), 6.02 (d, 1H), 7.08 - 7.26 (m, 3H), 7.96 (d, 1H), 8.24 - 8.27 (m, 3H), 8.60 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 350

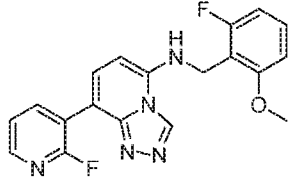
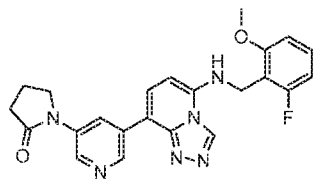
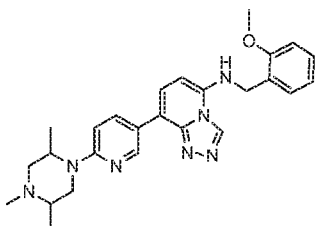
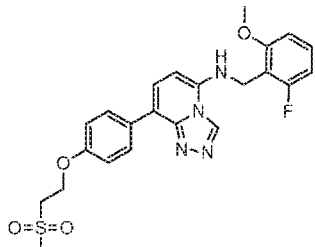
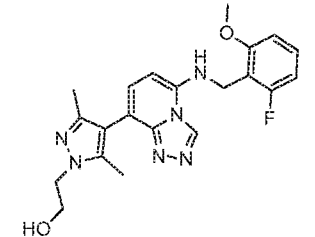
138		δ ppm 1.50 - 1.58 (m, 2H), 1.80 - 1.85 (m, 4H), 2.11 (s, 3H), 2.80 - 2.83 (d, 2H), 3.18 - 3.20 (m, 1H), 3.94 (s, 3H), 4.64 (d, 2H), 6.03 (d, 1H), 7.09 - 7.12 (m, 1H), 7.22 - 7.26 (m, 2H), 7.85 - 7.89 (m, 3H), 8.19 (s, 1H), 8.49 (d, 2H), 9.55 (s, 1H). / [MH] ⁺ = 510
139		δ ppm 2.15 (s, 3H), 2.32 (s, 3H), 3.89 (s, 3H), 4.53 (d, 2H), 6.36 (d, 1H), 6.88 - 6.99 (m, 2H), 7.39 - 7.45 (m, 1H), 7.56 (d, 1H), 7.93 (s, 1H), 9.60 (s, 1H). / [MH] ⁺ = 368
140		δ ppm 3.39 (s, 3H), 3.90 (s, 3H), 4.56 (s, 2H), 6.23 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.37 - 7.45 (m, 1H), 8.06 (d, 1H), 8.96 (d, 1H), 9.20 (t, 1H), 9.58 (s, 1H), 9.68 (d, 1H). / [MH] ⁺ = 428
141		δ ppm 3.18 (s, 6H), 3.88 (s, 3H), 4.49 (s, 2H), 6.11 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.36 - 7.43 (m, 1H), 7.46 (s, 1H), 7.61 (d, 1H), 9.09 (s, 2H), 9.50 (s, 1H). / [MH] ⁺ = 394
142		δ ppm 3.27 (s, 3H), 3.90 (s, 3H), 4.54 (s, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.37 - 7.44 (m, 1H), 7.73 (t, 2H), 7.83 (d, 1H), 7.88 (d, 1H), 8.54 (d, 1H), 8.79 (s, 1H), 9.55 (s, 1H). / [MH] ⁺ = 427
143		δ ppm 0.94 - 0.98 (m, 3H), 1.59 - 1.63 (m, 2H), 1.81 - 1.91 (m, 4H), 2.29 (q, 2H), 2.93 (d, 2H), 3.42 - 3.49 (m, 1H), 3.87 (s, 3H), 4.55 (s, 2H), 5.87 (d, 1H), 6.92 (t, 1H), 7.06 (d, 1H), 7.28 (t, 1H), 7.38 (d, 1H), 7.93 (d, 1H), 8.03 (d, 1H), 8.96 (dd, 1H), 9.47 (s, 1H), 9.53 (d, 1H). /

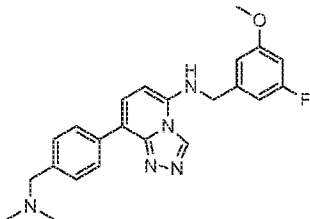
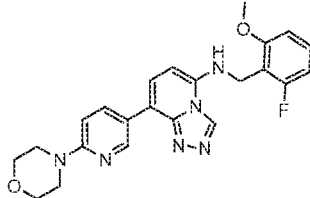
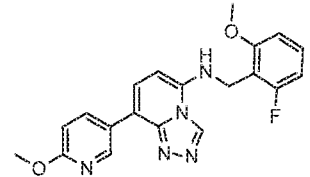
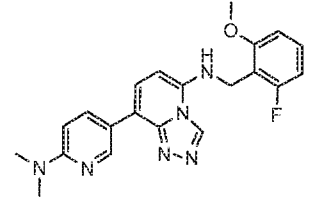
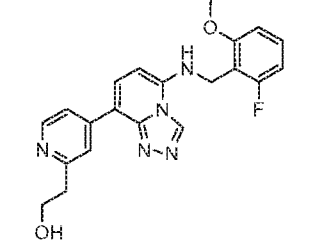
		[MH] ⁺ = 507
144		δ ppm 3.94 (s, 3H), 4.63 (s, 2H), 5.99 (d, 1H), 6.94 (s, 1H), 7.08 - 7.11 (m, 1H), 7.21 - 7.25 (m, 2H), 7.47 - 7.49 (m, 2H), 7.75 (d, 1H), 8.06 (t, 1H), 8.49 - 8.56 (m, 2H), 9.30 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 350
145		δ ppm 3.77 (q, 2H), 3.88 (s, 3H), 4.21 (t, 2H), 4.47 (d, 2H), 4.94 (t, 1H), 6.08 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.26 (t, 1H), 7.39 (q, 1H), 7.63 (d, 1H), 8.15 (s, 1H), 8.53 (s, 1H), 9.46 (s, 1H). / [MH] ⁺ = 383
146		δ ppm 2.19 (s, 6H), 3.44 (s, 2H), 3.91 (s, 3H), 4.61 (s, 2H), 5.92 (d, 1H), 7.14 (d, 1H), 7.15 - 7.32 (m, 2H), 7.36 (d, 2H), 7.61 (d, 1H), 7.89 (s, 1H), 8.09 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 424
147		δ ppm 3.88 (s, 3H), 4.53 (s, 2H), 6.20 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.39 (dd, 1H), 7.82 - 7.83 (m, 1H), 7.95 (d, 1H), 9.08 (s, 1H), 9.57 (s, 3H). / [MH] ⁺ = 351
148		δ ppm 3.91 (s, 3H), 3.90 (s, 3H), 4.54 (s, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.36 - 7.44 (m, 1H), 7.70 (s, 1H), 7.87 (d, 1H), 8.18 - 8.26 (m, 2H), 8.96 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 380

149		δ ppm 0.96 (t, 3H), 1.60 - 1.68 (m, 2H), 1.81 - 1.92 (m, 4H), 2.26 - 2.32 (m, 2H), 2.94 (d, 2H), 3.49 (t, 1H), 3.89 (s, 3H), 4.55 (s, 2H), 6.22 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.36 - 7.44 (m, 1H), 8.09 (d, 1H), 8.06 (d, 1H), 9.02 (dd, 1H), 9.53 - 9.60 (m, 2H). / [MH] ⁺ = 525
150		δ ppm 2.21 (s, 3H), 3.89 (s, 3H), 4.50 (s, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.30 (d, 1H), 7.35 (d, 1H), 7.38 - 7.44 (m, 1H), 8.43 - 8.47 (m, 2H), 9.50 (s, 1H). / [MH] ⁺ = 364
151		δ ppm 3.88 (s, 3H), 4.48 (s, 2H), 6.11 (d, 1H), 6.45 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.36 - 7.42 (m, 1H), 7.63 (d, 1H), 8.14 (dd, 1H), 8.68 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 366
152		δ ppm 1.05(t, 3H), 2.38 - 2.42 (m, 2H), 3.19 - 3.34 (m, 8H), 3.87(s, 3H), 4.52(d, 2H), 5.84(d, 1H), 6.89 - 7.07 (m, 4H), 7.26 - 7.32 (m, 2H), 7.46 (d, 1H), 7.69 (t, 1H), 8.01(d, 2H), 9.48 (s, 1H). / [MH] ⁺ = 443
153		δ ppm 1.53 - 1.57 (m, 2H), 1.81 - 1.86 (m, 4H), 2.11 (s, 3H), 2.81 - 2.83 (m, 2H), 3.20 (t, 1H), 3.89 (s, 3H), 4.53 (d, 2H), 5.97 (d, 1H), 6.75 (t, 1H), 7.01(d, 1H), 7.35(t, 1H), 7.84 - 7.90 (m, 3H), 8.08 (t, 1H), 8.48 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 510.2

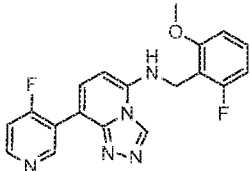
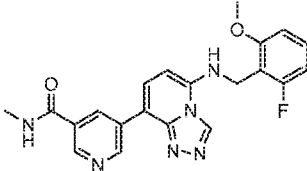
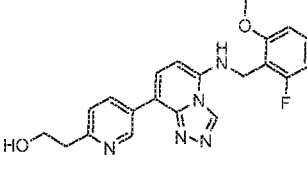
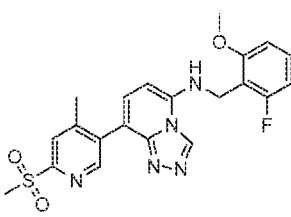
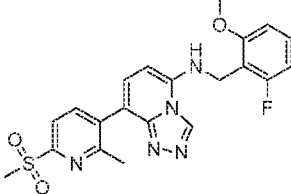
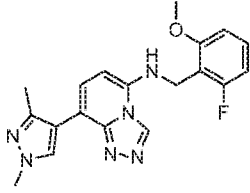
154		δ ppm 2.99 (s, 3H), 3.29 (s, 3H), 3.89 (s, 3H), 4.51 (s, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.41 (dd, 1H), 7.48 (d, 2H), 7.56 (s, 1H), 7.71 (d, 1H), 8.20 (d, 2H), 9.53 (s, 1H). / [MH] ⁺ = 456
155		δ ppm 1.52 - 1.57 (m, 2H), 1.81 - 1.86 (t, 4H), 2.11 (s, 3H), 2.80 - 2.83 (m, 2H), 3.20 (t, 1H), 3.71 (s, 3H), 4.62 (d, 2H), 6.06 (d, 1H), 6.91 (dd, 1H), 7.06 (dd, 1H), 7.21 (t, 1H), 7.86 - 7.90 (m, 3H), 8.18 (t, 1H), 8.48 (d, 2H), 9.53 (s, 1H). / [M+H] ⁺ = 510
156		δ ppm 2.09 (s, 6H), 3.41 (s, 2H), 3.85 (s, 3H), 4.56 (d, 2H), 5.96 (d, 1H), 7.00 - 7.03 (m, 1H), 7.19 (dd, 1H), 7.29 (dd, 1H), 7.35 (d, 2H), 7.59 (d, 1H), 7.94 (t, 1H), 8.08 (d, 2H), 9.47 (s, 1H). / [MH] ⁺ = 406
157		δ ppm 3.72 - 3.77 (m, 2H), 3.89 (s, 3H), 4.04 (t, 2H), 4.49 (d, 2H), 4.91 (t, 1H), 6.13 (d, 1H), 6.89 (t, 1H), 6.95 (d, 1H), 7.03 (d, 2H), 7.36 - 7.40 (m, 2H), 7.59 (d, 1H), 8.09 (d, 2H), 9.50 (s, 1H). / [MH] ⁺ = 409
158		δ ppm 3.89 (s, 3H), 4.55 (s, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.38-7.43 (m, 1H), 7.82 (t, 1H), 7.98 (d, 1H), 8.49 (d, 1H), 8.59 - 8.62 (m, 1H), 9.29 (s, 1H), 9.58 (s, 1H). / [MH] ⁺ = 368
159		δ ppm 3.89 (s, 3H), 4.52 (s, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.30 (dd, 2H), 7.39 (dd, 1H), 7.68 (t, 1H), 7.82 (d, 1H), 8.74 - 8.78 (m, 1H), 9.01 (s, 1H), 9.56 (s, 1H). / [MH] ⁺ = 368

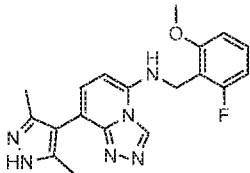
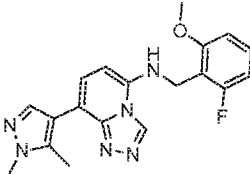
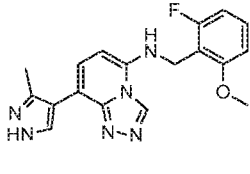
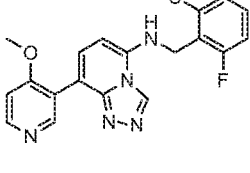
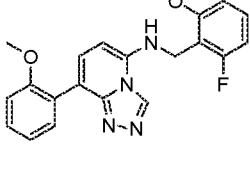
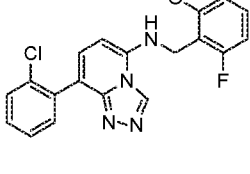
160		δ ppm 2.68 (s, 3H), 3.41(s, 3H), 3.89 (s, 3H), 4.56 (s, 2H), 6.22 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.39(dd, 1H), 7.92 (s, 1H), 8.01 (d, 1H), 8.75 (s, 1H), 9.33 (s, 1H), 9.59(s, 1H). / [MH] ⁺ = 442
161		δ ppm 2.66 (s, 3H), 3.89 (s, 3H), 4.53 (s, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (d, 1H), 7.89 (d, 1H), 9.45 (s, 2H), 9.55 (s, 1H). / [MH] ⁺ = 365
162		δ ppm 2.18 (s, 6H), 3.43 (s, 2H), 3.90 (s, 3H), 4.45-4.46 (m, 2H), 6.14 (d, 1H, J=8.0Hz), 6.91-6.95 (m, 2H), 7.36 (d, 2H), 7.41-7.42 (m, 1H), 7.67 (d, 1H, J=7.6Hz), 8.10 (d, 2H, J=8.0Hz), 9.48 (s, 1H). / [MH] ⁺ = 424
163		δ ppm 3.19(s, 3H), 3.34(s, 3H), 3.88(s, 3H), 4.52(s, 2H), 6.17(d, 1H), 6.87-6.91(m, 1H), 6.95(d, 1H), 7.40(d, 1H), 7.49-7.51(m, 1H), 7.66(s, 1H), 7.81(d, 1H), 8.61(d, 1H), 9.20(s, 1H), 9.55(s, 1H). / [MH] ⁺ = 457
164		δ ppm 2.51 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.17 (d, 1H), 6.89(t, 1H), 6.97 (d, 1H), 7.34(d, 1H), 7.40 (q, 1H), 7.58 (t, 1H), 7.76(d, 1H), 8.46 (dd, 2H), 9.19 (s, 1H), 9.53(s, 1H). / [MH] ⁺ = 364
165		δ ppm 2.07 (s, 3H), 3.88 (s, 3H), 4.50 (s, 2H), 6.16 (s, 1H), 6.87-6.96 (m, 2H), 7.39 (s, 1H), 7.63 (s, 1H), 7.77 (s, 1H), 8.36 (s, 2H), 9.10 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 364

166		δ ppm 3.87 (s, 3H), 4.51 (s, 2H), 6.16 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.38 (q, 1H), 7.47 (t, 1H), 7.59 (d, 1H), 7.70-7.71 (m, 1H), 8.20 (d, 1H), 8.58 (t, 1H), 9.52 (s, 1H). / [MH] ⁺ = 368
167		δ ppm 2.10-2.16 (m, 2H), 2.51-2.55 (m, 2H), 3.88 (s, 3H), 3.94 (t, 2H), 4.52 (d, 2H), 6.18 (d, 1H), 6.88 (t, 1H), 6.95 (d, 2H), 7.38 (t, 3H), 7.68 (t, 1H), 7.80 (d, 1H), 8.75 (s, 1H), 8.85 (s, 1H), 9.06 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 433
168		δ ppm 0.91-0.92 (d, 3H), 1.16-1.18 (d, 3H), 2.24 (s, 3H), 2.29-2.32 (dd, 1H), 2.72-2.76 (dd, 1H), 2.92-2.93 (m, 1H), 3.22-3.26 (dd, 1H), 3.87-3.93 (m, 4H), 4.43-4.45 (m, 1H), 4.51-4.52 (d, 2H), 5.82-5.84 (d, 1H), 6.84-6.86 (d, 1H), 6.90-6.93 (t, 2H), 7.05-7.07 (d, 1H), 7.27-7.32 (m, 2H), 7.47-7.49 (d, 1H), 7.68-7.71 (t, 1H), 8.23-8.26 (dd, 1H), 8.80-8.81 (d, 1H), 9.47 (s, 1H). / [MH] ⁺ = 458
169		δ ppm 3.09 (s, 3H), 3.64 (t, 2H), 3.87 (s, 3H), 4.39 (t, 2H), 4.48 (d, 2H), 6.12 (d, 1H), 6.83 (m, 1H), 6.83-6.89 (m, 1H), 7.07 (d, 2H), 7.39-7.41 (m, 2H), 7.59 (d, 1H), 8.11 (d, 2H), 9.49 (s, 1H). / [MH] ⁺ = 471
170		δ ppm 2.06 (s, 3H), 2.15 (s, 3H), 3.75 (t, 2H), 3.89 (s, 3H), 4.06 (t, 2H), 4.47 (d, 2H), 4.91 (t, 1H), 6.09 (d, 1H), 6.91 (t, 1H), 6.97 (d, 1H), 7.09 (d, 1H), 7.27 (t, 1H), 7.41 (q, 1H), 9.43 (s, 1H). / [MH] ⁺ = 411

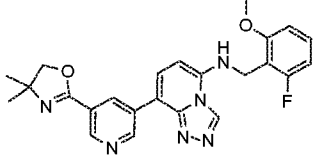
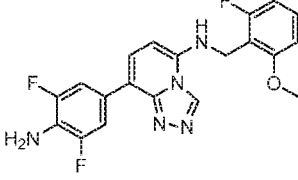
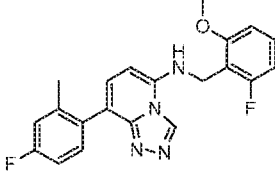
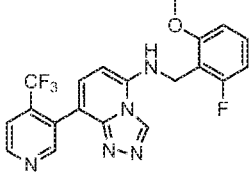
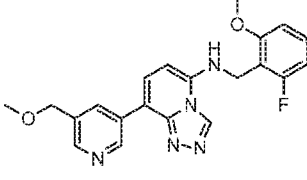
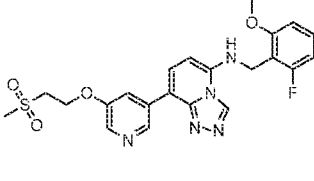
171		δ ppm 2.16 (s, 6H), 3.40 (s, 2H), 3.75 (s, 3H), 4.56 - 4.57 (d, 2H), 5.90-5.92 (d, 1H), 6.72-6.76 (dd, 1H), 6.85 - 6.89 (m, 2H), 7.33 - 7.35 (d, 2H), 7.57 - 7.59 (d, 1H), 7.96 - 7.98 (t, 1H), 8.06 - 8.08 (d, 2H), 9.45 (s, 1H). / [MH] ⁺ = 406
172		δ ppm 3.50 (broad, 4H), 3.72-3.73 (m, 4H), 3.88 (s, 3H), 4.49 (d, 2H), 6.13(d, 1H), 6.88-6.95 (m, 3H), 7.40 (s, 2H), 7.61 (d, 1H), 8.35 (d, 1H), 8.91 (s, 1H), 9.50 (s, 1H). / [MH] ⁺ = 435
173		δ ppm 3.88 (s, 3H), 3.92 (s, 3H), 4.53 (s, 2H), 6.41 (d, 1H), 6.86(t, 1H), 6.96 (q, 2H), 7.38 (q, 1H), 7.79 (d, 1H), 8.18 (dd, 1H), 8.63 (d, 1H), 9.57 (s, 1H). / [MH] ⁺ = 380
174		δ ppm 3.06 (s, 6H), 3.89 (s, 3H), 4.49 (d, 2H), 6.11 (d, 1H), 6.74 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.33 (t, 1H), 7.36-7.42 (m, 1H), 7.56 (d, 1H), 8.28 (d, 1H), 8.85 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 393
175		δ ppm 2.96 (t, 2H), 3.81 (t, 2H), 3.90 (s, 3H), 4.55-4.57 (m, 2H), 6.23 (d, 1H, J = 7.6Hz), 6.89 (t, 1H), 6.97 (d, 1H, J = 8.4Hz), 7.40 (dd, 1H), 7.90-7.91 (m, 1H), 8.03 (d, 1H, J = 8.0Hz), 8.18-8.22 (m, 2H), 8.51-8.52 (m, 1H), 9.58 (s, 1H). / [MH] ⁺ = 394

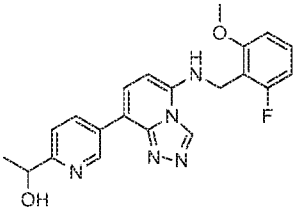
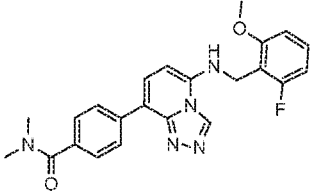
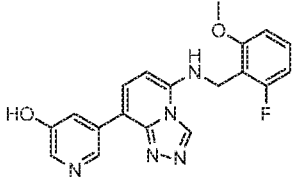
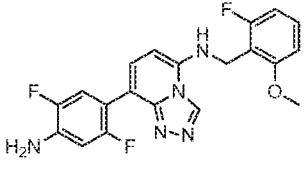
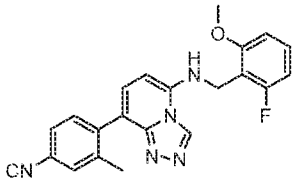
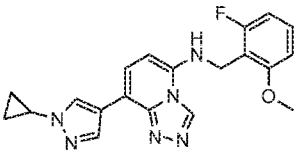
176		δ ppm 3.86 (s, 3H) 3.89 (s, 3H) 4.50 (s, 2H) 6.12 (d, 1H) 6.89 (t, 1H) 6.96 (d, 1H) 7.11 (dd, 1H) 7.36 - 7.44 (m, 1H) 7.56 (d, 1H) 8.15 - 8.22 (m, 2H) 9.48 (s, 1H). / [MH] ⁺ = 380
177		δ ppm 3.33 (s, 3H), 3.89 (s, 3H), 4.53 (s, 2H), 6.19 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.41 (q, 1H), 7.63 (d, 1H), 7.84 - 7.90 (m, 2H), 8.31 (t, 1H), 9.53 (s, 1H). / [MH] ⁺ = 445
178		δ ppm 3.00 (d, 6H), 3.89 (s, 3H), 4.52 (s, 2H), 6.17 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.32 - 7.44 (m, 3H), 7.53 (dd, 1H), 7.71 (s, 1H), 8.01 (t, 1H), 9.52 (s, 1H). / [MH] ⁺ = 438
179		δ ppm 1.41 - 1.55 (m, 2H), 1.73 (d, 2H), 1.82 (d, 1H), 2.40 - 2.49 (m, 2H), 2.98 (d, 2H), 3.53 - 3.65 (m, 1H), 3.89 (s, 3H), 4.56 (s, 2H), 6.25 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.37 - 7.45 (m, 1H), 7.98 (s, 1H), 8.10 (d, 1H), 8.07 (d, 1H), 9.02 (dd, 1H), 9.56 - 9.62 (m, 2H). / [MH] ⁺ = 497
180		δ ppm 1.15 - 1.16 (d, 3H), 1.91 - 1.95 (m, 1H), 2.11 - 2.14 (dd, 1H), 2.20 (s, 3H), 2.70 - 2.72 (d, 1H), 2.84 - 2.86 (d, 1H), 3.00 - 3.05 (m, 1H), 3.87 (s, 3H), 4.02 - 4.05 (d, 1H), 4.51 - 4.52 (d, 3H), 5.82 - 5.83 (d, 1H), 6.84 - 6.86 (d, 1H), 6.90 - 6.93 (t, 1H), 7.05 - 7.07 (d, 1H), 7.27 - 7.31 (m, 2H), 7.49 - 7.50 (d, 1H), 7.71 - 7.73 (t, 1H), 8.26 - 8.29 (dd, 1H), 8.84 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 444

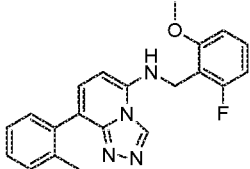
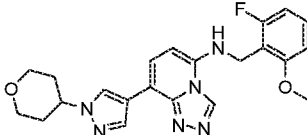
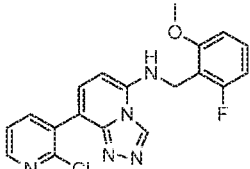
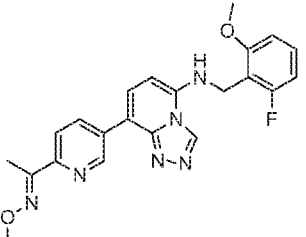
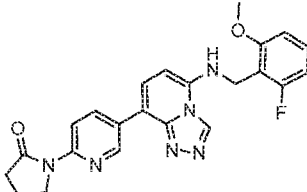
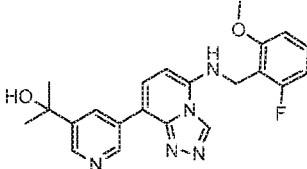
181		δ ppm 3.89 (s, 3H), 4.53 (s, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.37 - 7.48 (m, 2H), 7.54 (d, 1H), 7.69 (s, 1H), 8.57 - 8.61 (m, 1H), 9.04 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 368
182		δ ppm 2.84 (d, 3H), 3.89 (s, 3H), 4.54 (s, 2H), 6.22 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.38 - 7.43 (m, 1H), 7.74 (s, 1H), 7.89 (d, 1H), 8.70 - 8.71 (m, 1H), 8.88 (d, 2H), 9.49 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 407
183		δ ppm 2.92 (t, 2H), 3.78 (dd, 2H), 3.89 (s, 3H), 4.52 (d, 2H), 4.70 (t, 1H), 6.16 (d, 1H), 6.97 - 6.87 (m, 2H), 7.42 - 7.35 (m, 2H), 7.60 (t, 1H), 7.74 (d, 1H), 8.44 (dd, 1H), 9.19 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 394
184		δ ppm 2.37 (s, 3H), 3.34 (s, 3H), 3.89 (s, 3H), 4.52 (s, 2H), 6.17 (d, 1H), 6.90 (t, 1H), 6.96 (d, 1H), 7.41 - 7.45 (m, 2H), 7.69 (s, 1H), 8.05 (s, 1H), 8.71 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 442
185		δ ppm 2.50 (s, 3H), 3.32 (s, 3H), 3.89 (s, 3H), 4.52 (s, 2H), 6.17 (d, 1H), 6.90 (t, 1H), 6.96 (d, 1H), 7.40 - 7.44 (m, 2H), 7.66 (s, 1H), 7.95 (d, 1H), 8.11 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 442
186		δ ppm 2.35 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.47 (d, 2H), 6.08 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.22 - 7.24 (m, 1H), 7.40 - 7.34 (m, 2H), 8.36 (s, 1H), 9.46 (s, 1H). / [MH] ⁺ = 367

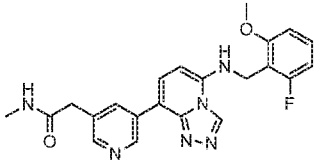
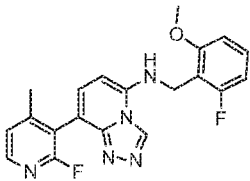
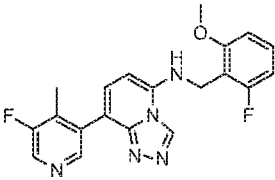
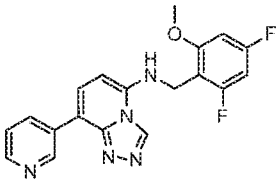
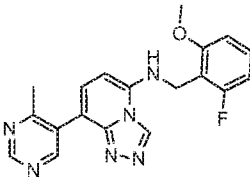
187		δ ppm 2.11 (s, 6H), 3.89 (s, 3H), 4.47 (d, 2H), 6.09 (d, 1H), 6.91 (t, 1H), 6.97 (d, 1H), 7.12 (d, 1H), 7.24 (t, 1H), 7.43 (q, 1H), 9.43 (s, 1H), 12.23 (s, 1H). / [MH] ⁺ = 367
188		δ ppm 2.34 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 4.45 (d, 2H), 6.06 (d, 1H), 6.89 - 6.84 (m, 2H), 6.94 (d, 1H), 7.25 - 7.19 (m, 2H), 7.41 - 7.35 (m, 1H), 7.78 (s, 1H), 9.43 (s, 1H). / [MH] ⁺ = 367
189		δ ppm 2.38 (s, 3H), 3.87 (s, 3H), 4.45 (d, 2H), 6.07 (d, 1H), 6.85 - 6.96 (m, 2H), 7.20 - 7.42 (m, 3H), 7.96 - 8.40 (m, 1H), 9.44 (s, 1H), 12.55 - 12.66 (m, 1H). / [MH] ⁺ = 353
190		δ ppm 3.81 (s, 3H), 3.89 (s, 3H), 4.50 (s, 2H), 6.11 (d, 1H), 6.89 (s, 1H), 6.96 (d, 1H), 7.18 (d, 1H), 7.37 - 7.42 (m, 2H), 8.45 (d, 1H), 8.62 (s, 1H), 9.47 (s, 1H). / [MH] ⁺ = 380
191		δ ppm 3.72 (s, 3H), 3.89 (s, 3H), 4.49 (s, 2H), 6.08 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.02 (t, 1H), 7.12 (d, 1H), 7.30 - 7.43 (m, 3H), 7.57 (d, 1H), 9.45 (s, 1H). / [MH] ⁺ = 379
192		δ ppm 3.89 (s, 3H), 4.50 (s, 2H), 6.12 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.31 (d, 1H), 7.38 - 7.45 (m, 3H), 7.54 (d, 1H), 7.55 - 7.60 (m, 2H), 9.49 (s, 1H). / [MH] ⁺ = 383

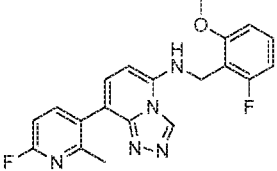
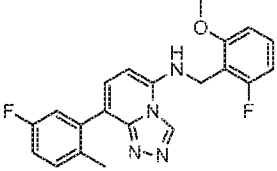
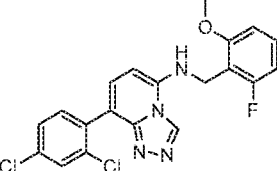
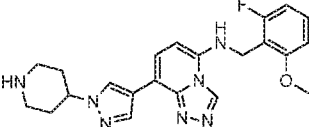
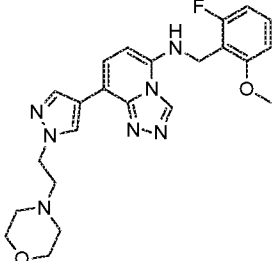
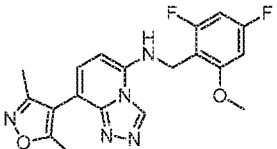
193		δ ppm 3.89 (s, 3H), 4.49 (s, 2H), 6.11 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.17 (d, 1H), 7.38 - 7.45 (m, 1H), 7.49 (s, 1H), 7.54 (d, 1H), 7.64 (t, 1H), 7.74 (t, 1H), 7.87 (d, 1H), 9.48 (s, 1H). / [MH] ⁺ = 417
194		δ ppm 3.03 (s, 6H), 3.89 (s, 3H), 4.54 (d, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (q, 1H), 7.65 (d, 1H), 7.75 (s, 1H), 7.91 (d, 1H), 8.70 - 8.73 (m, 1H), 9.36 (d, 1H), 9.57 (s, 1H). / [MH] ⁺ = 421
195		δ ppm 3.00 (s, 3H), 3.05 (s, 3H), 3.89 (s, 3H), 4.54 (d, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.37 - 7.41 (m, 1H), 7.74 - 7.46 (m, 1H), 7.93 (d, 1H), 8.52 (d, 1H), 8.68 (t, 1H), 9.38 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 421
196		δ ppm 2.12 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.41 (m, 1H), 7.58 (d, 1H), 7.75 (d, 1H), 8.15 (d, 1H), 8.48 - 8.51 (m, 1H), 9.16 (d, 1H), 9.54 (s, 1H), 10.61 (s, 1H). / [MH] ⁺ = 407
197		δ ppm 1.43 (d, 3H), 3.90 (s, 3H), 4.53 (d, 2H), 4.85 - 4.87 (m, 1H), 5.39 (d, 1H), 6.19 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.39 (q, 1H), 7.64 (t, 1H), 7.79 (d, 1H), 8.50 (d, 1H), 9.18 (s, 1H), 9.55 (s, 1H). / [MH] ⁺ = 394
198		δ ppm 2.18 - 2.22 (m, 2H), 3.03 (s, 3H), 3.30 (s, 2H), 3.88 (s, 3H), 4.24 (t, 2H), 4.52 (s, 2H), 6.17 (d, 1H), 6.88 (t, 1H), 6.95 (t, 1H), 7.38 (d, 1H), 7.68 (t, 1H), 7.86 (d, 2H), 8.21 - 8.24 (m, 2H), 8.94 (d, 1H), 9.54 (s, 1H). / [MH] ⁺ = 486

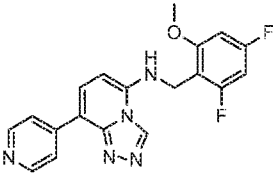
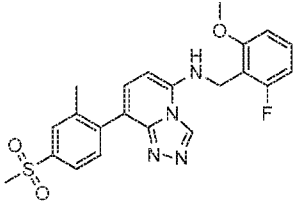
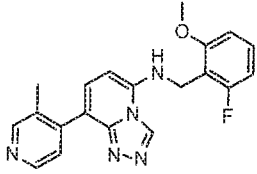
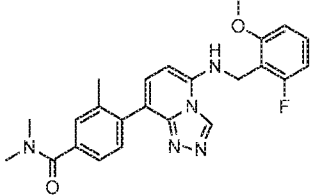
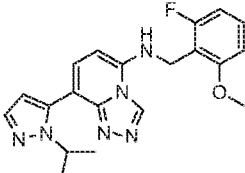
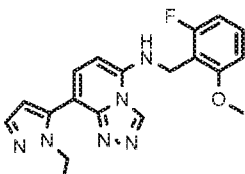
199		δ ppm 1.34 (s, 6H), 3.89 (s, 3H), 4.18 (s, 2H), 4.54 (d, 2H), 6.21 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.41 (q, 1H), 7.76 (t, 1H), 7.95 (d, 1H), 8.90 (s, 1H), 9.15 (s, 1H), 9.39 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 447
200		δ ppm 3.88 (s, 3H), 4.49 (s, 2H), 5.32 (s, 2H), 6.11 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.34 - 7.44 (m, 1H), 7.47 (s, 1H), 7.69 (d, 1H), 7.88 - 7.94 (m, 2H), 9.50 (s, 1H). / [MH] ⁺ = 400
201		δ ppm 2.17 (s, 3H), 3.89 (s, 3H), 4.48 (d, 2H), 6.10 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.05 - 7.11 (m, 1H), 7.16 - 7.21 (m, 2H), 7.32 - 7.44 (m, 3H), 9.47 (s, 1H). / [MH] ⁺ = 381
202		δ ppm 3.89 (s, 3H), 4.51 (s, 2H), 6.16 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.29 (d, 1H), 7.38 - 7.45 (m, 1H), 7.90 (d, 1H), 8.80 (s, 1H), 8.89 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 418
203		δ ppm 3.36 (s, 3H), 3.90 (s, 3H), 4.53 (s, 4H), 6.19 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (q, 1H), 7.68 (t, 1H), 7.84 (d, 1H), 8.45 (s, 1H), 8.56 (s, 1H), 9.24 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 394
204		δ ppm 3.11 (s, 3H), 3.68 (t, 2H), 3.86 (s, 3H), 4.49 - 4.52 (m, 4H), 6.14 - 6.16 (m, 1H), 6.87 (t, 1H), 6.94 (d, 1H), 7.35 - 7.41 (m, 1H), 7.21 - 7.75 (m, 1H), 7.88 (d, 1H), 8.26 (s, 2H), 9.01 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 472

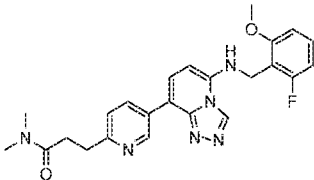
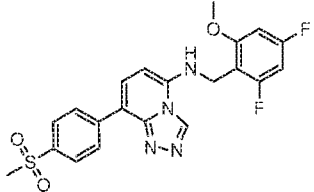
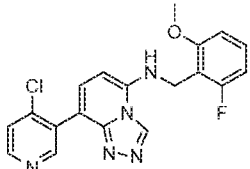
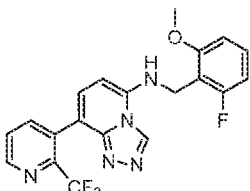
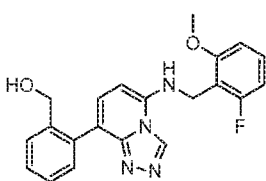
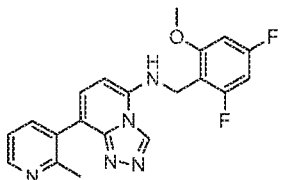
205		δ ppm 1.41 (d, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 4.77 (q, 1H), 5.40 (d, 1H), 6.17 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 7.57 - 7.62 (m, 2H), 7.76 (d, 1H), 8.52 - 8.54 (m, 1H), 9.19 (d, 1H), 9.54 (s, 1H). / [MH] ⁺ = 394
206		δ ppm 3.00 (s, 6H), 3.89 (s, 3H), 4.52 (d, 2H), 6.19 (d, 1H), 6.89 (t, 2H), 7.40 (q, 1H), 7.50 (d, 2H), 7.60 (d, 1H), 7.77 (d, 1H), 8.24 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 420
207		δ ppm 3.87 (s, 3H), 4.50 (s, 2H), 6.15 (d, 1H), 6.86 - 6.95 (m, 2H), 7.38 (s, 1H), 7.62 (s, 1H), 7.75 (d, 1H), 8.04 (s, 1H), 8.09 (s, 1H), 8.69 (s, 1H), 9.53 (s, 1H), 9.97 (s, 1H). / [MH] ⁺ = 366
208		δ ppm 3.88 (s, 3H), 4.48 (s, 2H), 5.60 (s, 2H), 6.10 (d, 1H), 6.63 (dd, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.35 - 7.45 (m, 3H), 7.69 (dd, 1H), 9.47 (s, 1H). / [MH] ⁺ = 400
209		δ ppm 2.23 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.30 (d, 1H), 7.37 - 7.45 (m, 1H), 7.56 (dd, 2H), 7.71 - 7.74 (m, 1H), 7.81 (s, 1H), 9.50 (s, 1H). / [MH] ⁺ = 388
210		δ ppm 1.01 - 1.09 (m, 2H) 1.10 - 1.18 (m, 2H) 3.85 (tt, 1H) 3.93 (s, 3H) 4.52 (d, 2H) 6.13 (d, 1H) 6.93 (t, 1H) 7.01 (d, 1H) 7.35 (br. s., 1H) 7.40 - 7.49 (m, 1H) 7.69 (d, 1H) 8.19 (s, 1H) 8.59 (s, 1H) 9.52 (s, 1H). / [MH] ⁺ = 379

211		δ ppm 2.16 (s, 3H), 3.89 (s, 3H), 4.49 (d, 2H), 6.11 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.19 (d, 1H), 7.23 - 7.32 (m, 4H), 7.36 - 7.44 (m, 2H), 9.47 (s, 1H). / [MH] ⁺ = 363
212		δ ppm 2.13 - 2.25 (m, 4H), 3.53 - 3.64 (m, 2H), 3.93 (s, 3H), 4.09 - 4.19 (m, 2H), 4.41 (dt, 1H), 4.61 (d, 2H), 4.91 (t, 1H), 6.22 (d, 1H), 6.72 - 6.82 (m, 2H), 7.50 (d, 1H), 8.02 (s, 1H), 8.68 (s, 1H), 8.80 (s, 1H). / [MH] ⁺ = 423
213		δ ppm 3.89 (s, 3H), 4.54 (d, 2H), 6.29 (d, 1H), 6.91 (t, 1H), 6.98 (d, 1H), 7.38 - 7.46 (m, 1H), 7.53 - 7.62 (m, 2H), 7.87 (s, 1H), 8.04 (dd, 1H), 8.48 (dd, 1H), 9.58 (s, 1H). / [M+H] ⁺ = 384
214		δ ppm 2.29 (s, 3H), 3.90 (s, 3H), 3.98 (d, 3H), 4.54 (s, 2H), 6.21 (d, 1H), 6.90 (d, 1H), 6.97 (d, 1H), 7.41 (t, 1H), 7.74 (d, 1H), 7.89 (d, 1H), 7.94 (d, 1H), 8.65 (d, 1H), 9.39 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 421
215		δ ppm 2.06 (t, 2H), 2.59 (t, 2H), 3.88 (s, 3H), 4.04 (t, 2H), 4.51 (d, 1H), 6.15 (d, 1H), 6.87 (t, 1H), 6.94 (d, 1H), 7.38 (dd, 1H), 7.59 (t, 1H), 7.74 (d, 1H), 8.35 (d, 1H), 8.55 (dd, 1H), 9.16 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 433
216		δ ppm 1.52 (s, 6H), 3.90 (s, 3H), 4.53 (d, 2H), 5.27 (s, 1H), 6.18 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 7.63 (t, 1H), 7.78 (d, 1H), 8.57 (d, 1H), 8.62 (d, 1H), 9.16 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 408

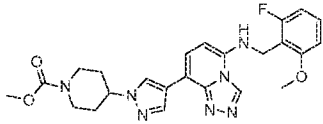
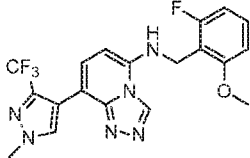
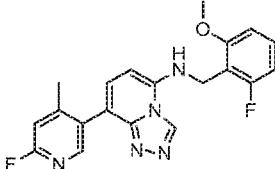
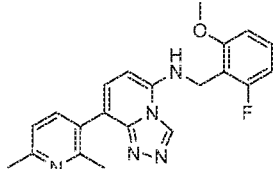
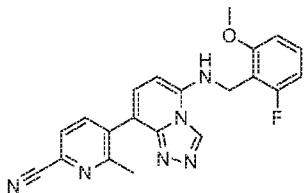
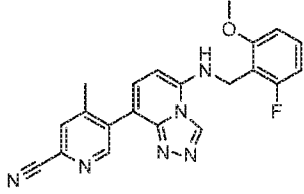
217		δ ppm 2.60 (d, 3H), 3.52 (s, 2H), 3.89 (s, 3H), 4.53 (d, 2H), 6.20 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (dd, 1H), 7.65 (t, 1H), 7.77 (d, 1H), 8.09 (s, 1H), 8.37 (d, 1H), 8.44 (d, 1H), 9.16 (d, 1H), 9.55 (s, 1H). / [MH] ⁺ = 421
218		δ ppm 2.18 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.15 (d, 1H), 6.92 (t, 1H), 6.98 (d, 1H), 7.32 - 7.42 (m, 3H), 7.59 (t, 1H), 8.15 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 382
219		δ ppm 2.12 (s, 3H), 3.88 (s, 3H), 4.50 (d, 2H), 6.14 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.34 - 7.40 (m, 2H), 7.61 (s, 1H), 8.39 (s, 1H), 8.50 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 382
220		δ ppm 3.90 (s, 3H), 4.48 (d, 2H), 6.17 (d, 1H), 6.90 - 6.95 (m, 2H), 7.48 (dd, 1H), 7.61 (t, 1H), 7.80 (d, 1H), 8.50 (dd, 1H), 8.55 (dd, 1H), 9.31 (d, 1H), 9.52 (s, 1H). / [MH] ⁺ = 368
221		δ ppm 2.41 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.17 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.40 - 7.42 (m, 1H), 7.64 (t, 1H), 8.72 (s, 1H), 9.06 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 365

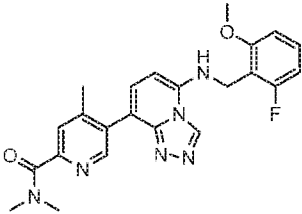
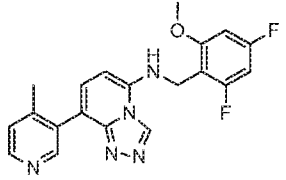
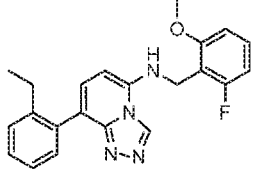
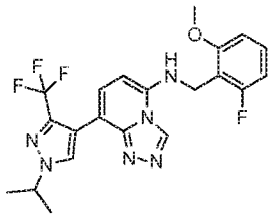
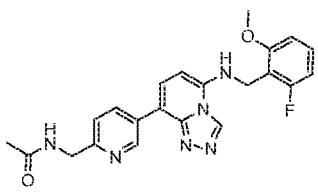
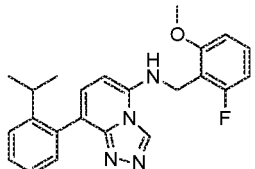
222		δ ppm 2.33 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.09 (dd, 1H), 7.31 (d, 1H), 7.41 (dd, 1H), 7.53 (t, 1H), 7.94 (t, 1H), 9.51 (s, 1H). / [MH] ⁺ = 382
223		δ ppm 2.14 (s, 3H), 3.89 (s, 3H), 4.49 (s, 2H), 6.11 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.11 - 7.19 (m, 2H), 7.25 (d, 1H), 7.34 (dd, 1H), 7.37 - 7.44 (m, 1H), 7.47 (s, 1H), 9.49 (s, 1H). / [MH] ⁺ = 381
224		δ ppm 3.89 (s, 3H), 4.50 (s, 2H), 6.12 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.34 (d, 1H), 7.37 - 7.45 (m, 1H), 7.52 (dd, 1H), 7.61 (d, 2H), 7.75 (d, 1H), 9.49 (s, 1H). / [MH] ⁺ = 417
225		δ ppm 1.81 (d, 2H), 1.99 (d, 2H), 2.59 - 2.68 (m, 2H), 3.05 (d, 2H), 3.87 (s, 3H), 4.26 (s, 1H), 4.46 (s, 2H), 6.08 (s, 1H), 6.82 - 7.00 (m, 2H), 7.26 (s, 1H), 7.39 (s, 1H), 7.63 (s, 1H), 8.15 (s, 1H), 8.52 (s, 1H), 9.46 (s, 1H). / [MH] ⁺ = 422
226		δ ppm 2.49 (s, 4H), 2.80 (t, 2H), 3.61 (t, 4H), 3.94 (s, 3H), 4.35 (t, 2H), 4.52 (d, 2H), 6.13 (d, 1H), 6.93 (s, 1H), 7.01 (d, 1H), 7.34 (s, 1H), 7.44 (d, 1H), 7.68 (d, 1H), 8.19 (s, 1H), 8.61 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 452
227		δ ppm 2.18 (s, 3H), 2.34 (s, 3H), 3.89 (s, 3H), 4.44 (d, 2H), 6.10 (d, 1H), 6.90 - 6.95 (m, 2H), 7.31 (d, 1H), 7.47 (t, 1H), 9.46 (s, 1H). / [MH] ⁺ = 386

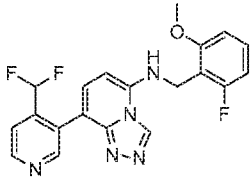
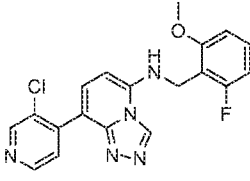
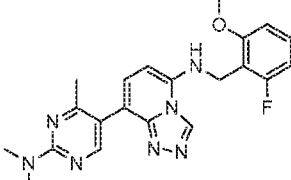
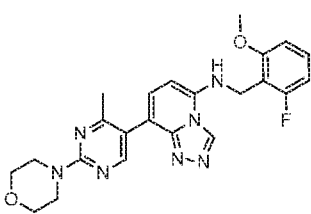
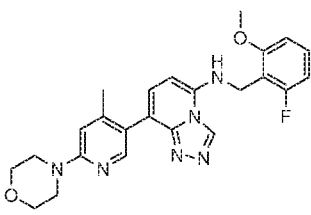
228		δ ppm 3.89 (s, 3H), 4.48 (d, 2H), 6.19 (d, 1H), 6.90 - 6.95 (m, 2H), 7.80 (d, 1H), 8.01 (d, 1H), 8.27 (d, 2H), 8.59 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 368
229		δ ppm 2.09 (s, 3H), 2.53 (s, 3H), 3.90 (s, 3H), 4.55 (d, 2H), 6.33 (d, 1H), 6.91 (t, 1H), 6.98 (d, 1H), 7.42 (q, 1H), 7.51 (t, 1H), 7.61 (d, 1H), 7.82 - 7.86 (m, 2H), 7.92 (s, 1H), 9.60 (s, 1H). [MH] ⁺ = 441
230		δ ppm 2.43 (s, 3H), 3.90 (s, 3H), 4.58 (d, 2H), 6.32 (d, 1H), 6.91 (t, 1H), 6.99 (d, 1H), 7.43 (q, 1H), 7.71 (d, 1H), 8.11 - 8.15 (m, 2H), 8.76 (d, 1H), 8.84 (s, 1H), 9.62 (s, 1H). / [MH] ⁺ = 364.
231		δ ppm 2.20 (s, 3H), 3.00 (s, 6H), 3.88 (d, 3H), 4.49 (d, 2H), 6.13 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.26 (dd, 2H), 7.34 - 7.46 (m, 4H), 9.49 (s, 1H), [MH] ⁺ = 434.
232		δ ppm 1.34 (d, 6H), 3.36 (s, 3H), 4.39 - 4.46 (m, 1H), 4.51 (s, 2H), 6.12 (d, 1H), 6.32 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 7.40 (dd, 1H), 7.54 (d, 1H), 7.65 (s, 1H), 9.52 (s, 1H). / [MH] ⁺ = 381
233		δ ppm 1.25 (t, 3 H), 3.89 (s, 3 H), 4.10 (q, 2 H), 4.51 (s, 2 H), 6.13 (d, 1 H), 6.40 (d, 1 H), 6.89 (t, 1 H), 6.96 (d, 1 H), 7.35 (d, 1 H), 7.41 (dd, 1 H), 7.52 (d, 1 H), 7.65 (s, 1 H), 9.52 (s, 1 H). / [MH] ⁺ = 367.0

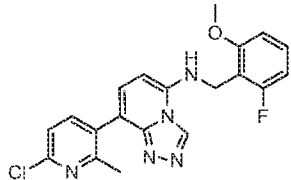
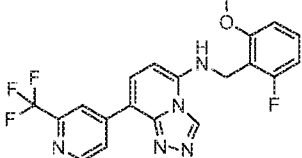
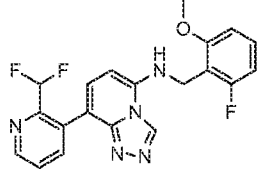
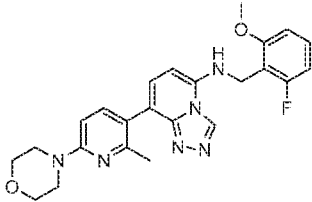
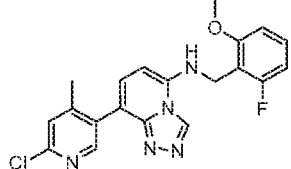
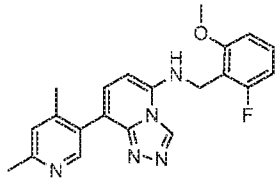
234		δ ppm 2.77 (t, 2H), 2.82 (s, 3H), 2.98 (m, 5H), 3.88 (s, 3H), 4.51 (d, 2H), 6.16 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.36 - 7.40 (m, 2H), 7.60 (t, 1H), 7.73 (d, 1H), 8.41 (dd, 1H), 9.18 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 449
235		δ ppm 3.25 (s, 3H), 3.90 (s, 3H), 4.49 (d, 2H), 6.20 (d, 1H), 6.90 - 6.96 (m, 2H), 7.75 (t, 1H), 7.91 (d, 1H), 7.98 (d, 2H), 8.50 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 445
236		δ ppm 3.90 (s, 3H), 4.58 (d, 2H), 6.45 (d, 1H), 6.92 (t, 1H), 6.99 (d, 1H), 7.43 (dd, 1H), 7.72 - 7.78 (m, 2H), 8.15 (s, 1H), 8.63 (d, 1H), 8.72 (s, 1H), 9.66 (s, 1H). / [MH] ⁺ = 384
237		δ ppm 3.88 (s, 3H), 4.50 (s, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.27 (d, 1H), 7.41 (dd, 1H), 7.59 (s, 1H), 8.01 (dd, 1H), 8.07 (d, 1H), 8.80 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 418
238		δ ppm 3.91 (s, 3H), 4.37 (s, 2H), 4.51 (s, 2H), 5.27 (s, 1H), 6.14 (d, 1H), 6.88 - 7.02 (m, 2H), 7.27 (d, 1H), 7.31 - 7.39 (m, 2H), 7.39 - 7.45 (m, 2H), 7.60 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 379
239		δ ppm 2.37 (s, 3H), 3.90 (s, 3H), 4.44 (d, 2H), 6.12 (d, 1H), 6.93 - 6.96 (m, 2H), 7.28 - 7.32 (m, 2H), 7.44 (t, 1H), 7.72 (d, 1H), 8.47 (d, 1H), 9.47 (s, 1H). / [MH] ⁺ = 382

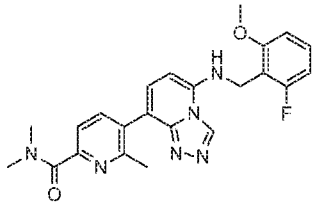
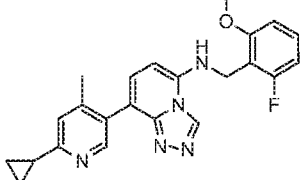
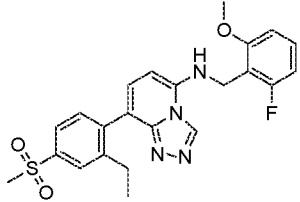
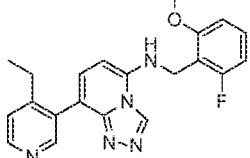
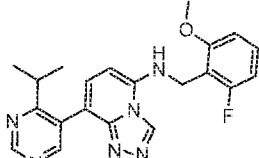
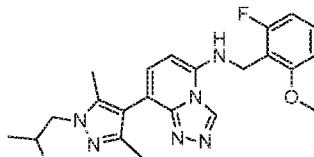
240		δ ppm 2.38 (s, 3H), 3.33 (s, 3H), 3.90 (s, 3H), 4.48 (d, 2H), 6.17 (d, 1H), 6.91 - 6.97 (m, 2H), 7.44 (d, 1H), 7.64 (t, 1H), 8.06 (s, 1H), 8.71 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 460
241		δ ppm 3.32 (s, 3H), 3.33 (s, 3H), 3.90 (s, 3H), 4.47 (d, 2H), 6.17 (d, 1H), 6.92 - 6.97 (m, 2H), 7.43 (d, 1H), 7.62 (t, 1H), 7.96 (d, 1H), 8.12 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 460 .1
242		δ ppm 3.87 (d, 3H), 4.57 (s, 2H), 6.18 (d, 1H), 6.93 (dd, 1H), 7.461 - 7.69 (m, 3H), 7.80 (d, 1H), 8.50 - 8.55 (m, 2H), 9.31 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 368
243		δ ppm 3.87 (d, 3H), 4.59 (s, 2H), 6.20 (d, 1H), 6.94 (d, 1H), 7.43 (q, 1H), 7.90 (s, 1H), 8.01 (d, 1H), 8.27 (d, 2H), 8.59 (d, 2H), 9.54 (s, 1H). / [MH] ⁺ = 368
244		δ ppm 3.25 (s, 3H), 3.87 (s, 3H), 4.58 (d, 2H), 6.22 (d, 1H), 6.93 (d, 1H), 7.44 (q, 1H), 7.83 (t, 1H), 7.92 (d, 1H), 7.98 (d, 2H), 8.49 (d, 2H), 9.53 (s, 1H). / [MH] ⁺ = 445
245		δ ppm 1.39 (d, 6H), 2.06 (s, 3H), 2.14 (s, 3H), 3.88 (d, 3H), 4.51 - 4.51 (m, 3H), 6.09 (d, 1H), 6.90 - 6.97 (m, 2H), 7.10 (d, 1H), 7.25 (t, 1H), 7.41 (q, 1H), 9.43 (s, 1H). / [MH] ⁺ = 409

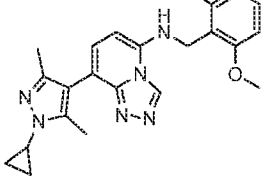
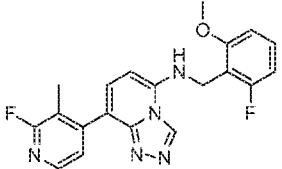
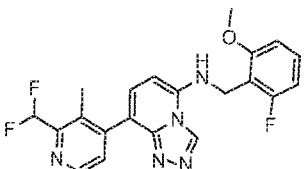
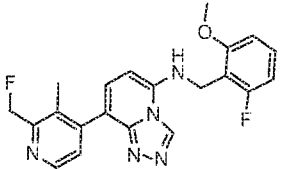
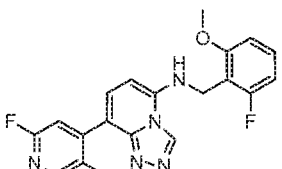
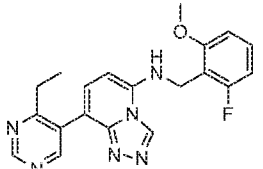
246		δ ppm 1.60 - 1.90 (m, 2H), 2.06 - 2.09 (m, 2H), 2.95 - 3.02 (m, 2H), 3.63 (s, 3H), 3.88 (s, 3H), 4.09 (t, 2H), 4.44 - 4.49 (m, 2H), 6.19 - 6.23 (m, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.50 (m, 2H), 7.73 (d, 1H), 8.15 (d, 1H), 8.52 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 480
247		δ ppm 3.88 (s, 3H), 4.01 (s, 3H), 4.48 (d, 2H), 6.13 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.31 - 7.49 (m, 3H), 8.53 (s, 1H), 9.50 (s, 1H). / [MH] ⁺ = 421
248		δ ppm 2.25 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.13 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.19 (s, 1H), 7.30 (d, 1H), 7.40 (dd, 1H), 7.55 (s, 1H), 8.13 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 382
249		δ ppm 2.37 (s, 3H), 2.51 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.15 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.25 - 7.30 (m, 2H), 7.40 (dd, 1H), 7.52 (t, 1H), 7.77 (d, 1H), 9.48 (s, 1H). / [MH] ⁺ = 378
250		δ ppm 2.43 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.18 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.40 - 7.43 (m, 2H), 7.70 (s, 1H), 7.98 (d, 1H), 8.05 (d, 1H), 9.53 (s, 1H). / [MH] ⁺ = 389
251		δ ppm 2.29 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.18 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.40 - 7.45 (m, 2H), 7.71 (s, 1H), 8.06 (s, 1H), 8.71 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 389

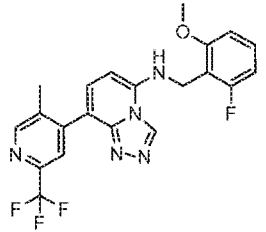
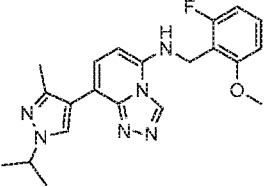
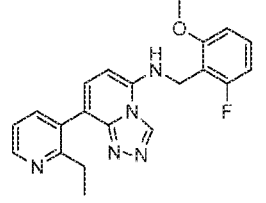
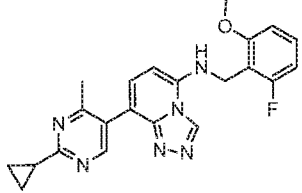
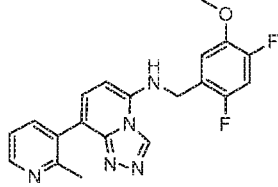
252		δ ppm 2.26 (s, 3H), 3.03 (d, 6H), 3.89 (s, 3H), 4.51 (d, 1H), 6.16 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.36 (d, 1H), 7.41 (dd, 2H), 7.53 (s, 1H), 7.58 (t, 1H), 8.49 (s, 1H), 9.52 (s, 1H). / [MH] ⁺ = 435
253		δ ppm 2.21 (s, 3H), 3.90 (s, 3H), 4.45 (d, 2H), 6.13 (d, 1H), 6.93 - 6.96 (m, 2H), 7.30 (d, 1H), 7.35 (d, 1H), 7.47 (t, 1H), 8.45 - 8.46 (m, 2H), 9.47 (s, 1H). / [MH] ⁺ = 382
254		δ ppm 1.00 (t, 3H), 2.46 - 2.50 (m, 2H), 3.90 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.91 (t, 1H), 6.98 (d, 1H), 7.17 (d, 1H), 7.24 - 7.27 (m, 2H), 7.35 - 7.45 (m, 4H), 9.47 (s, 1H). / [MH] ⁺ = 377
255		δ ppm 1.50 (d, 6H), 3.87 (s, 3H), 4.47 (s, 2H), 4.69 - 4.73 (m, 1H), 6.13 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.31 - 7.48 (m, 3H), 8.56 (s, 1H), 9.50 (s, 1H). / [MH] ⁺ = 449
256		δ ppm 1.92 (s, 3H), 3.89 (s, 3H), 4.38 (d, 2H), 4.52 (s, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.35-7.41 (m, 2H), 7.63 (t, 1H), 7.77 (d, 1H), 8.49 - 8.51 (t, 2H), 9.24 (s, 1H), 9.54 (s, 1H). / [MH] ⁺ = 421
257		δ ppm 1.08 (d, 6H), 2.74 - 2.87 (m, 1H), 3.89 (s, 3H), 4.48 (s, 2H), 6.11 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.13 (d, 1H), 7.20 - 7.23 (m, 2H), 7.31 - 7.49 (m, 4H), 9.46 (s, 1H). / [MH] ⁺ = 391

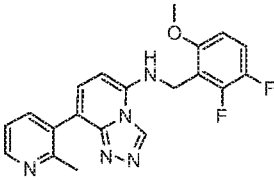
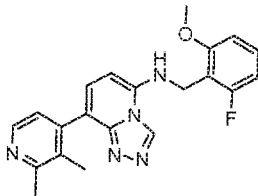
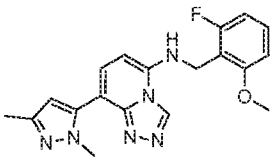
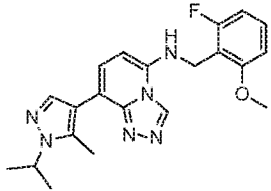
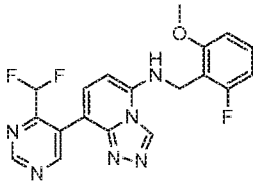
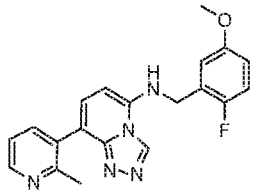
258		δ ppm 3.89 (s, 3H), 4.51 (d, 2H), 6.18 (d, 1H), 6.90 (t, 1H), 6.96 (d, 1H), 7.10 (t, 1H), 7.38 - 7.43 (m, 2H), 7.67 (t, 1H), 7.72 (d, 1H), 8.77 - 8.80 (m, 2H), 9.54 (s, 1H). / [MH] ⁺ = 400
259		δ ppm 3.89 (s, 3H), 4.52 (s, 2H), 6.18 (d, 1H), 6.92 (t, 1H), 6.96 (d, 1H), 7.39 (dd, 1H), 7.53 (d, 1H), 7.72 (d, 1H), 7.77 (s, 1H), 8.57 (d, 1H), 8.74 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 384
260		δ ppm 2.19 (s, 3H), 3.19 (s, 6H), 3.90 (s, 3H), 4.58 (d, 2H), 6.55 (d, 1H), 6.92 (t, 1H), 7.00 (d, 1H), 7.43 (dd, 1H), 7.70 (d, 1H), 8.15 (s, 1H), 8.22 (s, 1H), 9.69 (s, 1H). / [MH] ⁺ = 408
261		δ ppm 2.20 (s, 3H), 3.67 - 3.72 (m, 4H), 3.76 - 3.79 (m, 4H), 3.90 (s, 3H), 4.57 (d, 2H), 6.52 (d, 1H), 6.92 (t, 1H), 7.00 (d, 1H), 7.43 (dd, 1H), 7.68 (d, 1H), 8.13 (s, 1H), 8.26 (s, 1H), 9.68 (s, 1H). / [MH] ⁺ = 450
262		δ ppm 2.13 (s, 3H), 3.46 - 3.49 (m, 4H), 3.71 - 3.74 (m, 4H), 3.89 (s, 3H), 4.48 (d, 2H), 6.09 (d, 1H), 6.80 (s, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.18 (d, 1H), 7.35 - 7.41 (m, 2H), 8.02 (s, 1H), 9.46 (s, 1H). / [MH] ⁺ = 449.3

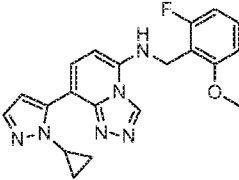
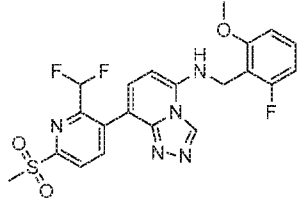
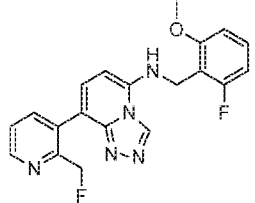
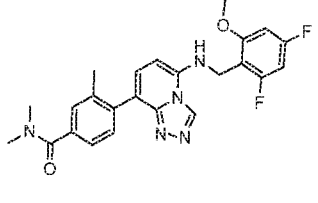
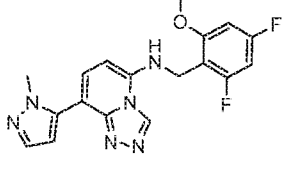
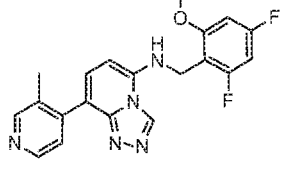
263		δ ppm 2.36 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.15 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.33 (q, 1H), 7.38-7.44 (m, 2H), 7.56 (t, 1H), 7.83 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 398
264		δ ppm 3.90 (s, 3H), 4.58 (s, 2H), 6.26 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (dd, 1H), 7.40 (q, 1H), 8.11 (s, 1H), 8.25 (d, 1H), 8.57 (d, 1H), 8.76 (d, 1H), 8.94 (s, 1H), 9.61 (s, 1H). / [MH] ⁺ = 418
265		δ ppm 3.90 (s, 3H), 4.51 (s, 2H), 6.18 (d, 1H), 6.78 - 6.99 (m, 3H), 7.31 (d, 1H), 7.41 (dd, 1H), 7.61 (t, 1H), 7.66 (dd, 1H), 8.02 (d, 1H), 8.74 (dd, 1H), 9.53 (s, 1H). / [MH] ⁺ = 400.1
266		δ ppm 2.24 (s, 3H), 3.48 (t, 4H), 3.72 (t, 4H), 3.88 (s, 3H), 4.47 (d, 2H), 6.09 (d, 1H), 6.72 (d, 1H), 6.89 (t, 1H), 6.95 (d, 1H), 7.16 (d, 1H), 7.34 (t, 2H), 7.40 (dd, 1H), 7.52 (d, 1H), 9.46 (s, 1H). / [MH] ⁺ = 449.3
267		δ ppm 2.23 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.98 (d, 1H), 7.34 (d, 1H), 7.41 (dd, 1H), 7.54 (s, 1H), 7.58 (t, 1H), 8.32 (s, 1H), 9.51 (s, 1H). / [MH] ⁺ = 398
268		δ ppm 2.16 (s, 3H), 2.47 (s, 3H), 3.89 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.20 (s, 1H), 7.24 (d, 1H), 7.40 (q, 1H), 7.47 (t, 1H), 8.31 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 378

269		δ ppm 2.40 (s, 3 H), 3.02 (d, 6 H), 3.89 (s, 3 H), 4.51 (d, 2 H), 6.16 (d, 1 H), 6.92 (t, 1 H), 6.97 (d, 1 H), 7.34 - 7.46 (m, 3 H), 7.54 (s, 1 H), 7.86 (d, 1 H), 9.51 (s, 1 H). / $[MH]^+ = 435$
270		δ ppm 0.95 (d, 4H), 2.12 - 2.08 (m, 1H), 2.15 (s, 3H), 3.88 (s, 3H), 4.49 (d, 2H), 6.11 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.22 (d, 1H), 7.25 (s, 1H), 7.40 (dd, 1H), 7.45 (t, 1H), 8.26 (s, 1H), 9.48 (s, 1H). / $[MH]^+ = 404.2$
271		δ ppm 1.04 (t, 3 H), 2.63 (q, 2 H), 3.28 (s, 3 H), 3.89 (s, 3 H), 4.50 (d, 2 H), 6.14 (d, 1 H), 6.90 (t, 1 H), 6.96 (d, 1 H), 7.26 (d, 1 H), 7.40 (q, 1 H), 7.51 - 7.56 (m, 2 H), 7.81 (d, 1 H), 7.89 (s, 1H), 9.50 (s, 1H). / $[M+H]^+ = 455.2$.
272		δ ppm 1.02 (t, 3 H), 2.54 (q, 2 H), 3.89 (s, 3 H), 4.49 (d, 2 H), 6.13 (d, 1 H), 6.89 (t, 1 H), 6.97 (d, 1 H), 7.25 (d, 1 H), 7.37 - 7.42 (m, 2 H), 7.48 (t, 1 H), 8.40 (s, 1 H), 8.50 (d, 1 H), 9.49 (s, 1 H). / $[M H]^+ = 378.3$
273		δ ppm 1.18 (d, 6H), 2.02 - 2.08 (m, 1H), 3.94 (s, 3H), 4.56 (d, 2H), 6.21 (d, 1H), 6.95 (t, 1H), 7.02 (d, 1H), 7.38 (d, 1H), 7.42 - 7.49 (m, 1H), 7.65 (d, 1H), 8.68 (s, 1H) 9.21 (s, 1H), 9.57 (s, 1H). / $[MH]^+ = 393.1$
274		δ ppm 1.10 (d, 3 H), 2.05 (s, 3 H), 2.14 (s, 3H), 3.30 (s, 2H), 3.87 (s, 3 H), 3.89-3.92 (m, 1 H), 4.45 (d, 2H), 4.90 (d, 1H), 6.07 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 6.96 (d, 1H), 7.08 (t, 1 H), 7.24 (q, 1H), 9.42 (s, 1 H). LCMS: $[MH]^+ = 425.2$

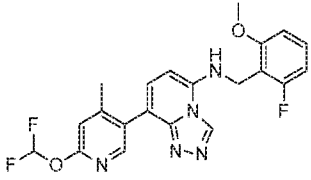
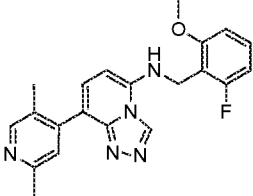
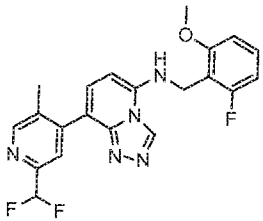
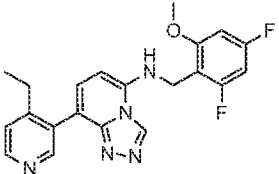
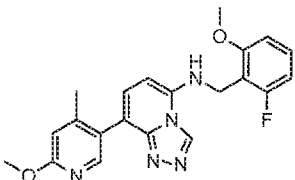
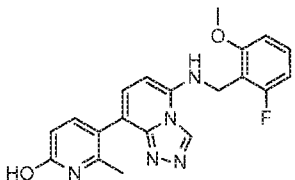
275		δ ppm 0.98-1.05 (m, 4 H), 2.02 (s, 3 H), 2.21 (s, 3H), 3.44-3.47 (m, 1H), 3.88 (s, 3 H), 4.46 (d, 2H), 6.08 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.09 (d, 1 H), 7.25 (t, 1H), 7.40 (q, 1H), 9.43 (s, 1H). / [MH] ⁺ = 407.2
276		δ ppm 2.12 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.38 - 7.43 (m, 3H), 7.69 (t, 1H), 8.09 (d, 1H), 9.53 (s, 1H). / [M+H] ⁺ = 382.2
277		¹ H NMR (400 MHz, Acetone) δ ppm 2.40 (s, 3 H), 3.95 (s, 3 H), 4.67 (s, 2 H), 6.30 (d, 1 H), 6.79 - 7.09 (m, 3 H), 7.36 - 7.43 (m, 2 H), 7.57 (d, 1 H), 8.52 (d, 1 H), 9.32 (s, 1 H). / [MH] ⁺ = 414.0
278		¹ H NMR (400 MHz, Acetone) δ ppm 2.33 (d, 3 H), 3.96 (s, 3 H), 4.67 (d, 2 H), 5.58 (s, 1 H), 5.70 (s, 1 H), 6.29 (d, 1 H), 6.78 - 6.86 (m, 2 H), 6.95 (d, 1 H), 7.33 - 7.37 (m, 1 H), 7.40 (d, 1 H), 7.42 - 7.46 (m, 1 H), 8.45 (d, 1 H), 9.30 (s, 1 H). / [MH] ⁺ = 396.0
279		δ ppm 2.20 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.16 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.24 (s, 1H), 7.40 - 7.43 (m, 2H), 7.70 (t, 1H), 8.17 (s, 1H), 9.53 (s, 1H). / [MH] ⁺ = 382
280		δ ppm 1.12 (t, 3H), 2.68 (q, 2H), 3.89 (s, 3H), 4.54 (d, 2H), 6.39 (s, 1H), 6.91 (t, 1H), 6.97 (d, 1 H), 7.39 - 7.45 (m, 1 H), 7.61 - 7.63 (m, 1 H), 7.97 - 8.01 (m, 1 H), 8.66 (s, 1 H), 9.16 (s, 1H), 9.63 (s, 1 H). / [MH] ⁺ = 379.2

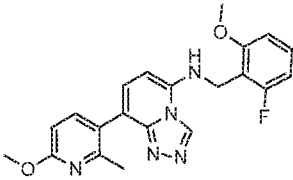
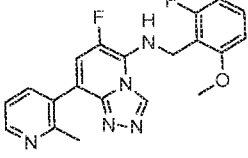
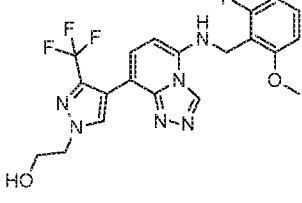
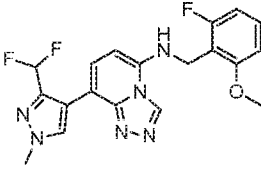
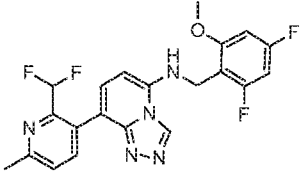
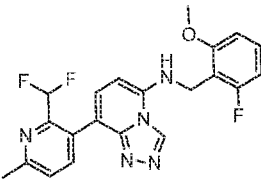
281		δ ppm 2.34 (s, 3H), 3.89 (s, 3H), 4.52 (s, 2H), 6.16 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (q, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 7.95 (s, 1H), 8.71 (s, 1H), 9.53 (s, 1H). / $[MH]^+ = 432$
282		δ ppm 1.44 (d, 6 H), 2.36 (s, 3 H), 3.88 (s, 3H), 4.45 - 4.49 (m, 3H), 6.08 (d, 1 H), 6.88 (t, 1H), 6.95 (d, 1H), 7.21 (t, 1H), 7.34 - 7.40 (m, 2H), 8.39 (s, 1 H), 9.45 (s, 1 H). / $[MH]^+ = 395$
283		δ ppm 1.08 (t, 3H), 2.64 (q, 2H), 3.89 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.23(d, 1H), 7.29 (dd, 1H), 7.37 - 7.47 (m, 2H), 7.65 - 7.67(m, 1H), 8.54(dd, 1H), 9.49(s, 1H). / $[MH]^+ = 378.3$
284		δ ppm 1.01 - 1.06 (m, 4H), 2.20 - 2.24 (m, 1H), 2.32 (s, 2H), 3.88 (s, 3H), 4.50 (d, 2H), 6.14 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.33 (d, 1H), 7.40 (q, 1H), 7.56 (t, 1H), 8.50 (s, 1H), 9.50 (s, 1H). / $[MH]^+ = 405$
285		δ ppm 2.36 (s, 3 H), 3.82 (s, 3 H), 4.56 (s, 2 H), 6.03 (d, 1 H), 7.26 - 7.41 (m, 4 H), 7.72 (dd, 1 H), 7.81 (s, 1 H), 8.47 (dd, 1 H), 9.46 (s, 1 H). / $[MH]^+ = 382$

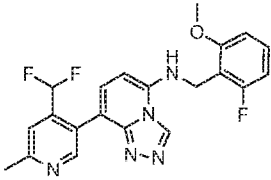
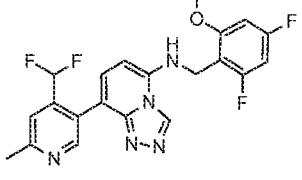
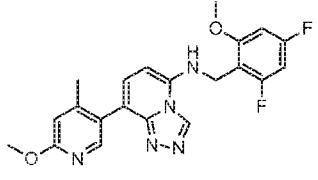
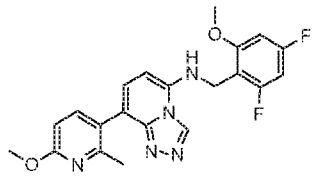
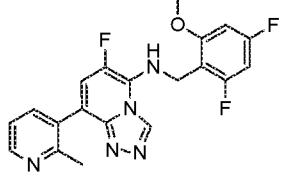
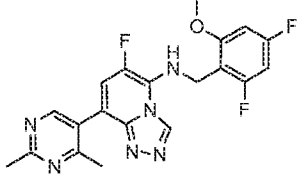
286		δ ppm 2.37 (s, 3H), 3.88 (s, 3H), 4.54 (d, 2H), 6.14 (d, 1H), 6.93 - 6.97 (m, 1H), 7.29 - 7.32 (m, 2H), 7.45 (q, 1H), 7.52 (t, 1H), 7.73 (dd, 1H), 8.47 (d, 1H), 9.46 (s, 1H). / $[\text{MH}]^+ = 382$
287		δ ppm δ 2.08 (s, 3H), 2.52 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.13 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.18 (d, 1H), 7.25 (d, 1H), 7.40 (dd, 1H), 7.52 (t, 1H), 8.29 (d, 1H), 9.49 (s, 1H). / $[\text{MH}]^+ = 378$
288		δ ppm 2.19 (s, 3H), 3.71 (s, 3H), 3.88 (s, 3H), 4.50 (s, 2H), 6.11 (d, 1H), 6.27 (s, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.37 - 7.43 (m, 2H), 7.63 (s, 1H), 9.51 (s, 1H). / $[\text{MH}]^+ = 367$
289		δ ppm 1.41 (d, 6H), 2.35 (s, 3H), 3.87 (s, 3H), 4.45 (d, 2H), 4.57 - 4.63 (m, 1H), 6.07 (d, 1H), 6.87 (t, 1H), 6.95 (d, 1H), 7.19 - 7.24 (m, 2H), 7.38 (q, 1H), 7.81 (s, 1H), 9.45 (s, 1H). / $[\text{MH}]^+ = 395$
290		^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 3.88 (s, 3H), 4.53 (d, 2H), 6.21 (d, 1H), 6.88 - 7.14 (m, 3H), 7.36 - 7.44 (m, 1H), 7.45 (d, 1H), 7.76 (t, 1H), 9.12 (s, 1H), 9.37 (s, 1H), 9.55 (s, 1H). / $[\text{MH}]^+ = 401$
291		δ ppm 2.34 (s, 3H), 3.72 (s, 3H), 4.59 (d, 2H), 5.98 (d, 1H), 6.90 - 6.93 (m, 1H), 7.06 - 7.09 (m, 1H), 7.18 - 7.32 (m, 3H), 7.72 (d, 1H), 7.89 (t, 1H), 8.47 (dd, 1H), 9.46 (s, 1H). / $[\text{MH}]^+ = 364$

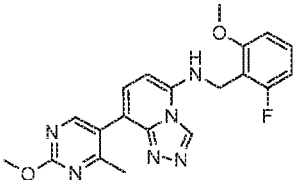
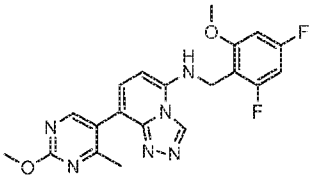
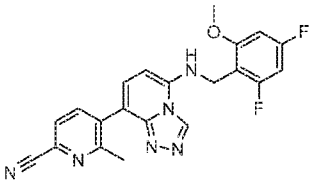
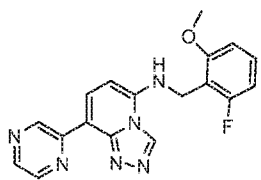
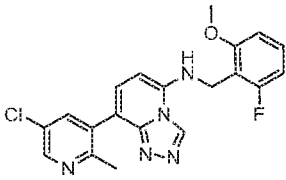
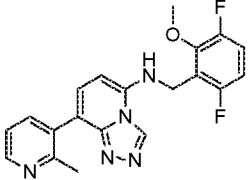
292		δ ppm 0.81 – 0.83 (m, 2H), 0.91 – 0.93 (m, 2H), 3.77 – 3.79 (m, 1H), 3.88 (s, 3H), 4.51 (d, 2H), 6.15 (d, 1H), 6.59 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (q, 1H), 7.44 (d, 1H), 7.57 (d, 1H), 7.61 (t, 1H), 9.51 (s, 1H). / [MH] ⁺ = 379.1.
293		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.39 (s, 3 H), 3.89 (s, 3 H), 4.53 (s, 2 H), 6.22 (d, 1 H), 6.90 (t, 1H), 6.97 - 7.17 (m, 2 H), 7.41 - 7.44 (m, 2 H), 7.79 (s, 1 H), 8.29 (d, 1 H), 8.43 (d, 1 H), 9.55 (s, 1H). / [MH] ⁺ = 478
294		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.89 (s, 3H), 4.51 (d, 2H), 5.40 (d, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.35 (d, 1H), 7.38 - 7.44 (m, 1H), 7.50 - 7.58 (m, 2H), 7.98 (d, 1H), 8.65 (dd, 1H), 9.52 (s, 1H). / [MH] ⁺ = 382
295		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.20 (s, 3H), 3.00 (s, 6H), 3.90 (s, 3H), 4.44 (d, 2H), 6.11 (d, 1H), 6.90 – 6.96 (m, 2H), 7.24 (d, 1H), 7.27 (d, 1H), 7.34 – 7.38 (m, 3H), 9.45 (s, 1H). / [MH] ⁺ = 452
296		¹ H-NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.81 (s, 3H), 3.90 (s, 3H), 4.46 (s, 2H), 6.12 (d, 1H), 6.49 (d, 1H), 6.91 – 6.95 (m, 2H), 7.42 (d, 1H), 7.49 (d, 1H), 7.60 (s, 1H), 9.49 (s, 1H). / [MH] ⁺ = 371.1
297		¹ H-NMR(500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.21 (s, 3H), 3.89 (s, 3H), 4.45 (d, 2H), 6.13 (d, 1H), 6.95 – 6.90 (m, 2H), 7.34 (d, 1H), 7.39 (d, 1H), 7.52 (t, 1H), 8.44 (d, 1H), 8.51 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 302.2

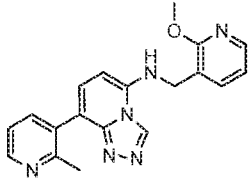
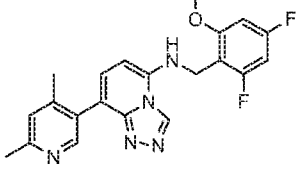
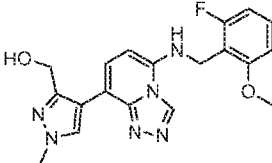
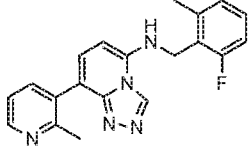
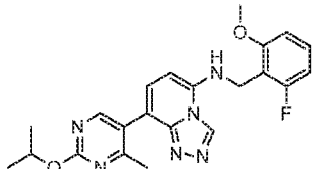
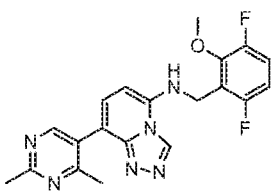
298		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 1.09 (t, 3H), 2.64 (q, 2H), 3.89 (s, 3H), 4.44 (d, 2H), 6.11 (d, 1H), 6.95 – 6.90 (m, 2H), 7.24 (d, 1H), 7.29 (dd, 1H), 7.41 (t, 1H), 7.67 (dd, 1H), 8.54 (dd, 1H), 9.46 (s, 1H). / [MH] ⁺ = 396.2
299		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.41 (s, 3H), 3.90 (s, 3H), 4.46 (d, 2H), 6.15 (d, 1H), 6.95 - 6.90 (m, 2H), 7.41 (d, 1H), 7.56 (t, 1H), 8.71 (s, 1H), 9.05 (s, 1H), 9.49 (s, 1H). / [MH] ⁺ = 383.2
300		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.36 (s, 3H), 2.64 (s, 3H), 3.90 (s, 3H), 4.46 (d, 1H), 6.13 (d, 1H), 6.90-6.95 (m, 2H), 7.36 (d, 1H), 7.52 (t, 1H), 8.58 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 397.2
301		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.40 (s, 3H), 3.89 (s, 3H), 4.54 (d, 2H), 6.24 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.28 (t, 1H), 7.42 (dd, 1H), 7.51 (d, 1H), 7.86 (s, 1H), 8.22 (s, 1H), 9.05 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 478.1
302		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.90 (s, 3H), 4.46 (d, 2H), 6.16 (d, 1H), 6.99 - 6.77 (m, 3H), 7.30 (d, 1H), 7.56 (t, 1H), 7.67 (dd, 1H), 8.02 (d, 1H), 8.74 (dd, 1H), 9.50 (s, 1H). / [MH] ⁺ = 418.1
303		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.90 (s, 3H), 4.45 (d, 2H), 4.51 (d, 2H), 5.19 (t, 1H), 6.16 (d, 1H), 6.90 (dd, 1H), 6.97 (t, 1H), 7.36 - 7.45 (m, 3H), 7.52 (t, 1H), 7.88 (dd, 1H), 8.59 (d, 1H), 9.51 (s, 1H). / [MH] ⁺ = 380.2

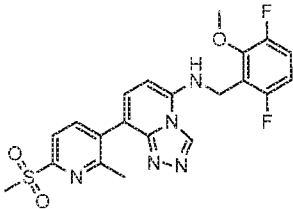
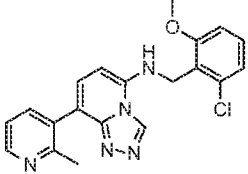
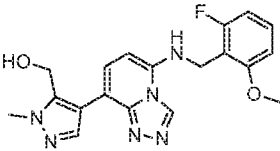
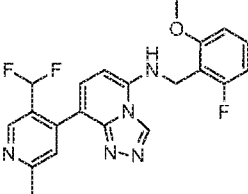
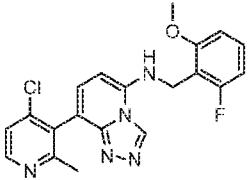
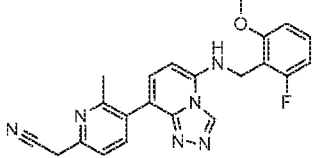
304		^1H NMR (500MHz, DMSO- d_6) δ ppm 2.22 (s, 3H), 3.88 (s, 3H), 4.50 (d, 2H), 6.12 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.08 (s, 1H), 7.28 (d, 1H), 7.40 (dd, 1H), 7.51 (t, 1H), 7.75 (t, 1H), 8.15 (s, 1H), 9.49 (s, 1H). / $[\text{MH}]^+ = 430.4$
305		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.14 (s, 3H), 2.46 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.13 (d, 1H), 6.89 (dd, 1H), 6.96 (d, 1H), 7.25 (s, 1H), 7.30 (d, 1H), 7.40 (dd, 1H), 7.54 (t, 1H), 8.36 (s, 1H), 9.50 (s, 1H). / $[\text{MH}]^+ = 378.2$
306		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.29 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.17 (d, 1H), 7.08 - 6.86 (m, 3H), 7.45 - 7.37 (m, 2H), 7.66 (t, 1H), 7.73 (s, 1H), 8.63 (s, 1H), 9.52 (s, 1H). / $[\text{MH}]^+ = 414.2$
307		^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.03 (t, 3H), 2.54 (q, 2H), 3.90 (s, 3H), 4.45 (d, 2H), 6.12 (d, 1H), 6.90 - 6.98 (m, 2H), 7.27 (d, 1H), 7.39 (d, 1H), 7.46 (t, 1H), 8.41 (s, 1H), 8.51 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 396.1$
308		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.30 (s, 3H), 3.89 (s, 6H), 4.49 (d, 2H), 6.11 (d, 1H), 6.71 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.22 (d, 1H), 7.39 (d, 2H), 7.65 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 394.1$
309		δ ppm 2.11 (s, 3H), 3.88 (s, 3H), 4.47 (s, 2H), 6.08 (d, 1H), 6.23 (d, 1H), 6.88 (dd, 1H), 6.96 (d, 1H), 7.19 (d, 1H), 7.36 - 7.42 (m, 2H), 7.46 (d, 1H), 9.46 (s, 1H), 11.71 (br s, 1H). / $[\text{MH}]^+ = 380.3$

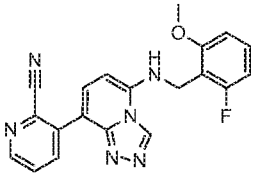
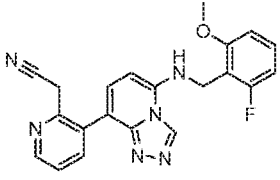
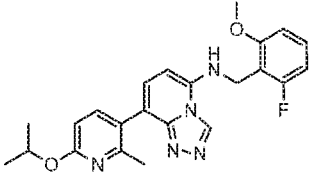
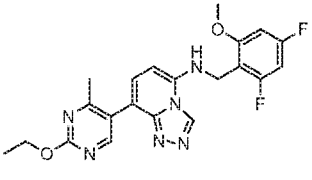
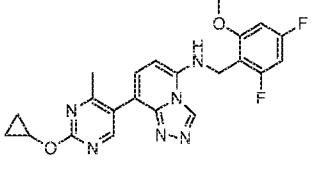
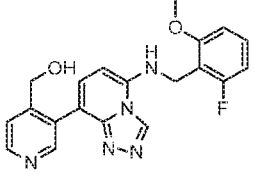
310		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.30 (s, 3H), 3.89 (s, 6H), 4.49 (d, 2H), 6.11 (d, 1H), 6.71 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.22 (d, 1H), 7.39 (d, 2H), 7.65 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 394.1$
311		^1H NMR (400 MHz, MeOD) δ ppm 2.48 (s, 3H), 3.75 (s, 3H), 4.79 (s, 2H), 6.74 (dd, 1H), 6.83 (d, 1H), 7.32 (dd, 1H), 7.41 (dd, 1H), 7.48 (d, 1H), 7.84 (d, 1H), 8.53 (d, 1H), 9.44 (s, 1H). / $[\text{MH}]^+ = 382.2$
312		δ ppm 3.82 (q, 2H), 3.87 (s, 3H), 4.32 (s, 2H), 4.48 (d, 2H), 5.03 (t, 1H), 6.14 (d, 1H), 6.89 (t, 1H), 6.81 (d, 1H), 6.96 (d, 1H), 7.33 (d, 1H), 7.38 – 7.47 (m, 2H), 8.57 (s, 1H), 9.50 (s, 1H). / $[\text{MH}]^+ = 451.1$
313		δ ppm 3.85 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.15 (d, 1H), 6.76 (s, 1H), 6.87 (s, 0.25H), 6.88 – 6.90 (m, 1H), 6.96 (d, 1H), 7.00 (s, 0.5H), 7.11 (s, 0.25H), 7.40 (q, 1H), 7.49 (d, 1H), 7.75 (t, 1H), 9.53 (s, 1H). / $[\text{MH}]^+ = 403.1$.
314		^1H -NMR (500 MHz, DMSO- d_6) δ ppm 2.60 (s, 3H), 3.90 (s, 3H), 4.45 (d, 2H), 6.15 (d, 1H), 6.95 - 6.71 (m, 3H), 7.25 (d, 1H), 7.52 (d, 2H), 7.89 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 432.1$
315		^1H -NMR (500 MHz, DMSO- d_6) δ ppm 2.59 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.16 (d, 1H), 6.92 - 6.71 (m, 2H), 6.97 (d, 1H), 7.24 (d, 1H), 7.40 (dd, 1H), 7.51 (d, 1H), 7.56 (t, 1H), 7.89 (d, 1H), 9.51 (s, 1H). / $[\text{MH}]^+ = 414.1$

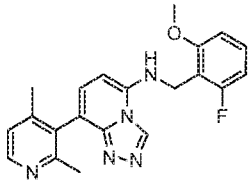
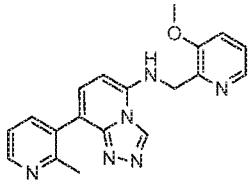
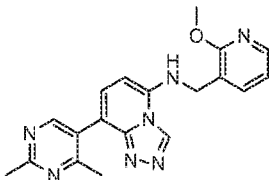
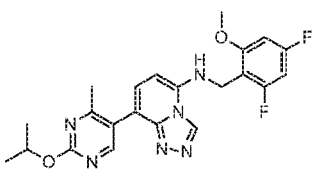
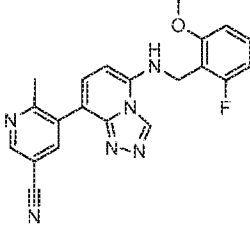
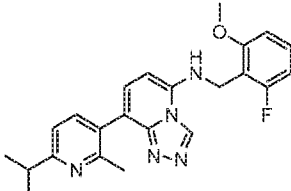
316		$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ ppm 2.62 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.17 (d, 1H), 6.90 (dd, 1H), 6.97 (dd, 1H), 7.05 (t, 1H), 7.34 (d, 1H), 7.41 (dd, 1H), 7.59 (s, 1H), 7.62 (t, 1H), 8.61 (s, 1H), 9.52 (s, 1H). / $[\text{MH}]^+ = 414.2$
317		$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ ppm 2.62 (s, 3H), 3.90 (s, 3H), 4.46 (d, 2H), 6.15 (d, 1H), 6.92 (dd, 2H), 7.05 (t, 1H), 7.34 (d, 1H), 7.57 (t, 1H), 7.59 (s, 1H), 8.61 (s, 1H), 9.49 (s, 1H). / $[\text{MH}]^+ = 432.1$
318		$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 2.15 (s, 3H), 3.88 (s, 6H), 4.43 (s, 1H), 6.08 (d, 1H), 6.79 (s, 1H), 6.94 (d, 2H), 7.22 (d, 1H), 7.37 (t, 1H), 8.04 (s, 1H), 9.44 (s, 1H). / $[\text{MH}]^+ = 412.1$
319		$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 2.30 (s, 3H), 3.89 (s, 6H), 4.44 (d, 1H), 6.10 (d, 1H), 6.72 (d, 1H), 6.92 - 6.95 (m, 2H), 7.23 (d, 1H), 7.36 (t, 1H), 7.65 (d, 1H), 9.45 (s, 1H). / $[\text{MH}]^+ = 412.1$
320		$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ ppm 2.38 (s, 3H), 3.71 (s, 3H), 4.63 (d, 2H), 6.76 (dd, 1H), 6.83 - 6.87 (m, 2H), 7.33 (dd, 1H), 7.54 (d, 1H), 7.78 (d, 1H), 8.52 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 400.1$
321		$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ ppm 2.37 (s, 3H), 2.65 (s, 3H), 3.73 (s, 3H), 4.65 (d, 2H), 6.84 - 6.87 (m, 3H), 7.63 (d, 1H), 8.63 (s, 1H), 9.50 (s, 1H). / $[\text{MH}]^+ = 415.1$

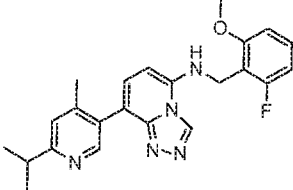
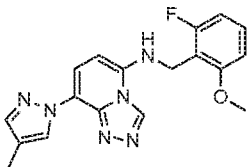
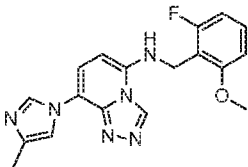
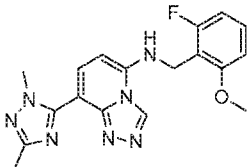
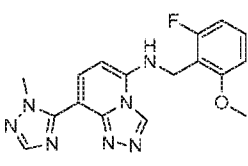
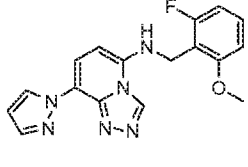
322		δ ppm 2.33 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 4.50 (s, 2H), 6.14 (d, 1H), 6.91 (dd, 1H), 6.97 (d, 1H), 7.33 (d, 1H), 7.40 (dd, 1H), 7.54 (t, 1H), 8.49 (s, 1H), 9.51 (s, 1H). / $[\text{MH}]^+ = 395.2$
323		δ ppm 2.34 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.45 (s, 2H), 6.12 (d, 1H), 6.91 - 6.96 (m, 2H), 7.33 (d, 1H), 7.49 (t, 1H), 8.50 (s, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 413.2$
324		^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 2.46 (s, 3H), 3.89 (s, 3H), 4.47 (d, 2H), 6.15 (d, 1H), 6.93 (dd, 2H), 7.42 (d, 1H), 7.62 (t, 1H), 7.96 (d, 1H), 8.04 (d, 1H), 9.50 (s, 1H). / $[\text{MH}]^+ = 407.1$
325		^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 3.89 (s, 3H), 4.60 (d, 2H), 6.47 (d, 1H), 6.90 (dd, 1H), 6.98 (d, 1H), 7.42 (dd, 1H), 8.23 (s, 1H), 8.55 (br s, 2H), 8.70 (s, 1H), 9.67 (s, 1H), 9.96 (s, 1H). $[\text{MH}]^+ = 351.1$
326		^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 2.37 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.14 (d, 1H), 6.89 (dd, 1H), 6.97 (d, 1H), 7.45 - 7.33 (m, 2H), 7.58 (t, 1H), 7.89 (d, 1H), 8.52 (d, 1H), 9.51 (s, 1H). / $[\text{MH}]^+ = 398.0$
327		δ ppm 2.37 (s, 3H), 3.96 (s, 3H), 4.55 (d, 2H), 6.14 (d, 1H), 7.07 - 7.12 (m, 1H), 7.30 - 7.42 (m, 3H), 7.60 (t, 1H), 7.72 (dd, 2H), 8.48 (d, 1H), 9.47 (s, 1H). / $[\text{MH}]^+ = 382.1$

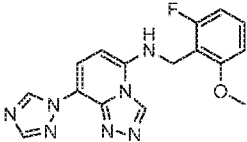
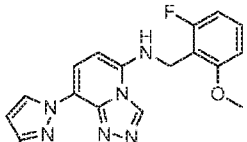
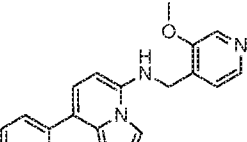
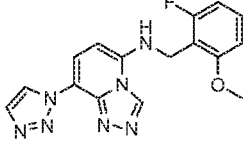
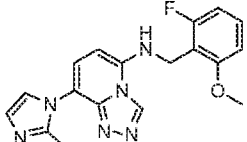
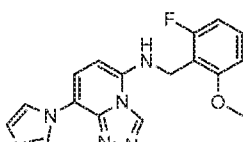
328		δ ppm 2.36 (s, 3H), 3.97 (s, 3H), 4.52 (s, 2H), 5.86 (d, 1H), 7.00 (m, 1H), 7.22 (d, 1H), 7.30 (m, 1H), 7.70 - 7.75 (m, 2H), 8.13 (m, 1H), 8.47 (m, 1H), 9.48 (s, 1H). / $[MH]^+ = 346.9$
329		1H -NMR (500 MHz, DMSO- d_6) δ ppm 2.16 (s, 3H), 2.48 (s, 3H), 3.89 (s, 3H), 4.44 (d, 2H), 6.10 (d, 1H), 6.92 (dd, 2H), 7.20 (s, 1H), 7.25 (d, 1H), 7.41 (t, 1H), 8.31 (s, 1H), 9.45 (s, 1H). / $[MH]^+ = 396.1$
330		1H NMR (500 MHz, DMSO- d_6) δ ppm 3.88 (s, 6H), 4.47 - 4.50 (m, 4H), 5.51 (t, 1H), 6.11 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.26 (t, 1H), 7.39 (dd, 1H), 7.69 (d, 1H), 8.42 (s, 1H), 9.47 (s, 1H). / $[MH]^+ = 383.2$
331		δ ppm 2.38 (s, 3 H), 2.44 (s, 3 H), 4.52 (s, 2 H), 6.17 (d, 1 H), 7.11 - 7.17 (m, 2 H), 7.30 - 7.37 (m, 3 H), 7.74 (dd, 1 H), 8.49 (dd, 1 H), 9.46 (s, 1 H). / $[MH]^+ = 348.0$
332		δ ppm 1.35 (d, 6H), 2.30 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 5.22 - 5.30 (m, 1H), 6.13 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 7.40 (d, 1H), 7.52 (t, 1H), 8.46 (s, 1H), 9.50 (s, 1H). / $[MH]^+ = 423.3$
333		δ ppm 2.35 (s, 3H), 2.63 (s, 3H), 3.95 (d, 3H), 4.54 (d, 2H), 6.15 (d, 1H), 7.08 - 7.11 (m, 1H), 7.30 - 7.40 (m, 2H), 7.68 (t, 1H), 8.58 (s, 1H), 9.48 (s, 1H). / $[MH]^+ = 397.2$

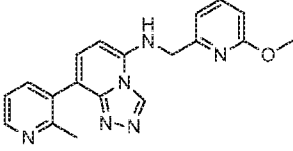
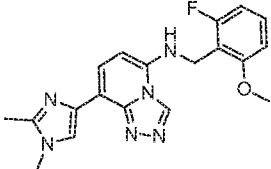
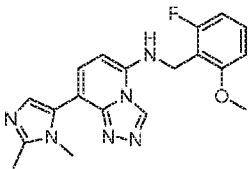
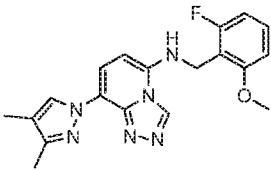
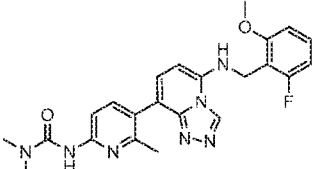
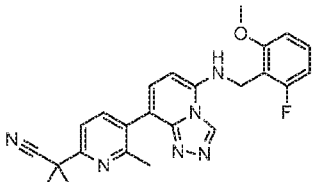
334		δ ppm 3.32 (s, 6H), 3.95 (d, 3H), 4.56 (d, 2H), 6.18 (d, 1H), 7.08 - 7.12 (m, 1H), 7.37 - 7.41 (m, 1H), 7.45 (d, 1H), 7.76 (t, 1H), 7.96 (d, 1H), 8.12 (d, 1H), 9.50 (s, 1H). / $[MH]^+ = 460.2$
335		1H NMR (500 MHz, DMSO- d_6) δ ppm 2.38 (s, 3H), 3.88 (s, 3H), 4.57 (d, 2H), 6.17 (d, 1H), 7.12 - 7.16 (dd, 2H), 7.29 - 7.36 (m, 3H), 7.41 (t, 1H), 7.73 (d, 1H), 8.48 (d, 1H), 9.51 (s, 1H). / $[MH]^+ = 380.1$
336		1H NMR (500 MHz, DMSO- d_6) δ ppm 3.88 (s, 3H), 3.90 (s, 3H), 4.48 (d, 2H), 4.52 (d, 2H), 5.84 (t, 1H), 6.11 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.32 (t, 1H), 7.39 (dd, 2H), 7.80 (s, 1H), 9.47 (s, 1H). / $[MH]^+ = 383.1$
337		1H NMR (500 MHz, DMSO- d_6) δ ppm 2.57 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.18 (d, 1H), 6.89 - 7.23 (m, 3H), 7.36 - 7.42 (m, 2H), 7.49 (s, 1H), 7.72 (t, 1H), 8.77 (s, 1H), 9.54 (s, 1H). / $[MH]^+ = 414.1$
338		1H NMR (500 MHz, DMSO- d_6) δ ppm 2.36 (s, 3H), 3.89 (s, 3H), 4.51 (d, 2H), 6.15 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.33 (d, 1H), 7.39 - 7.44 (m, 2H), 7.55 (t, 1H), 7.83 (d, 1H), 9.51 (s, 1H). / $[MH]^+ = 398.0$
339		1H NMR (500 MHz, DMSO- d_6) δ ppm 2.38 (s, 3H), 3.89 (s, 3H), 4.22 (s, 2H), 4.50 (d, 2H), 6.14 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.29 (d, 1H), 7.34 (d, 1H), 7.40 (dd, 1H), 7.50 (t, 1H), 7.77 (d, 1H), 9.50 (s, 1H). / $[MH]^+ = 403.1$

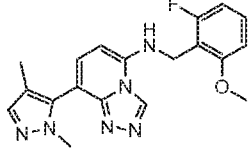
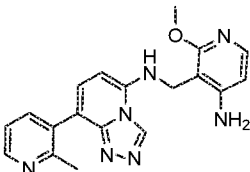
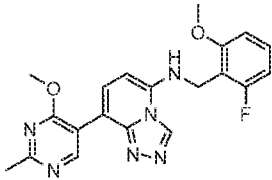
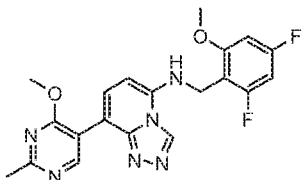
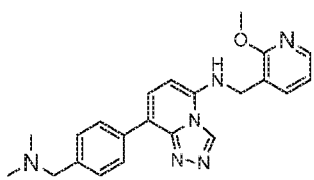
340		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.89 (s, 3 H), 4.55 (d, 2 H), 6.23 (d, 1 H), 6.90 (t, 1 H), 6.97 (d, 1 H), 7.40 - 7.42 (m, 1 H), 7.69 (d, 1 H), 7.82 (dd, 2 H), 8.39 (dd, 1 H), 8.73 (dd, 1 H), 9.57 (s, 1 H). / [MH] ⁺ = 375.1
341		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.89 (s, 3 H), 4.15 (s, 2 H), 4.51 (d, 2 H), 6.17 (d, 1 H), 6.89 (t, 1 H), 6.97 (d, 1 H), 7.36 - 7.42 (m, 2 H), 7.49 (dd, 1 H), 7.61 (t, 1 H), 7.86 (dd, 1 H), 8.61 (dd, 1 H), 9.52 (s, 1 H). / [MH] ⁺ = 389.2
342		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.89 (s, 3H), 4.15 (s, 2H), 4.51 (d, 2H), 6.17 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.36 - 7.42 (m, 2H), 7.49 (dd, 1 H), 7.61 (t, 1 H), 7.86 (dd, 1 H), 8.61 (dd, 1 H), 9.52 (s, 1 H). / [MH] ⁺ = 389.2
343		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 1.36 (t, 3H), 2.31 (s, 3H), 3.88 (s, 3H), 4.41 (q, 2H), 4.44 (d, 2H), 5.26 (s, 1H), 6.11 (d, 1H), 6.89 - 6.94 (m, 2H), 7.32 (d, 1H), 7.48 (s, 1H), 8.46 (s, 1H), 9.47 (s, 1H). / [MH] ⁺ = 441.3
344		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.74 - 0.80 (m, 4H), 2.32 (s, 3H), 3.89 (s, 3H), 4.33 - 4.36 (m, 1H), 4.43 (d, 2H), 6.12 (d, 1H), 6.89 - 6.95 (m, 2H), 7.34 (d, 1H), 7.50 (s, 1H), 8.50 (s, 1H), 9.47 (s, 1H). / [MH] ⁺ = 439.2
345		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 3.89 (s, 3H), 4.44 (d, 2H), 4.50 (d, 2H), 5.39 (t, 1H), 6.14 (d, 1H), 6.90 (dd, 1H), 6.97 (d, 1H), 7.31 (d, 1H), 7.40 (dd, 1H), 7.53 (t, 1H), 7.60 (d, 1H), 8.48 (s, 1H), 8.57 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 380.2

346		^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.99 (s, 3H), 2.17 (s, 3H), 3.89 (s, 3H), 4.49 (d, 2H), 6.13 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.18 - 7.20 (m, 2H), 7.44 - 7.39 (m, 2H), 8.33 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 377.9$
347		δ ppm 2.36 (s, 3H), 3.92 (s, 3H), 4.66 (s, 2H), 5.99 (d, 1H), 7.21 (d, 1H), 7.29 (dd, 1H), 7.36 (dd, 1H), 7.51 (dd, 1H), 7.71 (dd, 1H), 8.13 (dd, 1H), 8.47 (dd, 1H), 9.52 (s, 1H). / $[\text{MH}]^+ = 346.9$
348		δ ppm 2.36 (s, 3H), 2.64 (s, 3H), 3.97 (s, 3H), 4.54 (s, 2H), 5.90 (d, 1H), 7.00 (dd, 1H), 7.29 (d, 1H), 7.74 (dd, 1H), 7.97 (s, 1H), 8.14 (dd, 1H), 8.58 (s, 1H), 9.49 (s, 1H). / $[\text{MH}]^+ = 361.9$
349		^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.35 (d, 6H), 2.30 (s, 3H), 3.89 (s, 3H), 4.44 (d, 2H), 5.26 (q, 1H), 6.11 (d, 1H), 6.89 - 7.00 (m, 2H), 7.32 (d, 1H), 7.48 (s, 1H), 8.45 (s, 1H), 9.47 (s, 1H). / $[\text{MH}]^+ = 441.3$
350		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.48 (s, 3H), 3.89 (s, 3H), 4.52 (d, 2H), 6.16 (d, 1H), 6.90 (dd, 1H), 6.97 (d, 1H), 7.38 - 7.43 (m, 2H), 7.64 (t, 1H), 8.28 (d, 1H), 8.92 (d, 1H), 9.53 (s, 1H). / $[\text{MH}]^+ = 389.1$
351		^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.27 (d, 6H), 2.33 (s, 3H), 3.03 (q, 1H), 3.88 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.89 (dd, 1H), 6.96 (d, 1H), 7.17 (d, 1H), 7.26 (d, 1H), 7.39 (dd, 1H), 7.44 (t, 1H), 7.63 (d, 1H), 9.48 (s, 1H). / $[\text{MH}]^+ = 406.2$

352		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.27 (d, 6H), 2.18 (s, 3H), 3.03 (q, 1H), 3.89 (s, 3H), 4.49 (d, 2H), 6.12 (d, 1H), 6.89 (dd, 1H), 6.97 (d, 1H), 7.22 (s, 1H), 7.27 (d, 1H), 7.40 (dd, 1H), 7.46 (t, 1H), 8.35 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 406.2
353		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.14 (s, 3H), 3.88 (s, 3H), 4.47 (d, 2H), 6.14 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.40 – 7.43 (m, 2H), 7.57 (s, 1H), 7.81 (d, 1H), 8.82 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 353.2
354		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.19 (s, 3H), 3.88 (s, 3H), 4.48 (d, 2H), 6.06 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.39 (q, 1H), 7.50 (t, 1H), 7.57 (d, 2H), 8.33 (s, 1H), 9.56 (s, 1H). / [MH] ⁺ = 353.1
355		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.27 (s, 3H), 3.76 (s, 3H), 3.88 (s, 3H), 4.53 (d, 2H), 6.19 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.41 (dd, 1H), 7.60 (d, 1H), 7.87 (m, 1H), 9.55 (s, 1H). / [MH] ⁺ = 368.2
356		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 3.86 (s, 3H), 3.89 (s, 3H), 4.54 (s, 2H), 6.21 (d, 1H), 6.89 (t, 1H), 6.97 (d, 1H), 7.40 (dd, 1H), 7.62 (d, 1H), 7.91 (s, 1H), 8.02 (s, 1H), 9.57 (s, 1H). / [MH] ⁺ = 354.1
357		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 3.89 (s, 3H), 4.49 (d, 2H), 6.16 (d, 1H), 6.56 – 6.57 (m, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 7.47 (t, 1H), 7.76 (d, 1H), 7.87 (d, 1H), 9.02 (d, 1H), 9.59 (s, 1H). / [MH] ⁺ = 339.1.

358		^1H NMR (500 MHz, DMSO- d_6) δ ppm 3.89 (s, 3H), 4.51 (d, 2H), 6.18 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 7.72 (t, 1H), 7.87 (d, 1H), 8.28 (s, 1H), 9.53 (s, 1H), 9.63 (s, 1H). $[\text{MH}]^+ = 340.1$
359		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.30 (s, 3H), 3.88 (s, 3H), 4.47 (d, 2H), 6.14 (d, 1H), 6.34 (d, 1H), 6.88 (t, 1H), 6.96 (d, 1H), 7.44 – 7.36 (m, 2H), 7.80 (d, 1H), 8.92 (d, 1H), 9.56 (s, 1H). / $[\text{MH}]^+ = 353.1$
360		δ ppm 2.36 (s, 3 H), 4.00 (s, 3 H), 4.58 (s, 2 H), 5.78 (d, 1 H), 7.20 (d, 1 H), 7.30 (dd, 1 H), 7.35 (d, 1 H), 7.72 (dd, 1 H), 8.19 (d, 1 H), 8.41 (s, 1 H), 8.47 (dd, 1 H), 9.47 (s, 1 H). / $[\text{MH}]^+ = 346.9$
361		^1H NMR (500 MHz, DMSO- d_6) δ ppm 3.89 (s, 3H), 4.54 (s, 2H), 6.19 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.41 (dd, 1H), 7.84 (s, 1H), 7.99 (d, 2H), 8.99 (d, 1H), 9.64 (s, 1H). / $[\text{MH}]^+ = 340.1$
362		^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.18 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.07 (d, 1H), 6.90 (dd, 2H), 6.97 (d, 1H), 7.23 (d, 1H), 7.45 – 7.36 (m, 2H), 7.68 (t, 1H), 9.55 (s, 1H). / $[\text{MH}]^+ = 353.1$
363		^1H NMR (500 MHz, DMSO- d_6) δ ppm 3.88 (s, 3H), 4.50 (s, 2H), 6.08 (d, 1H), 6.89 (dd, 1H), 6.96 (d, 1H), 7.12 (s, 1H), 7.40 (dd, 1H), 7.57 (br s, 1H), 7.64 (d, 1H), 7.88 (s, 1H), 8.44 (s, 1H), 9.58 (s, 1H). / $[\text{MH}]^+ = 339.1$

364		¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 2.35 (s, 3H), 3.84 (s, 3H), 4.60 (d, 2H), 5.93 (d, 1H), 6.73 (d, 1H), 7.07 (d, 1H), 7.22 (d, 1H), 7.29 (dd, 1H), 7.65 - 7.74 (m, 2H), 8.06 (t, 1H), 8.47 (dd, 1H), 9.49 (s, 1H). / [MH] ⁺ = 347.2
365		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.33 (s, 3H), 3.63 (s, 3H), 3.88 (s, 3H), 4.45 (d, 2H), 6.11 (d, 1H), 6.87 (t, 1H), 6.95 (d, 1H), 7.18 (m, 1H), 7.38 (dd, 1H), 7.80 (d, 1H), 7.92 (s, 1H), 9.44 (s, 1H). / [MH] ⁺ = 366.8.
366		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.35 (s, 3H), 3.45 (s, 3H), 3.88 (s, 3H), 4.49 (d, 2H), 6.08 (d, 1H), 6.87 - 6.91 (m, 2H), 6.96 (d, 1H), 7.27 (d, 1H), 7.40 (dd, 1H), 7.51 (t, 1H), 9.49 (s, 1H). / [MH] ⁺ = 366.8
367		¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.06 (s, 3H), 2.21 (s, 3H), 3.88 (s, 3H), 4.46 (d, 2H), 6.12 (d, 1H), 6.88 (t, 1H), 6.95 (d, 1H), 7.33 (t, 1H), 7.39 (dd, 1H), 7.75 (d, 1H), 8.77 (s, 1H), 9.55 (s, 1H). / [MH] ⁺ = 367.0.
368		δ ppm 2.29 (s, 3H), 2.96 (s, 6H), 3.89 (s, 3H), 4.49 (d, 2H), 6.11 (d, 1H), 6.89 (t, 1H), 6.96 (d, 1H), 7.23 (d, 1H), 7.37 - 7.45 (m, 2H), 7.61 (d, 1H), 7.70 (d, 1H), 8.85 (s, 1H), 9.48 (s, 1H). / [MH] ⁺ = 450.3
369		δ ppm 1.75 (s, 6H), 2.40 (s, 3H), 3.89 (s, 3H), 4.50 (d, 2H), 6.14 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.32 (d, 1H), 7.37 - 7.43 (m, 1H), 7.49 - 7.54 (m, 2H), 7.82 (d, 1H), 9.50 (s, 1H). / [MH] ⁺ = 431.3

370		^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.92 (s, 3H), 3.65 (s, 3H), 3.89 (s, 3H), 4.51 (s, 2H), 6.16 (d, 1H), 6.90 (t, 1H), 6.97 (d, 1H), 7.33 (d, 2H), 7.41 (dd, 1H), 7.65 (s, 1H), 9.52 (s, 1H). / $[\text{MH}]^+ = 366.8$
371		^1H -NMR (500 MHz, DMSO- d_6) δ ppm 2.38 (s, 3H), 3.83 (s, 3H), 4.33 (d, 2H), 6.10 - 6.13 (m, 3H), 6.33 (d, 1H), 7.21 (s, 1H), 7.28 - 7.32 (m, 2H), 7.66 (d, 1H), 7.72 (dd, 1H), 8.47 (dd, 1H), 9.46 (s, 1H). / $[\text{MH}]^+ = 361.9$
372		δ ppm 2.59 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.51 (s, 2H), 6.13 (s, 1H), 6.88 - 6.93 (d, 2H), 7.40 (s, 1H), 7.58 (s, 2H), 8.91 (s, 1H), 9.49 (s, 1H). / $[\text{MH}]^+ = 395.2$
373		δ ppm 2.59 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.45 (s, 2H), 6.10 (d, 1H), 6.88 - 6.93 (d, 2H), 7.51 - 7.58 (m, 2H), 8.91 (s, 1H), 9.46 (s, 1H). / $[\text{MH}]^+ = 413.2$
374		δ ppm 2.17 (s, 6 H), 3.41 (s, 2 H), 3.97 (s, 3 H), 4.52 (s, 2 H), 5.87 (d, 1 H), 6.98 (dd, 1 H), 7.35 (d, 2 H), 7.58 (d, 1 H), 7.70 (d, 1 H), 7.79 (br. s., 1 H), 8.08 (d, 2 H), 8.12 (dd, 1 H), 9.48 (s, 1 H). / $[\text{MH}]^+ = 388.9$

VI. PHARMACOLOGY AND UTILITY

- [00236]** As a key component of PRC2 complex, EED has no intrinsic enzymatic activity. However, it is critical for proper PRC2 function. EED directly binds to H3K27me3 and this binding event localizes the PRC2 complex to the chromatin substrate and allosterically activates the methyltransferase activity. Targeting the allosteric site within the regulatory EED subunit of PRC2, may offer a novel and unique angle to be advantageous to, or complementary to, directly targeting the SAM competition mechanism of EZH2 or PRC2. Therefore, targeting EED represents a highly attractive

strategy for the development of a novel therapy for the treatment of many forms of cancers. In particular, the need exists for small molecules that inhibit the activity of PRC2 through targeting EED. It has now been found that triazolopyrimidine derivatives as presently disclosed are useful to target EED for the treatment of EED or PRC2-

5 mediated diseases or disorders, especially cancers.

[00237] The utility of the compounds of the present invention may be demonstrated using any one of the following test procedures. Compounds of the present invention were assessed for their ability to inhibit PRC2 activity in a pentameric complex of EZH2, SUZ12, EED, Rbap48 and AEBP in biochemical assays. The ability of compounds of the present invention to inhibit cellular activity of PRC2 was assessed by analysing histone H3 lysine 27 methylation in human cell lines. The ability of compounds of the present invention to inhibit cancers was derived from their ability to modulate activity in human cancer cell lines bearing specific dependence to PRC2 activity to maintain cancerous growth.

EED-H3K27Me3 peptide competition binding assay by AlphaScreen (α -screen)

[00238] To assess the compounds' potency in the EED-H3K27Me3 competition binding assay, compounds were serially diluted 3-fold in DMSO to obtain a total of twelve concentrations. Then compounds at each concentration (75 nL of each) were transferred by Mosquito into a 384-well Perkin Elmer ProxiPlate 384 plus plates. 8 μ L of solutions containing 30 nM EED (1-441)-His protein and 15 nM biotin-H3K27Me3 (19-33) peptide in the buffer (25 mM HEPES, pH 8, 0.02% Tween-20, 0.5% BSA) were added to the wells and then incubated with compound for 20 min. AlphaScreen detection beads mix was prepared immediately before use by mixing nickel chelate acceptor beads and streptavidin donor beads in a 1:1 ratio (Perkin Elmer, Product No.6760619C/M/R) into the buffer described above. Then 4 μ L of detection beads mix was added to the plate and incubate in the dark at the rt for 1 h. The final concentration of donor and acceptor beads was 10 μ g/mL for each. Plates were read on EnVision (PerkinElmer) using the AlphaScreen setting adapted for optimal signal detection with a 615 nm filter, after sample excitation at 680 nm. The emission signal at 615 nm was used to quantify compounds inhibition. AlphaScreen signals were normalized based on the reading coming from the positive (maximum signal control) and negative controls (minimum signal control) to give percentage of activities left. The data were then fit to a dose response equation using the program Helios (Novartis) to get the IC50 values. Helios is

a Novartis in-house assay data analysis software using the methods described by Normolle, D. P., *Statistics in Medicine*, 12:2025-2042 (1993); Formenko, I. et al, *Computer Methods and Programs in Biomedicine*, 82, 31-37 (2006); Sebaugh, J. L., *Pharmaceutical Statistics*, 10:128-134 (2011); Kelly, C. et al., *Biometrics*, 46(4):1071-1085 (1990); and Kahm, M. et al., *Journal of Statistical Software*, 33(7): (2010) (grofit: Fitting Biological Growth Curves with R, pages 1-21, available at <http://www.jstatsoft.org/>).

[00239] Each compound was counterscreened to determine if it interfered with the AlphaScreen beads. Compounds were diluted as described in the preceding section, and the assay was performed by adding 12 μ L of 10 nM biotin-miniPEG-His6 peptide in the above buffer and incubating for 20 min at rt prior to addition of the beads to 10 μ g/mL each. The plates were then incubated for 1 h at rt in dark before being read on EnVison.

EED LC-MS Assay

[00240] Representative compounds of the present invention were serially and separately diluted 3-fold in DMSO to obtain a total of eight or twelve concentrations. Then the test compounds at each concentration (120 nL of each) were transferred by Mosquito into a 384-well Perkin Elmer ProxiPlate 384 plus plates. Solutions (6 μ L) of 24 nM the wild type PRC2 (wtPRC2) complex and 2 μ M SAM in reaction buffer (20 mM Tris, pH 8.0, 0.1% BSA, 0.01% Triton, 0.5 mM DTT) were added to the wells that were then incubated with the test compound for 20 min. A 6 μ L solution of 3 μ M of the peptide substrate H3K27Me0 (histone H3[21-44]-biotin) in reaction buffer was added to initiate each reaction. The final components in the reaction solution include 12 nM wtPRC2 complex, 1 μ M SAM, and 1.5 μ M H3K27me0 peptide with varying concentration of the compounds. A positive control consisted of the enzyme, 1 μ M SAM and 1.5 μ M substrate in the absence of the test compound, and a negative control consisted of 1 μ M SAM and 1.5 μ M substrate only. Each reaction was incubated at rt for 120 min, then stopped by addition of 3 μ L per of quench solution (2.5% TFA with 320 nM d4-SAH). The reaction mixture was centrifuged (Eppendorf centrifuge 5810, Rotor A-4-62) for 2 min at 2000 rpm and read on an API 4000 triple quadrupole mass spec with Turbulon Spray (Applied Biosystem) coupled with Prominence UFLC (Shimadzu). The levels of SAH production were then normalized based on the values coming from the positive and negative controls to give percent enzyme activities. The data were then fit to a dose response equation using the program Helios to get the IC₅₀ values of the test compound.

ELISA (H3K27 methylation) assay

[00241] Representative compounds of the present invention were serially and separately diluted 3-fold in DMSO to obtain a total of eight or twelve concentrations.

5 Then the compounds were added to G401 cell cultured in 384-well plate at 1:500 dilution to obtain the highest concentration of 20 μ M. The cells were further cultured for 48 h before ELISA procedure.

[00242] Histone extraction: Cells, in 384-well plate, were washed with PBS (10 x PBS buffer (80 g NaCl (Sigma, S3014), 2 g KCl (Sigma, 60128), 14.4 g Na₂HPO₄ (Sigma, S5136), 2.4 g KH₂PO₄ (Sigma, P9791) to 1 L water, pH to 7.4) and lysed with the addition of lysis buffer (0.4N HCl; 45 μ L per well). The plate was gently agitated at 4°C for 30 min. The cell lysate was neutralized with neutralization buffer (0.5 M sodium phosphate dibasic, pH 12.5, 1 mM DTT; 36 μ L per well). The plate was agitated to
15 ensure the lysates were well mixed prior to the ELISA protocol.

[00243] ELISA protocol: Cell lysates were transferred to the wells of a 384-well plate and the final volume was adjusted to 50 μ L per well with PBS. The plate was sealed, centrifuged at 2,000 rpm for 2 min and incubated at 4°C for about 16 h. The plate was
20 washed with TBST buffer (1 x TBS (10x TBS: 24.2 g Tris (Sigma, T6066), 80 g NaCl (Sigma, S3014) to 1 L of water and adjust pH to 7.6 with HCl) with 0.1% Tween-20). Blocking buffer (TBST, 5% BSA; 50 μ L per well) was added and the plate was incubated for 1 h at rt. The blocking buffer was removed and primary antibody was added (30 μ L per well). The following dilutions were performed with blocking buffer: for anti-
25 H3K27me3 antibody (Cell Signaling Technology, #9733), dilution was 1:1000; for anti-H3K27me2 antibody (Cell Signaling Technology, #9288), dilution was 1:100; for anti-H3 antibody (Abcam, Cat#24834), dilution was 1:1000. The primary antibody was incubated in the plate at rt for 1 h. The wells were washed with TBST and incubated with secondary antibody for 1 h at rt. For secondary antibodies, the following dilutions were
30 carried out with blocking buffer: anti-rabbit antibody (Jackson ImmunoResearch, #111-035-003), dilution was 1:2000; and anti-mouse antibody (Cell signaling technology, #7076), dilution was 1:1000. After 1 h of incubation at rt, the wells were washed with TBST. ECL substrate (Pierce, #34080) was added at 30 μ L per well and the plates were centrifuged at 2,000 rpm for 2 min. The signal was read using a PerkinElmer Envision
35 Reader. The H3K27 methylation readouts were normalized using H3 signal and then

percentage inhibition was calculated against the samples treated with DMSO. The data were then fit to a dose response curve using the program Helios to get the IC₅₀ values of the test compound.

5 Western Blot Analysis

[00244] Representative compounds of the present invention were analyzed for their ability to selectively inhibit PRC2. Western blot was performed using standard molecular biology techniques. Cell was lysed in SDS lysis buffer (Millipore, Cat#20-163) and protein concentration was measured by BCA protein assay (Pierce, Cat# PI-23221).

10 Antibodies for western blots: anti-EZH2 (#3147), anti-H3 (#9715), anti-H3K4me1 (#9723), anti-H3K4me2 (#9725), anti-H3K4me3 (#9727), anti-H3K9me2 (#9753), anti-H3K36me2 (#9758), anti-H3K27me2 (#9755), and anti-H3K27me3 (#9756) were purchased from Cell Signaling Technology (Danvers, MA, USA). Anti-H3K9me1 (#07-395), anti-H3K27me1 (#07-448), and anti-H3K36me1 (#07-548) were purchased from
15 Millipore (Billerica, MA, USA). Anti-H3K36me3 (ab9050-100) was purchased from Abcam (Cambridge, UK). Anti-H3K9me3 (#39161) was purchased from Active Motif (Carlsbad, CA, USA).

[00245] Compounds of the present invention specifically inhibit the methylation of the PRC2 substrate H3K27. This can be demonstrated by their ability to inhibit H3K27me2
20 and H3K27me3 in a number of human cancer cell lines, examples include rhabdoid cells (G401) and lymphoma cells (WSU-DLCL2, KARPAS422, SU-DHL4). Selectivity is profiled against a number of other methylation marks, for example: H3K4me2; H3K9me2; H3K36me3; and H3K79me3.

25 Analysis of Cell Proliferation

[00246] B cell lymphoma cell KARPAS422 was cultured using standard cell culture conditions in RPMI-1640 (Invitrogen, cat #11875) supplemented with 15% FBS (Invitrogen, cat #10099-141) in humidified incubator at 37°C, 5% CO₂. To assess the effect of PRC2 inhibition on cell proliferation, exponentially growing cells were seeded at
30 a density of 1×10^5 cells/mL in 12-well plate (Corning, cat #CLS3513). After cell seeding, a compound of the present invention was added to the cell media (in concentrations ranging from 0 to 100 μ M, 3x dilution series). Viable cell numbers were determined every 3–4 days for up to 14 days using Vi-CELL (Beckman Coulter). On days of cell counting, fresh growth media and compound were replenished and cells split
35 back to a density of 1×10^5 cells/mL. Total cell number is expressed as split-adjusted

viable cells per mL. The dose response curves and IC₅₀ values were generated using Prism.

Analysis of Pharmacokinetic Properties

- 5 **[00247]** Pharmacokinetic properties of the compounds as presently disclosed can be determined by using the below described protocol.

[00248] A representative compound of the present invention was dissolved in 10% PEG300, 10% Solutol HS 15 and 80% pH 4.65 Acetate buffer to yield a final concentration of 0.2 mg/mL for intravenous (IV) and oral administration (PO).

- 10 **[00249]** For rat PK studies, a total of three male Sprague Dawley rats each were used for rat IV and PO PK study, respectively. The formulation solution was administered via a single bolus IV at 1 mg/kg and a single oral gavage (PO) at 2 mg/kg, respectively. Blood samples (approximately 150 µL) were collected via jugular cannula at appropriate time points.

- 15 **[00250]** For mouse PK study, a total of twelve male ICR mice were used for IV and PO study, respectively. The formulation solution was administered via a single bolus IV at 1 mg/kg and a single oral gavage (PO) at 2 mg/kg, respectively. Blood samples (approximately 150 µL) were collected via retro-orbital puncture (~150 µL/mouse) after anesthetized by isoflurane or via cardiac puncture (terminal collection) at appropriate time points (n=3).

[00251] Samples were collected in tubes containing K3-EDTA and stored on ice until centrifuged. The blood samples were centrifuged at approximately 8000 rpm for 6 min at 2-8°C and the resulting plasma was separated and stored frozen at approximately -80°C. After adding the internal standard, the plasma samples were quantified by LC-

- 25 MS/MS using the calibration curve. PK parameters including area under concentration curve (AUC), mean residence time (MRT), plasma clearance (Cl), steady state volume of distribution (V_{dss}), elimination half-life (t_{1/2}), maximum concentration (C_{max}), time of maximum concentration (T_{max}) and oral bioavailability (F %) were calculated using the following equations:

$$AUC = \int_0^{\infty} C \, dt$$

$$MRT = \frac{\int_0^{\infty} tC \, dt}{\int_0^{\infty} C \, dt} = \frac{AUMC}{AUC}$$

30

t is time and C is plasma concentration at the time (t);

Dose_{iv} is the dose for intravenous administration; and Dose_{oral} is the dose for oral administration.

$$Cl = \text{Dose}_{iv} / AUC$$

$$t_{1/2} = 0.693 \times MRT$$

5 $V_{dss} = Cl \times MRT$

$$F \% = (\text{Dose}_{iv} \times AUC_{oral}) / (\text{Dose}_{oral} \times AUC_{iv}) \times 100\%$$

Protocol for High-Throughput Equilibrium Solubility Assay

[00252] Compounds of the present invention were first solubilized at 10 mM in pure
10 DMSO. 20 μ L each of the DMSO stock solution was then transferred into 6 wells on 96-
well plate. The DMSO solvent was dried with GeneVac solvent evaporator at 30 °C, 1
mbar vacuum for 1 h. After the addition of 200 μ L of buffer solutions (pH 6.8, or FaSSIF),
the plate was sealed and shaken at 160 rpm for 24 h at rt. The plate was centrifuged at
3750 rpm for 20 min, 5 μ L of supernatant is mixed with 495 μ L of MeOH/H₂O (1:1). 0.01
15 μ M, 0.1 μ M, 1 μ M, 10 μ M stock solutions were prepared by series of dilution for the
calibration curves. The supernatant was quantified by HPLC or LC/MS using the
calibration curve. High-Throughput equilibrium solubility was determined based on the
concentration of the supernatant.

20 Efficacy studies in mouse xenograft model

[00253] All experiments conducted were performed in female athymic Nude-nu mice
in an AAALAC certificated facility. The animals were kept under SPF conditions in
individual ventilation cages at constant temperature and humidity (i.e., 20-26 °C; 40-
70%) with 5 or less animals in each cage. Animals had free access to irradiation
25 sterilized dry granule food and sterile drinking water. All procedures and protocols were
approved by the Institutional Animal Care and Use and internal committee.

[00254] The cells Karpas 422 human B cell lymphoma were cultured in RPMI-1640
medium (Gibco; 11875-093) supplemented with 15% FBS (Gibco; 10099-141) and 1%
Pen Strep (Gibco; 15140-122) at 37°C in an atmosphere of 5% CO₂ in air. Cells were
30 maintained in suspension cultures at concentrations between 0.5 - 2 x 10⁶ cells/ml. Cells
were split at 1:3 every 2-4 days. To establish xenograft tumor models the cells were
collected, suspended in PBS, mixed with Matrigel (BD Bioscience) at a volume ratio of
1:1 at a concentration of 1x10⁸ cells/mL and then injected subcutaneously into the right
flank of balb/c nude mice (Vital River) at a concentration of 5x10⁶ cells per animal.

[00255] The compound was formulated as a suspension in 0.5% methyl cellulose (MC) and 0.5% Tween 80 in 50 mM pH6.8 buffer (prepared in house according to the USP) and administered orally by gavage at specific doses.

[00256] Treatment was initiated when the average tumor volume reached 100-300 mm³. Tumor growth and body weights were monitored at regular intervals. The two largest diameters, width (W) and length (L), of the xenograft tumors were measured manually with calipers and the tumor volume was estimated using the formula: $0.5 \times L \times W^2$.

[00257] When applicable, results are presented as mean \pm SEM. Graphing and statistical analysis was performed using GraphPad Prism 5.00 (GraphPad Software). Tumor and body weight change data were analyzed statistically. If the variances in the data were normally distributed (Bartlett's test for equal variances), the data were analyzed using one-way ANOVA with *post hoc* Dunnett's test for comparison of treatment versus control group. The *post hoc* Tukey test was used for intragroup comparison. Otherwise, the Kruskal-Wallis ranked test *post hoc* Dunn's was used.

[00258] As a measure of efficacy the %T/C value is calculated at the end of the experiment according to:

$$(\Delta \text{tumor volume}^{\text{treated}} / \Delta \text{tumor volume}^{\text{control}}) * 100$$

Tumor regression was calculated according to:

$$-(\Delta \text{tumor volume}^{\text{treated}} / \text{tumor volume}^{\text{treated at start}}) * 100$$

[00259] Where Δ tumor volumes represent the mean tumor volume on the evaluation day minus the mean tumor volume at the start of the experiment.

[00260] The exemplified Examples disclosed below were tested in the EED Alphascreen binding, LC-MS and/or ELISA assays described above and found to have EED inhibitory activity. A range of IC₅₀ values of $\leq 5 \mu\text{M}$ (5000 nM) was observed.

[00261] Table 3 below lists IC₅₀ values in the EED (a) Alphascreen binding Qualified, (b) LC-MS Qualified and/or (c) ELISA Qualified assays measured for the following examples. "N/A" stands for "not assessed".

30

Table 3

Ex #	IUPAC name	(a) IC ₅₀ (μM)	(b) IC ₅₀ (μM)	(c) IC ₅₀ (μM)
1	N-(2-fluoro-6-methoxy benzyl)-8-(1-methyl-1H-pyrazol-5-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0277	0.0112	0.0181
2	N-(2-fluoro-6-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0109	0.0188	0.0087
3	8-(2,4-dimethylpyrimidin-5-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0175	0.0236	0.0107
4	N-(2-fluoro-6-methoxy benzyl)-8-(2-isobutyl-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3a]pyridin-5-amine	0.0086	0.0066	0.0057
5	N-(2-fluoro-6-methoxy benzyl)-8-(pyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0482	0.1373	0.0426
6	N-(2-fluoro-6-methoxy benzyl)-8-(3-methylpyridin-2-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0909	0.1492	0.057
7	8-(2,4-dimethyl-1H-imidazol-1-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0187	0.0114	0.0101
8	N-(2-fluoro-6-methoxy benzyl)-8-(1-methyl-1H-imidazol-5-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0106	0.0352	0.0043
9	N-(2-fluoro-6-methoxy benzyl)-8-(5-methyl-1,3,4-oxadiazol-2-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0339	0.0624	0.0024
10	8-(5-ethyl-1,2,4-oxadiazol-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0611	0.1981	0.0093
11	N-(2-fluoro-6-methoxy benzyl)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0307	0.1192	0.0405

12	8-(2,4-dimethylpyrimidin-5-yl)-6-fluoro-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.5593	N/A	0.4835
13	8-(4-((dimethylamino)methyl)phenyl)-N-(3-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0711	0.4697	0.068
14	8-(4-((dimethylamino) methyl)phenyl)-N-(3-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.3253	N/A	0.2802
15	8-(4-((dimethylamino) methyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0149	0.0663	0.0175
16	N-(2-methoxybenzyl)-8-(6-methoxypyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0562	0.3771	0.1582
17	N-benzyl-8-(4-((dimethylamino)methyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.2342	N/A	0.2489
18	N-(2-methoxybenzyl)-8-(4-((4-methylpiperazin-1-yl) sulfonyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0817	0.9301	0.1145
19	N-(2-(difluoromethoxy) benzyl)-8-(4-((dimethylamino)methyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1694	0.5868	0.3626
20	N-(2-methoxybenzyl)-8-(5-methyl-6-(4-methyl piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.079	0.2478	0.1852
21	N-(2-methoxybenzyl)-8-(6-(4-methylpiperazin-1-yl) pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1245	1.0634	0.2335
22	N-(2-methoxybenzyl)-8-(4-(4-methylpiperazin-1-yl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0562	0.3648	0.0423
23	N-(2-methoxybenzyl)-8-phenyl-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1795	N/A	0.5213
24	N-(2-methoxybenzyl)-8-(pyridin-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0464	0.0921	0.0478

25	N-(2-methoxybenzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0336	0.1506	0.0503
26	N-(2-methoxybenzyl)-8-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0734	0.4981	0.0477
27	N-(2-methoxybenzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0444	0.2663	0.0515
28	8-(3-((dimethylamino) methyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0379	0.2906	0.054
29	8-(4-(azetidin-1-ylmethyl) phenyl)-N-(2-methoxybenzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.013	0.0877	0.0231
30	N-(2-methoxybenzyl)-8-(4-(morpholinomethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0382	0.4829	0.1133
31	8-(4-((dimethylamino) methyl)phenyl)-N-(2-methylbenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.3939	N/A	0.5081
32	N-(2-methoxybenzyl)-8-(4-(1-(pyrrolidin-1-yl)ethyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0174	0.1419	0.038
33	8-(4-((dimethylamino) methyl)phenyl)-N-(4-fluoro-2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0842	0.2938	0.277
34	4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-N,N-dimethyl benzenesulfonamide	0.0045	0.3582	0.0184
35	8-(4-((dimethylamino) methyl)phenyl)-N-(3-fluorobenzyl)-[1,2,4] triazolo [4,3-a]pyridin-5-amine	2.5736	N/A	3.4948
36	8-(4-((dimethylamino) methyl)phenyl)-N-(2-fluorobenzyl)-[1,2,4] triazolo [4,3-a]pyridin-5-amine	1.0108	N/A	0.9368
37	8-(4-((dimethylamino) methyl)phenyl)-N-(4-fluorobenzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	1.5219	N/A	1.804

38	N-(2-methoxybenzyl)-8-(6-(morpholinomethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0325	0.4376	0.0469
39	N-(2-methoxybenzyl)-8-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0155	0.2693	0.0375
40	1-(4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)-N,N-dimethylmethanamine oxide	0.078	0.4568	0.1375
41	4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-N,N-dimethyl benzamide	0.0249	0.3048	0.0474
42	(4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl) (pyrrolidin-1-yl)methanone	0.0165	0.2056	0.0279
43	8-(4-((dimethylamino) methyl)-3,5-difluorophenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0095	0.7846	0.0038
44	8-(3,5-difluoro-4-(piperidin-1-ylmethyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0748	1.0975	0.112
45	8-(4-((dimethylamino) methyl)phenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0177	0.0233	0.0076
46	N-(2-methoxybenzyl)-8-(o-tolyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.16	N/A	0.5293
47	8-(2-fluorophenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0985	1.3342	0.293
48	8-(4-((dimethylamino) methyl)phenyl)-N-(pyridin-3-ylmethyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	4.2257	N/A	2.2844
49	8-(4-((dimethylamino) methyl)phenyl)-N-(2-fluoro-5-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1644	N/A	0.1399
50	8-(5-fluoro-6-methoxy pyridin-3-yl)-N-(2-methoxybenzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0915	3.1921	0.3744

51	N-(2-methoxybenzyl)-8-(5-methoxypyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1267	N/A	0.159
52	N-(2-methoxybenzyl)-8-(2-methoxypyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0894	0.735	0.1057
53	N-(2-methoxybenzyl)-8-(4-(piperidin-4-ylsulfonyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0279	0.1436	0.0365
54	8-(4-((3,3-difluoroazetidin-1-yl)methyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.019	0.2297	0.0566
55	1-(4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a] pyridin-8-yl)benzyl) pyrrolidin-2-one	0.0151	N/A	0.0441
56	8-(4-(ethylsulfonyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.033	0.1298	0.0885
57	8-(4-(isopropylsulfonyl) phenyl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0159	0.1835	0.0395
58	N-(2-methoxybenzyl)-8-(pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0598	N/A	0.0663
59	N-(2-methoxybenzyl)-8-(2-methoxypyridin-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0316	N/A	0.1677
60	N-(2-methoxybenzyl)-8-(4-(pyrrolidin-1-ylmethyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0402	N/A	0.0565
61	N-(2-methoxybenzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0438	0.5379	0.0619
62	8-(3,5-dimethylisoxazol-4-yl)-N-(2-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0436	0.321	0.0667
63	1-(4-(5-((2-methoxybenzyl) amino)-[1,2,4]triazolo[4,3-a] pyridin-8-yl)phenyl) ethanone	0.0768	1.7044	0.2752

64	2-chloro-4-(5-((2-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) benzamide	0.0317	0.9143	0.126
65	8-(3-chloro-4-morpholinophenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	1.6631	N/A	10.9523
66	8-(4-((3-fluoroazetidin-1-yl) methyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0118	0.2524	0.0299
67	N-(2-methoxybenzyl)-8-(2-(4-methylpiperazin-1-yl) pyridin-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0546	0.1969	0.045
68	N-(2-methoxybenzyl)-8-(4-(pyrrolidin-1-ylsulfonyl) phenyl)-[1,2,4] triazolo[4,3-a] pyridin-5-amine	0.0167	0.3114	0.0497
69	8-(6-(4-ethylpiperazin-1-yl) pyridin-3-yl)-N-(2-methoxy benzyl)-[1,2,4] triazolo[4,3-a] pyridin-5-amine	0.0282	0.3041	0.0737
70	8-(4-((dimethylamino) methyl)-2-fluorophenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0376	0.1881	0.3338
71	3-fluoro-4-(5-((2-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylbenzamide	0.0349	0.2751	0.0434
72	4-(5-((2-methoxybenzyl) amino)-[1,2,4] triazolo[4,3-a] pyridin-8-yl) benzamide	0.0129	1.005	0.0433
73	4-(5-((2-methoxybenzyl) amino)-[1,2,4] triazolo[4,3-a] pyridin-8-yl) benzene sulfonamide	0.0452	0.2364	0.3969
74	8-(4-(2H-tetrazol-5-yl) phenyl)-N-(2-methoxy benzyl)-[1,2,4] triazolo[4,3-a] pyridin-5-amine	0.3199	N/A	4.2377
75	8-(5-chloro-6-(4-methyl piperazin-1-yl)pyridin-3-yl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1322	N/A	0.4876
76	8-(4-((1H-imidazol-1-yl) methyl)phenyl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0419	0.4201	0.1333

77	8-(4-(4-isopropylpiperazin-1-yl)phenyl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0146	0.1065	0.0217
78	N-(2-fluoro-6-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.018	0.0751	0.0261
79	4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylbenzene sulfonamide	0.1158	N/A	0.0785
80	N-(4-(5-((2-methoxy benzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl) acetamide	0.2245	N/A	0.7787
81	8-(4-((dimethylamino)methyl)phenyl)-N-(5-fluoro-2-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.3874	N/A	0.9277
82	N-(4-(5-((2-methoxy benzyl) amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl) methanesulfonamide	0.0803	0.5087	0.3298
83	N-(4-fluoro-2-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0557	0.4911	0.8152
84	4-(5-((4-fluoro-2-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylbenzene sulfonamide	0.1767	N/A	1.1753
85	N-(4-(5-((4-fluoro-2-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)methane sulfonamide	0.1857	N/A	1.0265
86	8-(4-((dimethylamino) methyl)phenyl)-N-(3-fluoro-2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.2183	N/A	0.5286
87	8-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0392	0.2387	0.0901
88	N-(4-fluoro-2-methoxybenzyl)-8-(6-(4-isopropylpiperazin-1-yl) pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1775	N/A	0.5005

89	4-(5-((4-fluoro-2-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)benzenesulfonamide	0.132	N/A	1.4779
90	N-(4-fluoro-2-methoxy benzyl)-8-(6-(4-isopropylpiperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.4096	N/A	2.1345
91	N-(2-methoxybenzyl)-8-(2-methylpyridin-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0375	0.2775	0.0608
92	N-(4-fluoro-2-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1379	N/A	0.2987
93	N-(4-fluoro-2-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1618	N/A	0.3999
94	8-(3-(2-(dimethylamino) ethyl)phenyl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0265	0.0623	0.0411
95	N-(2-methoxybenzyl)-8-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1766	N/A	0.1636
96	(4-(5-((4-fluoro-2-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) phenyl)(pyrrolidin-1-yl) methanone	0.1055	N/A	0.2527
97	8-(5-chloro-6-(4-isopropyl piperazin-1-yl)pyridin-3-yl)-N-(4-fluoro-2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.105	N/A	0.7755
98	N-(2,4-difluoro-5-methoxy benzyl)-8-(4-((dimethylamino)methyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.359	N/A	0.2871
99	N-(2-fluoro-5-methoxybenzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.2548	N/A	0.3846
100	4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)benzenesulfonamide	0.0124	0.1392	0.04

101	N-(2-hydroxyethyl)-4-(5-((2-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)benzenesulfonamide	0.0501	2.5837	0.1023
102	N-(2-methoxybenzyl)-8-(4-(methylsulfinyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0619	1.4563	0.0689
103	N-(4,5-difluoro-2-methoxy benzyl)-8-(4-((dimethylamino)methyl)phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	2.8618	N/A	8.2146
104	N-(4-fluoro-2-methoxy benzyl)-8-(2-(4-isopropyl piperazin-1-yl)pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1601	N/A	0.1315
105	N-(4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)methane sulfonamide	0.0215	0.2815	0.0433
106	N-(2-fluoro-4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a] pyridin-8-yl)phenyl) methanesulfonamide	0.0468	0.4538	0.053
107	(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) phenyl)(pyrrolidin-1-yl) methanone	0.0214	0.1079	0.0126
108	N-(2-fluoro-6-methoxy benzyl)-8-(6-(4-isopropyl piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0708	0.35	0.191
109	8-(5-chloro-6-(4-isopropylpiperazin-1-yl) pyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0271	0.2986	0.1033
110	N-(2-methoxybenzyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1267	N/A	0.0742
111	N-(2-methoxybenzyl)-8-(6-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0765	0.4046	0.0567
112	N-(2-fluoro-6-methoxy benzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0098	0.2564	0.0049

113	N-(2-fluoro-6-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0387	0.1175	0.0274
114	N-(2-fluoro-6-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.016	0.0906	0.0095
115	N-(5-fluoro-2-methoxy benzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.8312	N/A	0.6955
116	N-(5-fluoro-2-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2763	N/A	0.7483
117	N-(5-fluoro-2-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.8458	N/A	0.895
118	N-(5-fluoro-2-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	1.2637	N/A	1.2725
119	N-(3-fluoro-2-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.677	N/A	5.1432
120	N-(2-fluoro-5-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2441	N/A	0.1898
121	N-(2-fluoro-5-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.6797	N/A	0.2988
122	N-(2-fluoro-5-methoxy benzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.3131	N/A	0.1379
123	8-(4-(2-(dimethylamino) ethyl)phenyl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.042	0.3676	0.0994
124	N-(2-fluoro-6-methoxy benzyl)-8-(1,3,5-trimethyl-1H-pyrazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0521	0.0645	0.0247

125	N-(2-fluoro-6-methoxy benzyl)-8-(1-methyl-1H-pyrazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1534	N/A	0.1729
126	4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N-(2-hydroxyethyl) benzenesulfonamide	0.0115	1.7394	0.005
127	8-(6-(isopropylsulfonyl) pyridin-3-yl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0217	0.572	0.0142
128	N-(2-methoxybenzyl)-8-(4-((1-methylpiperidin-4-yl) sulfonyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0332	0.2241	0.0185
129	N-(2-fluoro-4-(5-((4-fluoro-2-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)methane sulfonamide	0.3811	N/A	0.8537
130	N-(2-fluoro-6-methoxy benzyl)-8-(6-(4-isopropyl piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0311	0.0625	0.0809
131	N-(2-fluoro-6-methoxy benzyl)-8-(2-(4-isopropyl piperazin-1-yl)pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0322	0.1807	0.0812
132	N-(2-fluoro-6-methoxy benzyl)-8-(4-(piperidin-4-yl sulfonyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0691	0.0649	0.0218
133	N-(2-fluoro-6-methoxy benzyl)-8-(4-((1-methyl piperidin-4-yl)sulfonyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.005	0.0658	0.0053
134	N-(4-fluoro-2-methoxy benzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1766	N/A	0.5381
135	N-(5-fluoro-2-methoxy benzyl)-8-(4-((1-methyl piperidin-4-yl)sulfonyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.4437	N/A	0.2791
136	N-(3-fluoro-2-methoxy benzyl)-8-(6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	2.8816	N/A	11.3854

137	N-(3-fluoro-2-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.3436	N/A	0.7332
138	N-(3-fluoro-2-methoxy benzyl)-8-(4-((1-methylpiperidin-4-yl) sulfonyl)phenyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	1.2687	N/A	2.9009
139	8-(3,5-dimethylisoxazol-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.026	0.0465	0.0117
140	N-(2-fluoro-6-methoxy benzyl)-8-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0175	0.2683	0.0188
141	8-(2-(dimethylamino) pyrimidin-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1178	N/A	0.761
142	N-(2-fluoro-6-methoxy benzyl)-8-(3-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0136	0.1063	0.0348
143	8-(6-((1-ethylpiperidin-4-yl)sulfonyl)pyridin-3-yl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0311	0.3228	0.0532
144	N-(3-fluoro-2-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	1.269	N/A	0.9858
145	2-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-1H-pyrazol-1-yl)ethanol	0.1253	N/A	0.1184
146	N-(3,5-difluoro-2-methoxy benzyl)-8-(4-((dimethylamino)methyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	1.9773	N/A	4.106
147	N-(2-fluoro-6-methoxy benzyl)-8-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0774	0.0608	0.0425
148	N-(2-fluoro-6-methoxy benzyl)-8-(5-methoxy pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0289	0.0998	0.0606

149	8-(6-((1-ethylpiperidin-4-yl) sulfonyl)pyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0182	0.0271	0.0149
150	N-(2-fluoro-6-methoxy benzyl)-8-(4-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0356	0.0948	0.0142
151	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-ol	0.0664	0.6758	0.0803
152	8-(4-(4-ethylpiperazin-1-yl) phenyl)-N-(2-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0659	0.2066	0.1013
153	N-(4-fluoro-2-methoxy benzyl)-8-(4-((1-methyl piperidin-4-yl)sulfonyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.168	N/A	0.2228
154	N-(4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)phenyl)-N-methyl methanesulfonamide	0.0045	0.0834	0.0049
155	N-(2-fluoro-5-methoxy benzyl)-8-(4-((1-methyl piperidin-4-yl)sulfonyl) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.3199	N/A	0.1832
156	8-(4-((dimethylamino) methyl)phenyl)-N-(4-fluoro-3-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	1.3457	N/A	0.7877
157	2-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) phenoxy)ethanol	0.0404	0.152	0.0431
158	N-(2-fluoro-6-methoxy benzyl)-8-(5-fluoropyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0138	0.0389	0.0196
159	N-(2-fluoro-6-methoxy benzyl)-8-(6-fluoropyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.049	0.1017	0.041
160	N-(2-fluoro-6-methoxy benzyl)-8-(5-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0157	0.3509	0.0148

161	N-(2-fluoro-6-methoxy benzyl)-8-(2-methyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0487	0.0901	0.0261
162	N-(2,4-difluoro-6-methoxybenzyl)-8-(4-((dimethylamino)methyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0166	0.0775	0.0143
163	N-(5-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)-N-methylmethanesulfonamide	0.0166	0.0505	0.0107
164	N-(2-fluoro-6-methoxybenzyl)-8-(6-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0332	0.1196	0.036
165	N-(2-fluoro-6-methoxybenzyl)-8-(5-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0159	0.038	0.014
166	N-(2-fluoro-6-methoxybenzyl)-8-(2-fluoropyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0252	0.0204	0.0333
167	1-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-3-yl)pyrrolidin-2-one	0.0134	0.6789	0.0103
168	N-(2-methoxybenzyl)-8-(6-(2,4,5-trimethylpiperazin-1-yl)pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0505	0.168	0.1052
169	N-(2-fluoro-6-methoxy benzyl)-8-(4-(2-(methylsulfonyl)ethoxy) phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0845	0.3051	0.1047
170	2-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-3,5-dimethyl-1H-pyrazol-1-yl)ethanol	0.0258	0.0672	0.0186
171	8-(4-((dimethylamino) methyl)phenyl)-N-(3-fluoro-5-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.8391	N/A	1.1047
172	N-(2-fluoro-6-methoxy benzyl)-8-(6-morpholino pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0564	0.1619	0.111

173	N-(2-fluoro-6-methoxy benzyl)-8-(6-methoxy pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0363	0.1227	0.0403
174	8-(6-(dimethylamino)pyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0472	0.1355	0.0767
175	2-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)ethanol	0.0359	0.1479	0.0239
176	N-(2-fluoro-6-methoxy benzyl)-8-(2-methoxy pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0329	0.1762	0.0586
177	8-(2-fluoro-4-(methylsulfonyl)phenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0158	0.0323	0.0123
178	3-fluoro-4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-N,N-dimethyl benzamide	0.0065	0.0188	0.0065
179	N-(2-fluoro-6-methoxy benzyl)-8-(6-(piperidin-4-ylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0248	0.174	0.0132
180	8-(6-(2,4-dimethylpiperazin-1-yl)pyridin-3-yl)-N-(2-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0557	0.1708	0.0579
181	N-(2-fluoro-6-methoxy benzyl)-8-(4-fluoropyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0112	0.0442	0.0114
182	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N-methylnicotinamide	0.0204	0.5197	0.0165
183	2-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)ethanol	0.0199	0.0416	0.0173
184	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0464	0.0777	0.025

185	N-(2-fluoro-6-methoxy benzyl)-8-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0079	0.0185	0.0036
186	8-(1,3-dimethyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0659	0.014	0.0409
187	8-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0416	0.1718	0.0528
188	8-(1,5-dimethyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0552	0.0931	0.0348
189	N-(2-fluoro-6-methoxy benzyl)-8-(3-methyl-1H-pyrazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0536	0.0711	0.0564
190	N-(2-fluoro-6-methoxy benzyl)-8-(4-methoxy pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0415	0.2399	0.0131
191	N-(2-fluoro-6-methoxy benzyl)-8-(2-methoxy phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.4791	N/A	0.996
192	8-(2-chlorophenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0888	0.3483	0.1181
193	N-(2-fluoro-6-methoxy benzyl)-8-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2828	N/A	0.7042
194	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylpicolinamide	0.0165	0.0494	0.0063
195	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylnicotinamide	0.0176	0.0613	0.008
196	N-(5-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)acetamide	0.0253	0.164	0.0438
197	1-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-3-yl)ethanol	0.4144	N/A	0.1609

198	N-(2-fluoro-6-methoxy benzyl)-8-(5-(3-(methylsulfonyl)propoxy)pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0345	0.2352	0.032
199	8-(5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)pyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0237	0.3281	0.0313
200	8-(4-amino-3,5-difluorophenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0711	0.2246	0.1095
201	8-(4-fluoro-2-methylphenyl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0465	0.3656	0.0717
202	N-(2-fluoro-6-methoxy benzyl)-8-(4-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2698	N/A	0.3179
203	N-(2-fluoro-6-methoxy benzyl)-8-(5-(methoxymethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0538	0.073	0.0387
204	N-(2-fluoro-6-methoxy benzyl)-8-(5-(2-(methylsulfonyl)ethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1433	N/A	0.0958
205	1-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)ethanol	0.0531	0.1602	0.0437
206	4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N-dimethylbenzamide	0.024	0.048	0.0241
207	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-3-ol	0.0249	0.4675	0.0748
208	8-(4-amino-2,5-difluorophenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1048	N/A	0.1396
209	4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-3-methylbenzonitrile	0.1193	N/A	0.0762

210	8-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0424	0.1649	0.0619
211	N-(2-fluoro-6-methoxy benzyl)-8-(o-tolyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1027	N/A	0.1513
212	N-(2-fluoro-6-methoxy benzyl)-8-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.018	0.0756	0.0226
213	8-(2-chloropyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0205	0.02	0.0165
214	(E)-1-(5-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)ethanone O-methyl oxime	0.0552	0.9646	0.0627
215	1-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)pyrrolidin-2-one	0.02	0.1496	0.055
216	2-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-3-yl)propan-2-ol	0.033	0.4494	0.0255
217	2-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-3-yl)-N-methyl acetamide	0.0343	0.9464	0.025
218	8-(2-fluoro-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0383	0.0795	0.042
219	8-(5-fluoro-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0291	0.2126	0.0267
220	N-(2,4-difluoro-6-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.046	0.1418	0.0556
221	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0216	0.0149	0.0121

222	8-(6-fluoro-2-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0099	0.1216	0.0099
223	8-(5-fluoro-2-methylphenyl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0233	0.2302	0.0667
224	8-(2,4-dichlorophenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1366	N/A	0.2199
225	N-(2-fluoro-6-methoxy benzyl)-8-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0269	0.1472	0.0159
226	N-(2-fluoro-6-methoxy benzyl)-8-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0433	0.092	0.0388
227	N-(2,4-difluoro-6-methoxy benzyl)-8-(3,5-dimethyl isoxazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0455	0.1311	0.0402
228	N-(2,4-difluoro-6-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0789	0.0986	0.0437
229	N-(2-fluoro-6-methoxy benzyl)-8-(2-methyl-4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0161	0.0559	0.0135
230	N-(2-fluoro-6-methoxy benzyl)-8-(3-methylpyridin-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0129	0.0272	0.0094
231	4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N,3-trimethylbenzamide	0.0077	0.0291	0.0034
232	N-(2-fluoro-6-methoxy benzyl)-8-(1-isopropyl-1H-pyrazol-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.05	0.1593	0.0622
233	8-(1-ethyl-1H-pyrazol-5-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.014	0.0478	0.0153
234	3-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)-N,N-dimethyl	0.035	0.1492	0.0263

	propanamide			
235	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0687	0.1074	0.1384
236	8-(4-chloropyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0836	0.1158	0.0663
237	N-(2-fluoro-6-methoxy benzyl)-8-(2-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0869	0.1157	0.1161
238	(2-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl) phenyl)methanol	0.0745	0.1529	0.0853
239	N-(2,4-difluoro-6-methoxybenzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0246	0.0396	0.02
240	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0521	0.0534	0.0295
241	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0162	0.0562	0.0126
242	N-(2,3-difluoro-6-methoxy benzyl)-8-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1769	N/A	0.4545
243	N-(2,3-difluoro-6-methoxy benzyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.3289	N/A	0.3493
244	N-(2,3-difluoro-6-methoxy benzyl)-8-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2312	N/A	0.2766
245	N-(2-fluoro-6-methoxy benzyl)-8-(1-isopropyl-3,5-dimethyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0146	0.0277	0.0082
246	methyl 4-(4-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-1H-pyrazol-1-	0.0689	0.1063	0.2424

	yl)piperidine-1-carboxylate			
247	N-(2-fluoro-6-methoxy benzyl)-8-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0358	0.7002	0.0427
248	8-(6-fluoro-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0165	0.0818	0.0096
249	8-(2,6-dimethylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0227	0.0419	0.0124
250	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-6-methylpicolinonitrile	0.0143	0.0202	0.0065
251	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-4-methylpicolinonitrile	0.0157	0.0418	0.0086
252	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N,4-trimethylpicolinamide	0.0141	0.0079	0.0044
253	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0662	0.2889	0.0592
254	8-(2-ethylphenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.2634	N/A	0.7611
255	N-(2-fluoro-6-methoxy benzyl)-8-(1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.1893	N/A	0.0768
256	N-((5-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)pyridin-2-yl)methyl)acetamide	0.0251	0.159	0.0104
257	N-(2-fluoro-6-methoxy benzyl)-8-(2-isopropyl phenyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.9058	N/A	62.5
258	8-(4-(difluoromethyl)pyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4] triazolo [4,3-a]pyridin-5-amine	0.0245	0.0716	0.0167

259	8-(3-chloropyridin-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0175	N/A	0.0091
260	8-(2-(dimethylamino)-4-methylpyrimidin-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0354	0.0459	0.0217
261	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl-2-morpholinopyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0176	N/A	0.0078
262	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl-6-morpholinopyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0124	N/A	0.0156
263	8-(6-chloro-2-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0169	N/A	0.0154
264	N-(2-fluoro-6-methoxy benzyl)-8-(2-(trifluoromethyl)pyridin-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0148	N/A	0.0147
265	8-(2-(difluoromethyl)pyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0141	0.0063	0.0071
266	N-(2-fluoro-6-methoxy benzyl)-8-(2-methyl-6-morpholinopyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0089	0.0562	0.0099
267	8-(6-chloro-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.017	0.0758	0.0146
268	8-(4,6-dimethylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0194	0.034	0.0214
269	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-N,N,6-trimethylpicolinamide	0.0089	0.0601	0.0048
270	8-(6-cyclopropyl-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0273	0.1064	0.0423

271	8-(2-ethyl-4-(methylsulfonyl)phenyl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0332	0.0803	0.03
272	8-(4-ethylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0347	0.0575	0.0618
273	N-(2-fluoro-6-methoxy benzyl)-8-(4-isopropyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.069	0.0997	0.0613
274	1-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-3,5-dimethyl-1H-pyrazol-1-yl)propan-2-ol	0.0146	0.0253	0.0154
275	8-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0233	0.0718	0.0216
276	8-(2-fluoro-3-methylpyridin-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0139	0.0505	0.008
277	8-(2-(difluoromethyl)-3-methylpyridin-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0142	0.0322	0.012
278	N-(2-fluoro-6-methoxy benzyl)-8-(2-(fluoromethyl)-3-methylpyridin-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.011	0.027	0.0064
279	8-(2-fluoro-5-methylpyridin-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0158	0.0751	0.0121
280	8-(4-ethylpyrimidin-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0237	0.3172	0.0118
281	N-(2-fluoro-6-methoxy benzyl)-8-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.023	0.124	0.0169
282	N-(2-fluoro-6-methoxy benzyl)-8-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0107	0.0157	0.0081

283	8-(2-ethylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0396	0.576	0.0621
284	8-(2-cyclopropyl-4-methyl pyrimidin-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0096	0.0444	0.0105
285	N-(2,4-difluoro-5-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1763	N/A	0.1118
286	N-(2,3-difluoro-6-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1123	N/A	0.1152
287	8-(2,3-dimethylpyridin-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0101	0.0386	0.0066
288	8-(1,3-dimethyl-1H-pyrazol-5-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0127	0.0234	0.0063
289	N-(2-fluoro-6-methoxy benzyl)-8-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0284	0.1285	0.0303
290	8-(4-(difluoromethyl) pyrimidin-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0307	0.0332	0.004
291	N-(2-fluoro-5-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1836	N/A	0.0849
292	8-(1-cyclopropyl-1H-pyrazol-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.029	0.1953	0.0114
293	8-(2-(difluoromethyl)-6-(methylsulfonyl)pyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0314	0.0201	0.0106
294	N-(2-fluoro-6-methoxy benzyl)-8-(2-(fluoromethyl) pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0239	0.1164	0.0094
295	4-(5-((2,4-difluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-N,N,3-trimethyl benzamide	0.0307	0.3207	0.0124

296	N-(2,4-difluoro-6-methoxy benzyl)-8-(1-methyl-1H-pyrazol-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.013	0.1264	0.0051
297	N-(2,4-difluoro-6-methoxy benzyl)-8-(3-methylpyridin-4-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0423	0.618	0.0175
298	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-ethylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0679	0.3622	0.0869
299	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-methyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0276	0.0666	0.0119
300	N-(2,4-difluoro-6-methoxy benzyl)-8-(2,4-dimethyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0359	0.0607	0.0206
301	8-(4-(difluoromethyl)-6-(methylsulfonyl)pyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0237	0.0934	0.0064
302	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-(difluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0133	0.0393	0.0098
303	(3-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)methanol	0.0276	0.0204	0.0155
304	8-(6-(difluoromethoxy)-4-methylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0266	0.0483	0.018
305	8-(2,5-dimethylpyridin-4-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0526	0.0946	0.0282
306	8-(2-(difluoromethyl)-5-methylpyridin-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0309	0.0418	0.0155
307	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-ethylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.205	N/A	0.2257

308	N-(2-fluoro-6-methoxy benzyl)-8-(6-methoxy-4-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0186	0.1171	0.0174
309	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-6-methylpyridin-2-ol	0.0158	0.0606	0.0116
310	N-(2-fluoro-6-methoxy benzyl)-8-(6-methoxy-2-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0136	0.0561	0.0166
311	6-fluoro-N-(2-fluoro-6-methoxybenzyl)-4-(2-methyl pyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-7-amine	0.4205	N/A	0.8333
312	2-(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethanol	0.0312	0.171	0.0225
313	8-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0034	0.0147	0.004
314	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-(difluoromethyl)-6-methyl pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0223	0.1099	0.0186
315	8-(2-(difluoromethyl)-6-methylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0077	0.0215	0.0078
316	8-(4-(difluoromethyl)-6-methylpyridin-3-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0157	0.2148	0.0173
317	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-(difluoromethyl)-6-methyl pyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0356	0.2179	0.0532
318	N-(2,4-difluoro-6-methoxy benzyl)-8-(6-methoxy-4-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0716	N/A	0.0716
319	N-(2,4-difluoro-6-methoxy benzyl)-8-(6-methoxy-2-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0285	0.1299	0.0407

320	N-(2,4-difluoro-6-methoxy benzyl)-6-fluoro-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.4248	N/A	0.4342
321	N-(2,4-difluoro-6-methoxy benzyl)-8-(2,4-dimethylpyrimidin-5-yl)-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-5-amine	2.6557	N/A	1.5349
322	N-(2-fluoro-6-methoxy benzyl)-8-(2-methoxy-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0091	0.0323	0.0071
323	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-methoxy-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0246	0.0312	0.0143
324	5-(5-((2,4-difluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-methylpicolinonitrile	0.0179	0.0638	0.0159
325	N-(2-fluoro-6-methoxy benzyl)-8-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.037	0.1412	0.0338
326	8-(5-chloro-2-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0261	0.0716	0.0298
327	N-(3,6-difluoro-2-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0483	0.172	0.0519
328	N-((2-methoxypyridin-3-yl) methyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0735	0.2837	0.0763
329	N-(2,4-difluoro-6-methoxy benzyl)-8-(4,6-dimethylpyridin-3-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0311	1.357	0.048
330	(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-1-methyl-1H-pyrazol-3-yl) methanol	0.024	0.0962	0.024
331	N-(2-fluoro-6-methyl benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.459	N/A	0.519

332	N-(2-fluoro-6-methoxy benzyl)-8-(2-isopropoxy-4-methylpyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0082	0.0266	0.0073
333	N-(3,6-difluoro-2-methoxy benzyl)-8-(2,4-dimethyl pyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0951	0.2863	0.0676
334	N-(3,6-difluoro-2-methoxy benzyl)-8-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.038	0.1438	0.0316
335	N-(2-chloro-6-methoxy benzyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0845	0.254	0.3179
336	(4-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-1-methyl-1H-pyrazol-5-yl) methanol	0.0128	0.0595	0.0121
337	8-(5-(difluoromethyl)-2-methylpyridin-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0238	0.1665	0.0431
338	8-(4-chloro-2-methylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0074	0.0421	0.0162
339	2-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-6-methylpyridin-2-yl) acetonitrile	0.006	0.0209	0.0067
340	3-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) picolinonitrile	0.0125	0.5226	0.0255
341	2-(3-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-2-yl)acetonitrile	0.0216	0.0955	0.0219
342	N-(2-fluoro-6-methoxy benzyl)-8-(6-isopropoxy-2-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0105	0.0475	0.0153
343	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-ethoxy-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0257	0.4921	0.0365

344	8-(2-cyclopropoxy-4-methyl pyrimidin-5-yl)-N-(2,4-difluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0255	N/A	N/A
345	(3-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl) pyridin-4-yl)methanol	0.0076	0.0245	0.0104
346	8-(2,4-dimethylpyridin-3-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1421	N/A	0.2605
347	N-((3-methoxypyridin-2-yl) methyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.7914	N/A	0.7713
348	8-(2,4-dimethylpyrimidin-5-yl)-N-((2-methoxypyridin-3-yl)methyl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0851	0.2088	0.0455
349	N-(2,4-difluoro-6-methoxy benzyl)-8-(2-isopropoxy-4-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0229	0.2909	0.0312
350	5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-6-methylnicotinonitrile	0.0322	0.0454	0.0164
351	N-(2-fluoro-6-methoxy benzyl)-8-(6-isopropyl-2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0234	0.0229	0.0155
352	N-(2-fluoro-6-methoxy benzyl)-8-(6-isopropyl-4-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0295	0.1056	0.032
353	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl-1H-pyrazol-1-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0258	0.1563	0.0393
354	N-(2-fluoro-6-methoxy benzyl)-8-(4-methyl-1H-imidazol-1-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0261	0.0606	0.0214
355	8-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0158	0.0305	0.0117
356	N-(2-fluoro-6-methoxy benzyl)-8-(1-methyl-1H-1,2,4-triazol-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.019	0.1175	0.014

357	N-(2-fluoro-6-methoxy benzyl)-8-(1H-pyrazol-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0256	0.1437	0.0389
358	N-(2-fluoro-6-methoxy benzyl)-8-(1H-1,2,4-triazol-1-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0171	0.2857	0.0195
359	N-(2-fluoro-6-methoxy benzyl)-8-(3-methyl-1H-pyrazol-1-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0429	0.2745	0.0551
360	N-((3-methoxypyridin-4-yl) methyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	4.0904	N/A	3.0448
361	N-(2-fluoro-6-methoxy benzyl)-8-(1H-1,2,3-triazol-1-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0151	0.0696	0.0211
362	N-(2-fluoro-6-methoxy benzyl)-8-(2-methyl-1H-imidazol-1-yl)-[1,2,4]triazolo [4,3-a]pyridin-5-amine	0.0398	0.0334	0.017
363	N-(2-fluoro-6-methoxy benzyl)-8-(1H-imidazol-1-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.025	0.0554	0.0193
364	N-((6-methoxypyridin-2-yl) methyl)-8-(2-methylpyridin-3-yl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.1195	N/A	0.0806
365	8-(1,2-dimethyl-1H-imidazol-4-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1975	N/A	0.2785
366	8-(1,2-dimethyl-1H-imidazol-5-yl)-N-(2-fluoro-6-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0133	0.0455	0.0034
367	8-(3,4-dimethyl-1H-pyrazol-1-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0235	0.1129	0.0291
368	3-(5-(5-((2-fluoro-6-methoxy benzyl)amino)-[1,2,4] triazolo[4,3-a]pyridin-8-yl)-6-methylpyridin-2-yl)-1,1-dimethylurea	0.0117	0.0709	0.0065
369	2-(5-(5-((2-fluoro-6-methoxybenzyl)amino)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)-6-methylpyridin-2-yl)-2-methylpropanenitrile	0.0052	0.2046	0.0029

370	8-(1,4-dimethyl-1H-pyrazol-5-yl)-N-(2-fluoro-6-methoxy benzyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0258	0.1075	0.02
371	N-((4-amino-2-methoxy pyridin-3-yl)methyl)-8-(2-methylpyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.1025	N/A	0.0927
372	N-(2-fluoro-6-methoxy benzyl)-8-(4-methoxy-2-methylpyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-5-amine	0.0211	0.1182	0.0338
373	N-(2,4-difluoro-6-methoxy benzyl)-8-(4-methoxy-2-methylpyrimidin-5-yl)-[1,2,4] triazolo[4,3-a]pyridin-5-amine	0.0487	0.4937	0.0641
374	8-(4-((dimethylamino) methyl)phenyl)-N-((2-methoxypyridin-3-yl) methyl)-[1,2,4]triazolo[4,3-a] pyridin-5-amine	0.0583	0.144	0.0467

[00262] Accordingly, the compounds of the present invention have been found to inhibit EED and are therefore useful in the treatment of diseases or disorders associated with EED and PRC2, which include, but are not limited to, diffused large B cell lymphoma (DLBCL), follicular lymphoma, other lymphomas, leukemia, multiple myeloma, mesothelioma, gastric cancer, malignant rhabdoid tumor, hepatocellular carcinoma, prostate cancer, breast carcinoma, bile duct and gallbladder cancers, bladder carcinoma, brain tumors including neuroblastoma, glioma, glioblastoma and astrocytoma, cervical cancer, colon cancer, melanoma, endometrial cancer, esophageal cancer, head and neck cancer, lung cancer, nasopharyngeal carcinoma, ovarian cancer, pancreatic cancer, renal cell carcinoma, rectal cancer, thyroid cancers, parathyroid tumors, uterine tumors, and soft tissue sarcomas selected from rhabdomyosarcoma (RMS), Kaposi sarcoma, synovial sarcoma, osteosarcoma and Ewing's sarcoma.

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VI. PHARMACEUTICAL COMPOSITIONS AND COMBINATIONS

[00263] The compounds of the present invention are typically used as a pharmaceutical composition (e.g., a compound of the present invention and at least one pharmaceutically acceptable carrier). A "pharmaceutically acceptable carrier (diluent or excipient)" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, generally recognized as safe

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(GRAS) solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, buffering agents (e.g., maleic acid, tartaric acid, lactic acid, citric acid, acetic acid, sodium bicarbonate, sodium phosphate, and the like), disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Allen, L.V., Jr. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012). For purposes of this invention, solvates and hydrates are considered pharmaceutical compositions comprising a compound of the present invention and a solvent (i.e., solvate) or water (i.e., hydrate).

[00264] The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above.

[00265] The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00266] The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product. The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment;

the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

- 5 **[00267]** In certain instances, it may be advantageous to administer the compound of the present invention in combination with at least one additional pharmaceutical (or therapeutic) agent, such as other anti-cancer agents, immunomodulators, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.
- 10 **[00268]** The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic disease, disorder or condition described in the present invention. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration
- 15 encompasses co-administration in multiple, or in separate containers (e.g., capsules, powders, and liquids) for each active ingredient. The compound of the present invention and additional therapeutic agents can be administered via the same administration route or via different administration routes. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also
- 20 encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

- [00269]** General chemotherapeutic agents considered for use in combination
- 25 therapies include anastrozole (Arimidex[®]), bicalutamide (Casodex[®]), bleomycin sulfate (Blenoxane[®]), busulfan (Myleran[®]), busulfan injection (Busulfex[®]), capecitabine (Xeloda[®]), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin[®]), carmustine (BiCNU[®]), chlorambucil (Leukeran[®]), cisplatin (Platinol[®]), cladribine (Leustatin[®]), cyclophosphamide (Cytoxan[®] or Neosar[®]), cytarabine, cytosine
- 30 arabinoside (Cytosar-U[®]), cytarabine liposome injection (DepoCyt[®]), dacarbazine (DTIC-Dome[®]), dactinomycin (Actinomycin D, Cosmegen), daunorubicin hydrochloride (Cerubidine[®]), daunorubicin citrate liposome injection (DaunoXome[®]), dexamethasone, docetaxel (Taxotere[®]), doxorubicin hydrochloride (Adriamycin[®], Rubex[®]), etoposide (Vepesid[®]), fludarabine phosphate (Fludara[®]), 5-fluorouracil (Adrucil[®], Efudex[®]),

flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycytidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), nab-paclitaxel (Abraxane®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepe, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

10 **[00270]** Anti-cancer agents of particular interest for combinations with the compounds of the present invention include:

[00271] *Cyclin-Dependent Kinase (CDK) inhibitors:* (Chen, S. et al., *Nat Cell Biol.*, 12(11):1108-14 (2010); Zeng, X. et al., *Cell Cycle*, 10(4):579-83 (2011)) Aloisine A; Alvocidib (also known as flavopiridol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-
15 [(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone, and described in US Patent No. 5,621,002); Crizotinib (PF-02341066, CAS 877399-52-5); 2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(2R,3S)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]-4H-1-benzopyran-4-one, hydrochloride (P276-00, CAS 920113-03-7); 1-Methyl-5-[[2-[5-(trifluoromethyl)-1H-imidazol-2-yl]-4-pyridinyl]oxy]-N-[4-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine
20 (RAF265, CAS 927880-90-8); Indisulam (E7070); Roscovitine (CYC202); 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, hydrochloride (PD0332991); Dinaciclib (SCH727965); N-[5-[[5-(tert-Butyloxazol-2-yl)methyl]thio]thiazol-2-yl]piperidine-4-carboxamide (BMS 387032, CAS 345627-80-7);
25 4-[[9-Chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]-benzoic acid (MLN8054, CAS 869363-13-3); 5-[3-(4,6-Difluoro-1H-benzimidazol-2-yl)-1H-indazol-5-yl]-N-ethyl-4-methyl-3-pyridinemethanamine (AG-024322, CAS 837364-57-5); 4-(2,6-Dichlorobenzoylamino)-1H-pyrazole-3-carboxylic acid N-(piperidin-4-yl)amide (AT7519, CAS 844442-38-2); 4-[2-Methyl-1-(1-methylethyl)-1H-imidazol-5-yl]-N-[4-(methylsulfonyl)phenyl]-2-pyrimidinamine (AZD5438, CAS 602306-29-6); Palbociclib
30 (PD-0332991); and (2R,3R)-3-[[2-[[3-[[S(R)]-S-cyclopropylsulfonimidoyl]-phenyl]amino]-5-(trifluoromethyl)-4-pyrimidinyl]oxy]-2-butanol (BAY 10000394).

[00272] *Checkpoint Kinase (CHK) inhibitors:* (Wu, Z. et al., *Cell Death Differ.*, 18(11):1771-9 (2011)) 7-Hydroxystaurosporine (UCN-01); 6-Bromo-3-(1-methyl-1H-pyrazol-4-yl)-5-(3R)-3-piperidinyl-pyrazolo[1,5-a]pyrimidin-7-amine (SCH900776, CAS

- 891494-63-6); 5-(3-Fluorophenyl)-3-ureidothiophene-2-carboxylic acid N-[(S)-piperidin-3-yl]amide (AZD7762, CAS 860352-01-8); 4-[(3S)-1-Azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one (CHIR 124, CAS 405168-58-3); 7-Aminodactinomycin (7-AAD), Isogranulatimide, debromohymenialdisine; N-[5-Bromo-4-methyl-2-[(2S)-2-morpholinylmethoxy]-phenyl]-N'-(5-methyl-2-pyrazinyl)urea (LY2603618, CAS 911222-45-2); Sulforaphane (CAS 4478-93-7, 4-Methylsulfinylbutyl isothiocyanate); 9,10,11,12-Tetrahydro- 9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*][1,6]benzodiazocine-1,3(2*H*)-dione (SB-218078, CAS 135897-06-2); and TAT-S216A (YGRKKRRQRRRLYRSPAMPENL), and CBP501 ((d-Bpa)sws(d-Phe-F5)(d-Cha)rrrqr); and (αR)-α-amino-N-[5,6-dihydro-2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-1*H*-pyrrolo[4,3,2-*ef*][2,3]benzodiazepin-8-yl]-Cyclohexaneacetamide (PF-0477736).
- [00273]** *Protein Kinase B (PKB) or AKT inhibitors:* (Rojanasakul, Y., *Cell Cycle*, 12(2):202-3 (2013); Chen B. et al., *Cell Cycle*, 12(1):112-21 (2013)) 8-[4-(1-Aminocyclobutyl)phenyl]-9-phenyl-1,2,4-triazolo[3,4-*f*][1,6]naphthyridin-3(2*H*)-one (MK-2206, CAS 1032349-93-1); Perifosine (KRX0401); 4-Dodecyl-*N*-1,3,4-thiadiazol-2-yl-benzenesulfonamide (PHT-427, CAS 1191951-57-1); 4-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[(3*S*)-3-piperidinylmethoxy]-1*H*-imidazo[4,5-*c*]pyridin-4-yl]-2-methyl-3-butyn-2-ol (GSK690693, CAS 937174-76-0); 8-(1-Hydroxyethyl)-2-methoxy-3-[(4-methoxyphenyl)methoxy]- 6*H*-dibenzo[*b,d*]pyran-6-one (palomid 529, P529, or SG-00529); Tricirbine (6-Amino-4-methyl-8-(β-D-ribofuranosyl)-4*H*,8*H*-pyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]pyridazine); (αS)-α-[[[5-(3-Methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy]methyl]-benzeneethanamine (A674563, CAS 552325-73-2); 4-[(4-Chlorophenyl)methyl]-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)- 4-piperidinamine (CCT128930, CAS 885499-61-6); 4-(4-Chlorophenyl)-4-[4-(1*H* pyrazol-4-yl)phenyl]-piperidine (AT7867, CAS 857531-00-1); and Archexin (RX-0201, CAS 663232-27-7).
- [00274]** *C-Raf Inhibitors:* (Chang, C. et al., *Cancer Cell*, 19(1):86-100 (2011)) Sorafenib (Nexavar®); 3-(Dimethylamino)-*N*-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-benzamide (ZM336372, CAS 208260-29-1); and 3-(1-cyano-1-methylethyl)-*N*-[3-[(3,4-dihydro-3-methyl-4-oxo-6-quinazolinyl)amino]-4-methylphenyl]-benzamide (AZ628, CAS 1007871-84-2).
- [00275]** *Phosphoinositide 3-kinase (PI3K) inhibitors:* (Gonzalez, M. et al., *Cancer Res.*, 71(6): 2360-2370 (2011)) 4-[2-(1*H*-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-*d*]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730); 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-*c*]quinolin-1-

yl]phenyl]propionitrile (also known as BEZ235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806); 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine (also known as BKM120 or NVP-BKM120, and described in PCT Publication No. WO2007/084786); Tozasertib (VX680 or MK-0457, CAS 639089-54-6);

5 (5Z)-5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione (GSK1059615, CAS 958852-01-2); (1E,4S,4aR,5R,6aS,9aR)-5-(Acetyloxy)-1-[(di-2-propenylamino)methylene]-4,4a,5,6,6a,8,9,9a-octahydro-11-hydroxy-4-(methoxymethyl)-4a,6a-dimethyl-cyclopenta[5,6]naphtho[1,2-c]pyran-2,7,10(1H)-trione (PX866, CAS 502632-66-8); 8-Phenyl-2-(morpholin-4-yl)-chromen-4-one (LY294002, CAS 154447-36-

10 6); 2-Amino-8-ethyl-4-methyl-6-(1H-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (SAR 245409 or XL 765); 1,3-Dihydro-8-(6-methoxy-3-pyridinyl)-3-methyl-1-[4-(1-piperazinyl)-3-(trifluoromethyl)phenyl]-2H-imidazo[4,5-c]quinolin-2-one,, (2Z)-2-butenedioate (1:1) (BGT 226); 5-Fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)ethyl]-4(3H)-quinazolinone (CAL101); 2-Amino-N-[3-[N-[3-[(2-chloro-5-methoxyphenyl)amino]quinoxalin-2-yl]

15 sulfamoyl]phenyl]-2-methylpropanamide (SAR 245408 or XL 147); and (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (BYL719).

[00276] *BCL-2 inhibitors:* (Béguelin, W. et al., *Cancer Cell*, 23(5):677-92(2013)) 4-[4-[[2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[(1R)-3-

20 (4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386); Tetrocarcin A; Antimycin; Gossypol ((-)BL-193); Obatoclax; Ethyl-2-amino-6-cyclopentyl-4-(1-cyano-2-ethoxy-2-oxoethyl)-4Hchromone-3-carboxylate (HA14 – 1); Oblimersen (G3139, Genasense®); Bak BH3

25 peptide; (-)-Gossypol acetic acid (AT-101); 4-[4-[(4'-Chloro[1,1'-biphenyl]-2-yl)methyl]-1-piperazinyl]-N-[[4-[(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-benzamide (ABT-737, CAS 852808-04-9); and Navitoclax (ABT-263, CAS 923564-51-6).

[00277] *Mitogen-activated protein kinase (MEK) inhibitors:* (Chang, C. J. et al., *Cancer Cell*, 19(1):86-100 (2011)) XL-518 (also known as GDC-0973, Cas No. 1029872-29-4, available from ACC Corp.); Selumetinib (5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide, also known as AZD6244 or ARRY 142886, described in PCT Publication No. WO2003077914); Benimetinib (6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-

35 carboxylic acid (2-hydroxyethoxy)-amide, also known as MEK162, CAS 1073666-70-2,

- described in PCT Publication No. WO2003077914); 2-[(2-Chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro-benzamide (also known as CI-1040 or PD184352 and described in PCT Publication No. WO2000035436); N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]- benzamide (also known as PD0325901 and described in PCT Publication No. WO2002006213); 2,3-Bis[amino[(2-aminophenyl)thio]methylene]-butanedinitrile (also known as U0126 and described in US Patent No. 2,779,780); N-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-1-[(2R)-2,3-dihydroxypropyl]- cyclopropanesulfonamide (also known as RDEA119 or BAY869766 and described in PCT Publication No. WO2007014011); (3S,4R,5Z,8S,9S,11E)-14-(Ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9, 19-tetrahydro-1H-2-benzoxacyclotetradecine-1,7(8H)-dione] (also known as E6201 and described in PCT Publication No. WO2003076424); 2'-Amino-3'-methoxyflavone (also known as PD98059 available from Biaffin GmbH & Co., KG, Germany); Vemurafenib (PLX-4032, CAS 918504-65-1); (R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (TAK-733, CAS 1035555-63-5); Pimasertib (AS-703026, CAS 1204531-26-9); Trametinib dimethyl sulfoxide (GSK-1120212, CAS 1204531-25-80); 2-(2-Fluoro-4-iodophenylamino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (AZD 8330); and 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-N-(2-hydroxyethoxy)-5-[(3-oxo-[1,2]oxazinan-2-yl)methyl]benzamide (CH 4987655 or Ro 4987655).
- [00278]** *Aromatase inhibitors:* (Pathiraja, T. et al., *Sci. Transl. Med.*, 6(229):229 ra41 (2014)) Exemestane (Aromasin®); Letrozole (Femara®); and Anastrozole (Arimidex®).
- [00279]** *Topoisomerase II inhibitors:* (Bai, J. et al., *Cell Prolif.*, 47(3):211-8 (2014)) Etoposide (VP-16 and Etoposide phosphate, Toposar®, VePesid® and Etopophos®); Teniposide (VM-26, Vumon®); and Tafluposide .
- [00280]** *SRC inhibitors:* (Hebbard, L., *Oncogene*, 30(3):301-12 (2011)) Dasatinib (Sprycel®); Saracatinib (AZD0530, CAS 379231-04-6); Bosutinib (SKI-606, CAS 380843-75-4); 5-[4-[2-(4-Morpholinyl)ethoxy]phenyl]-N-(phenylmethyl)- 2-pyridineacetamide (KX2-391, CAS 897016-82-9); and 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (AZM475271, CAS 476159-98-5).
- [00281]** *Histone deacetylase (HDAC) inhibitors:* (Yamaguchi, J. et al., *Cancer Sci.*, 101(2):355-62 (2010)) Voninostat (Zolinza®); Romidepsin (Istodax®); Treichostatin A (TSA); Oxamflatin; Vorinostat (Zolinza®, Suberoylanilide hydroxamic acid); Pyroxamide (syberoyl-3-aminopyridineamide hydroxamic acid); Trapoxin A (RF-1023A); Trapoxin B (RF-10238); Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-O-methyl-D-tyrosyl-L-

- isoleucyl-L-prolyl] (Cyl-1); Cyclo[(α S,2S)- α -amino- η -oxo-2-oxiraneoctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-(2S)-2-piperidinecarbonyl] (Cyl-2); Cyclic[L-alanyl-D-alanyl-(2S)- η -oxo-L- α -aminooxiraneoctanoyl-D-prolyl] (HC-toxin); Cyclo[(α S,2S)- α -amino- η -oxo-2-oxiraneoctanoyl-D-phenylalanyl-L-leucyl-(2S)-2-piperidinecarbonyl] (WF-3161);
- 5 Chlamydocin ((S)-Cyclic(2-methylalanyl-L-phenylalanyl-D-prolyl- η -oxo-L- α -aminooxiraneoctanoyl); Apicidin (Cyclo(8-oxo-L-2-aminodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-2-piperidinecarbonyl); Romidepsin (Istodax®, FR-901228); 4-Phenylbutyrate; Spiruchostatin A; Mylproin (Valproic acid); Entinostat (MS-275, N-(2-Aminophenyl)-4-[N-(pyridine-3-yl-methoxycarbonyl)-amino-methyl]-benzamide); and
- 10 Depudecin (4,5:8,9-dianhydro-1,2,6,7,11-pentadeoxy- D-*threo*-D-*ido*-Undeca-1,6-dienitol).
- [00282]** *Anti-tumor antibiotics:* (Bai, J. et al., *Cell Prolif.*, 47(3):211-8 (2014)) Doxorubicin (Adriamycin® and Rubex®); Bleomycin (lenoxane®); Daunorubicin (daunorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, Cerubidine®);
- 15 Daunorubicin liposomal (daunorubicin citrate liposome, DaunoXome®); Mitoxantrone (DHAD, Novantrone®); Epirubicin (Ellence™); Idarubicin (Idamycin®, Idamycin PFS®); Mitomycin C (Mutamycin®); Geldanamycin; Herbimycin; Ravidomycin; and Desacetylravidomycin.
- [00283]** *Demethylating agents:* (Musch, T. et al., *PLoS One*, (5):e10726 (2010))
- 20 5-Azacitidine (Vidaza®); and Decitabine (Dacogen®).
- [00284]** *Anti-estrogens:* (Bhan, A. et al., *J Mol Biol.*, S0022-2836(14)00373-8 (2014)) Tamoxifen (Novaldex®); Toremifene (Fareston®); and Fulvestrant (Faslodex®).
- [00285]** Some patients may experience allergic reactions to the compounds of the present invention and/or other anti-cancer agent(s) during or after administration;
- 25 therefore, anti-allergic agents are often administered to minimize the risk of an allergic reaction. Suitable anti-allergic agents include corticosteroids (Knutson, S., et al., *PLoS One*, DOI:10.1371/journal.pone.0111840 (2014)), such as dexamethasone (e.g., Decadron®), beclomethasone (e.g., Beclovent®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold
- 30 under the tradenames Ala-Cort®, hydrocortisone phosphate, Solu-Cortef®, Hydrocort Acetate® and Lanacort®), prednisolone (sold under the tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium
- 35 succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol®

and Solu-Medrol®); antihistamines, such as diphenhydramine (e.g., Benadryl®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (e.g., Proventil®), and terbutaline (Brethine®).

[00286] Immunomodulators of particular interest for combinations with the compounds of the present invention include one or more of: an activator of a costimulatory molecule or an inhibitor of an immune checkpoint molecule (e.g., one or more inhibitors of PD-1, PD-L1, LAG-3, TIM-3 or CTLA4) or any combination thereof.

[00287] In certain embodiments, the immunomodulator is an activator of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

[00288] In certain embodiments, the immunomodulator is an inhibitor of an immune checkpoint molecule. In one embodiment, the immunomodulator is an inhibitor of PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. In one embodiment, the inhibitor of an immune checkpoint molecule inhibits PD-1, PD-L1, LAG-3, TIM-3 or CTLA4, or any combination thereof. The term "inhibition" or "inhibitor" includes a reduction in a certain parameter, e.g., an activity, of a given molecule, e.g., an immune checkpoint inhibitor. For example, inhibition of an activity, e.g., a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40% or more is included by this term. Thus, inhibition need not be 100%.

[00289] Some patients may experience nausea during and after administration of the compound of the present invention and/or other anti-cancer agent(s); therefore, anti-emetics are used in preventing nausea (upper stomach) and vomiting. Suitable anti-emetics include aprepitant (Emend®), ondansetron (Zofran®), granisetron HCl (Kytril®), lorazepam (Ativan®), dexamethasone (Decadron®), prochlorperazine (Compazine®), casopitant (Rezonic® and Zunrisa®), and combinations thereof.

[00290] Medication to alleviate the pain experienced during the treatment period is often prescribed to make the patient more comfortable. Common over-the-counter analgesics, such as Tylenol®, are often used. However, opioid analgesic drugs such as hydrocodone/paracetamol or hydrocodone/acetaminophen (e.g., Vicodin®), morphine (e.g., Astramorph® or Avinza®), oxycodone (e.g., OxyContin® or Percocet®), oxymorphone hydrochloride (Opana®), and fentanyl (e.g., Duragesic®) are also useful for moderate or severe pain.

[00291] In an effort to protect normal cells from treatment toxicity and to limit organ toxicities, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy. Suitable cytoprotective agents include Amifostine (Ethyol®),
5 glutamine, dimesna (Tavocept®), mesna (Mesnex®), dexrazoxane (Zinecard® or Totect®), xaliproden (Xapila®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

[00292] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The
10 Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00293] In one embodiment, the present invention provides pharmaceutical compositions comprising at least one compound of the present invention (e.g., a compound of the present invention) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier suitable for administration to a
15 human or animal subject, either alone or together with other anti-cancer agents.

[00294] In one embodiment, the present invention provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as cancer. The present invention provides methods of treating a human or animal subject in need of such treatment, comprising administering to the subject a therapeutically effective
20 amount of a compound of the present invention (e.g., a compound of the present invention) or a pharmaceutically acceptable salt thereof, either alone or in combination with other anti-cancer agents.

[00295] In particular, compositions will either be formulated together as a combination therapeutic or administered separately.

25 **[00296]** In combination therapy for treatment of a malignancy, the compound of the present invention and other anti-cancer agent(s) may be administered simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the subject.

[00297] In a preferred embodiment, the compound of the present invention and the
30 other anti-cancer agent(s) is generally administered sequentially in any order by infusion or orally. The dosing regimen may vary depending upon the stage of the disease, physical fitness of the patient, safety profiles of the individual drugs, and tolerance of the individual drugs, as well as other criteria well-known to the attending physician and medical practitioner(s) administering the combination. The compound of the present
35 invention and other anti-cancer agent(s) may be administered within minutes of each

other, hours, days, or even weeks apart depending upon the particular cycle being used for treatment. In addition, the cycle could include administration of one drug more often than the other during the treatment cycle and at different doses per administration of the drug.

5 **[00298]** In another aspect of the present invention, kits that include one or more compound of the present invention and a combination partner as disclosed herein are provided. Representative kits include (a) a compound of the present invention or a pharmaceutically acceptable salt thereof, (b) at least one combination partner, e.g., as indicated above, whereby such kit may comprise a package insert or other labeling
10 including directions for administration.

15 **[00299]** A compound of the present invention may also be used to advantage in combination with known therapeutic processes, for example, the administration of hormones or especially radiation. A compound of the present invention may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

20 **[00300]** In another aspect of the present invention, kits that include one or more compound of the present invention and a combination partner as disclosed herein are provided. Representative kits include (a) a compound of the present invention or a pharmaceutically acceptable salt thereof, (b) at least one combination partner, e.g., as indicated above, whereby such kit may comprise a package insert or other labeling including directions for administration.

25 **[00301]** In the combination therapies of the invention, the compound of the present invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present invention and the other therapeutic (or pharmaceutical agent) may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (e.g. in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, e.g. during sequential administration
30 of the compound of the invention and the other therapeutic agent.

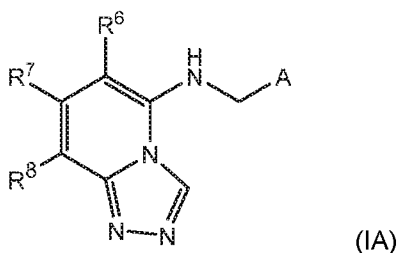
35 **[00302]** The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving EED and/or PRC2. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving myeloperoxidase activity. For example, a compound of the present invention could be used as a reference in an assay

to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness. The compounds of the present invention may also be used in diagnostic assays involving EED and/or PRC2.

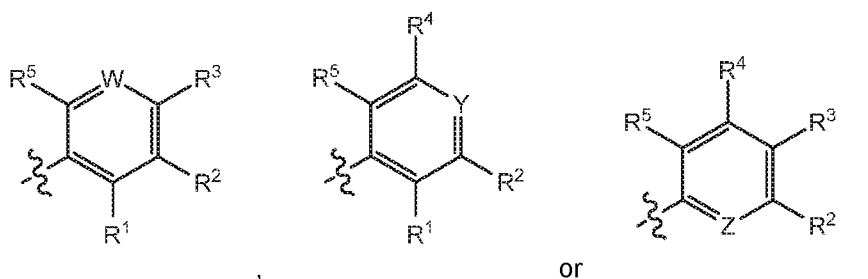
[00303] The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

WHAT IS CLAIMED IS:

1. A compound of Formula (IA):



5 or a pharmaceutically acceptable salt thereof, wherein:



A is

W is independently N or CR⁴;

Y is independently N or CR³;

Z is independently N or CR¹;

10 R¹ is independently H, halogen, or NH₂;

R² is independently H, OCH₃, or halogen;

R³ is independently H or halogen;

R⁴ is independently H, halogen, CH₃, or OCH₃;

R⁵ is independently H, halogen, CH₃, OH, OCH₃, OCH₂F, OCHF₂, or OCF₃;

15 R⁶ and R⁷ are independently selected from: H and halogen;

R⁸ is independently selected from: halogen, phenyl, and a 5- to 6-membered

heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^a, O, and S(O)_p; wherein said phenyl and heteroaryl are substituted with 0-4 R^{8A};

each R^{8A} is independently selected from: halogen, CN, OH, -(O)_m-(C₁-C₆ alkyl

20 substituted with 0-1 R^{8B}), C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, R^{8C}, -OR^{8C}, -C(=O)R^{8D},

NR^{8E}R^{8F}, -C(C₁-C₄ alkyl)=N(C₁-C₄ alkoxy), -C(=O)NR^{8E}R^{8F}, -NHC(=O)R^{8D},

-NHC(=O)NR^{8E}R^{8F}, -S(=O)R^{8D}, -S(=O)₂R^{8D}, -S(=O)₂NR^{8E}R^{8F}, -NHS(=O)₂R^{8D},

-NR^{8E}(S(=O)₂(C₁-C₄ alkyl)), and -CR^{8C}R^{8E}R^{8G};

R^{8B} is independently selected from: CN, OH, NR^eR^f, C₁-C₄ alkoxy, -C(=O)NR^eR^f,

25 -NHC(=O)(C₁-C₄ alkyl), -N(→O)(C₁-C₄ alkyl)₂, -S(=O)₂(C₁-C₄ alkyl), and a 4- to 6-

membered heterocycloalkyl comprising carbon atoms and 1-2 heteroatoms selected from N, NR^a, O, and S(O)_p; wherein said heterocycloalkyl is substituted with 0-2 R^c;

each R^{8C} is independently selected from: C₃-C₆ cycloalkyl, phenyl, and a 4- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N,

5 NR^a, O, and S(O)_p; wherein each moiety is substituted with 0-2 R^c;

each R^{8D} is independently selected from: C₁-C₄ alkyl and R^{8C};

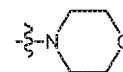
R^{8E} and R^{8G} are, at each occurrence, independently selected from: H and C₁-C₄ alkyl;

each R^{8F} is independently selected from: H and C₁-C₄ alkyl substituted with 0-1

10 R^d;

each R^a is independently selected from: H, →O, C₁-C₄ alkyl substituted with 0-1 R^b, -C(=O)H, -C(=O)(C₁-C₄ alkyl), -CO₂(C₁-C₄ alkyl), C₃-C₆ cycloalkyl, benzyl, and a 4- to 6-membered heterocycloalkyl comprising carbon atoms and 1-2 heteroatoms selected from N, NR^g, O, and S(O)_p;

15 R^b is independently selected from: halogen, OH, C₁-C₄ alkoxy, and



;

each R^c is independently selected from: =O, halogen, OH, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

R^d is independently selected from: OH and NR^eR^f;

R^e and R^f are, at each occurrence, independently selected from: H and

20 C₁-C₄ alkyl;

R^g is independently selected from: H, C₁-C₄ alkyl, -C(=O)(C₁-C₄ alkyl), and -CO₂(C₁-C₄ alkyl);

each p is independently selected from 0, 1 and 2; and

m is independently selected from 0 and 1.

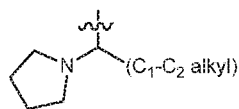
25

2. A compound or a pharmaceutically acceptable salt thereof, according to claim 1, wherein:

each R^{8A} is independently selected from: halogen, CN, OH, -(O)_m-(C₁-C₆ alkyl substituted with 0-1 R^{8B}), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, R^{8C}, -C(=O)R^{8D}, NR^{8E}R^{8F},

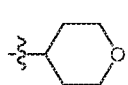
30 -C(=O)NR^{8E}R^{8F}, -NHC(=O)R^{8D}, -NHC(=O)NR^{8E}R^{8F}, -S(=O)R^{8D}, -S(=O)₂R^{8D},

-S(=O)₂NHR^{8F}, -NHS(=O)₂R^{8D}, -NR^{8E}(S(=O)₂(C₁-C₄ alkyl)), -O-C₃-C₆ cycloalkyl, and

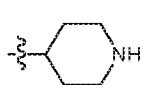


; and

each R^a is independently selected from: H, $\rightarrow O$, C_1-C_4 alkyl substituted with 0-1 R^b , $-C(=O)H$, $-C(=O)(C_1-C_4 \text{ alkyl})$, $-CO_2(C_1-C_4 \text{ alkyl})$, C_3-C_6 cycloalkyl, benzyl,

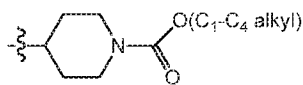


,



,

and



5

3. A compound or a pharmaceutically acceptable salt thereof, according to claim 1 or claim 2, wherein:

R^1 is independently H, F, or Cl;

R^2 is independently H, OCH_3 , or F;

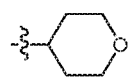
10 R^3 is independently H or F;

R^4 is independently H, F, CH_3 , or OCH_3 ;

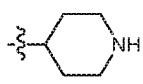
R^5 is independently H, F, CH_3 , OH, OCH_3 , OCH_2F , $OCHF_2$, or OCF_3 ;

R^6 and R^7 are independently selected from: H and F; and

R^a is independently selected from: H, C_1-C_4 alkyl substituted with 0-1 R^b , C_3-C_6

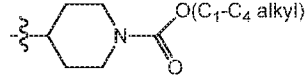


,



,

and



15

cycloalkyl,

4. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, wherein:

R^6 and R^7 are H;

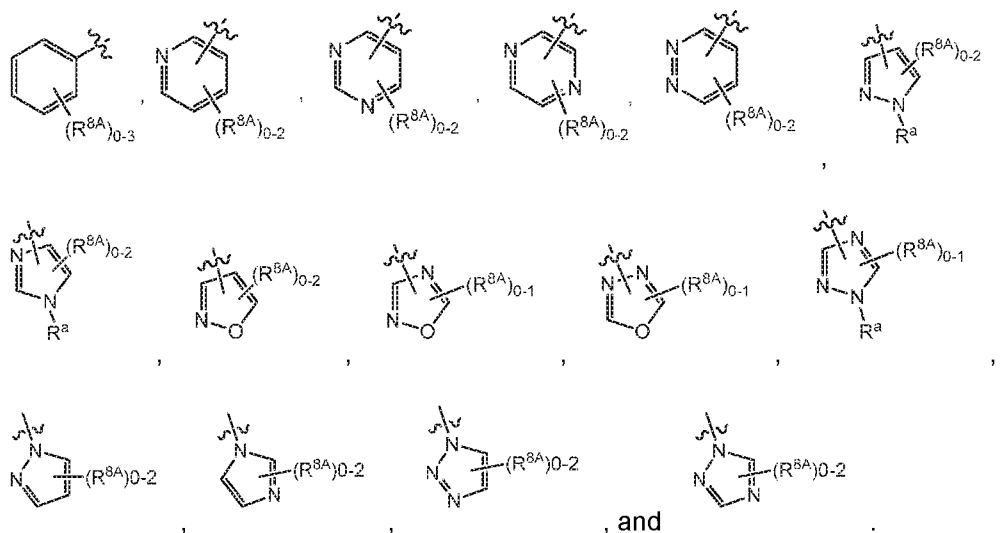
20 R^8 is independently selected from: phenyl, and a 6-membered heteroaryl

comprising carbon atoms and 1-2 heteroatoms selected from N and NR^a ; wherein said phenyl and heteroaryl are substituted with 0-3 R^{8A} .

5. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4, wherein:

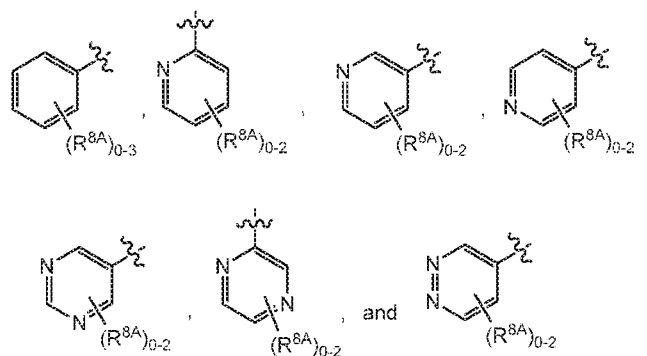
25

R^8 is independently selected from:



6. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5, wherein:

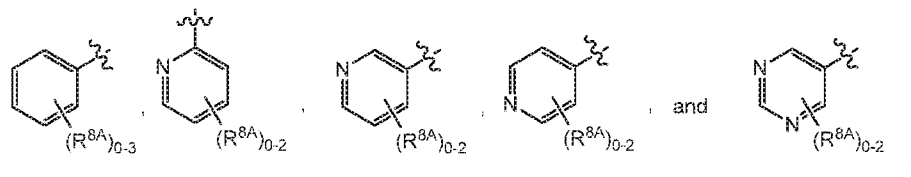
R^8 is independently selected from:



5

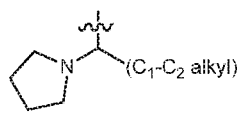
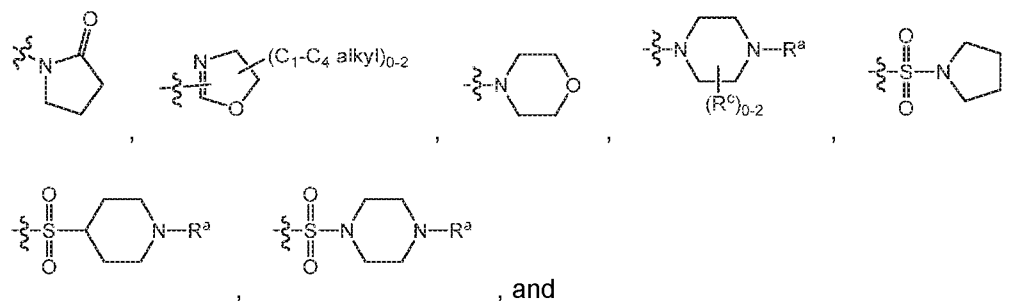
7. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6, wherein:

R^8 is independently selected from:



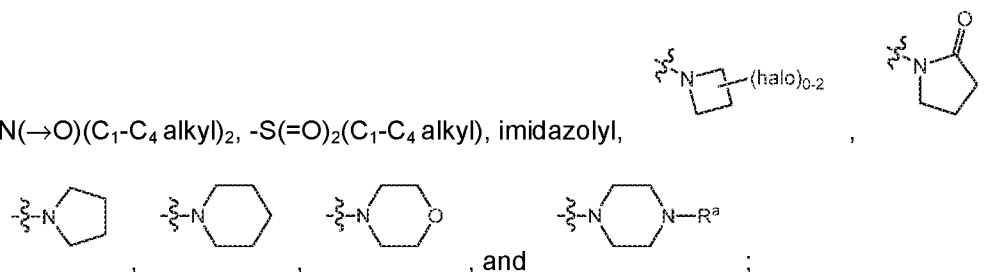
each R^{8A} is independently selected from: halogen, CN, OH, $-(O)_m-(C_1-C_6 \text{ alkyl})$ substituted with 0-1 R^{8B} , C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NH_2 , $-N(C_1-C_4 \text{ alkyl})_2$, C_3-C_6 cycloalkyl, $-O-C_3-C_6$ cycloalkyl, $-C(=O)(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-NHC(=O)N(C_1-C_4 \text{ alkyl})_2$, $-S(=O)(C_1-C_4 \text{ alkyl})$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1-C_4 \text{ alkyl})$ substituted with 0-1 OH, $-S(=O)_2N(C_1-C_4 \text{ alkyl})_2$,

$-NHS(=O)_2(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})(S(=O)_2(C_1-C_4 \text{ alkyl}))$, tetrazolyl,



R^{8B} is independently selected from: CN, OH, C_1-C_4 alkoxy, $-N(C_1-C_4 \text{ alkyl})_2$, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$,

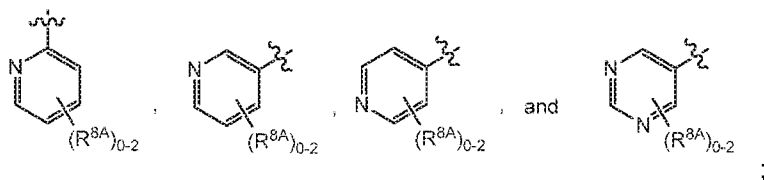
$-N(\rightarrow O)(C_1-C_4 \text{ alkyl})_2$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$, imidazolyl,



- 5 R^a is independently selected from: H and C_1-C_4 alkyl; and
 R^c is independently C_1-C_4 alkyl.

8. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7, wherein:

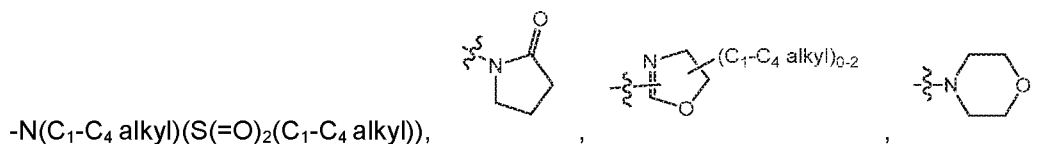
- 10 R^8 is independently selected from:



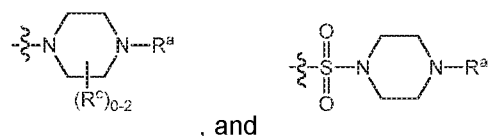
each R^{8A} is independently selected from: halogen, CN, OH, $-(O)_m-(C_1-C_6 \text{ alkyl})$ substituted with 0-1 R^{8B} , C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $N(C_1-C_4 \text{ alkyl})_2$,

C_3-C_6 cycloalkyl, $-O-C_3-C_6$ cycloalkyl, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$,

5 $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-NHC(=O)N(C_1-C_4 \text{ alkyl})_2$, $-S(=O)_2(C_1-C_4 \text{ alkyl})$,



$-N(C_1-C_4 \text{ alkyl})(S(=O)_2(C_1-C_4 \text{ alkyl}))$,

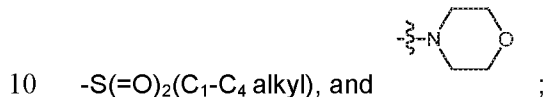


, and

;

R^{8B} is independently selected from: CN, OH, C_1-C_4 alkoxy, $-N(C_1-C_4 \text{ alkyl})_2$,

$-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$,



10 $-S(=O)_2(C_1-C_4 \text{ alkyl})$, and

;

R^a is independently selected from: H and C_1-C_4 alkyl; and

R^c is independently C_1-C_4 alkyl.

9. A compound or a pharmaceutically acceptable salt thereof, according to any one
15 of claims 1 to 8, wherein:

W is independently N or CR^4 ;

R^1 is independently H or F;

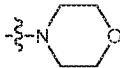
R^2 is independently H or F;


R^3 is independently H or F;

R^4 is independently H or F;

R^5 is independently H or $-OCH_3$;

R^{8A} is independently selected from: C₁-C₆ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,

-N(C₁-C₄ alkyl)₂, C₃-C₆ cycloalkyl, -O-C₃-C₆ cycloalkyl, , and

; and

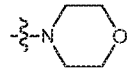
R^a is independently selected from: H and C₁-C₄ alkyl.

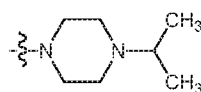
10. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9, wherein:

5 W is independently CR⁴;

R^4 is independently H or F;

R^{8A} is independently selected from: CH₃, CH(CH₃)₂, CH(CH₃)(CH₂CH₃), OCH₃,

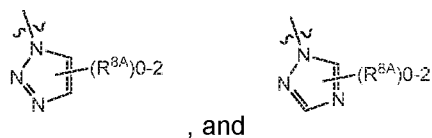
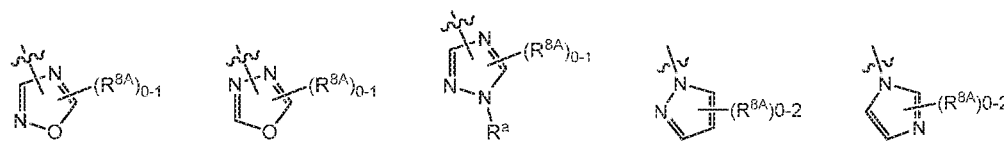
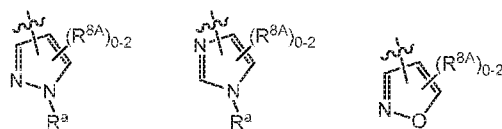
OCH₂CH₃, OCH(CH₃)₂, CHF₂, N(CH₃)₂, cyclopropyl, -O-cyclopropyl, , and

.

11. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 and 5, wherein:


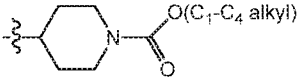
R^6 and R^7 are H;

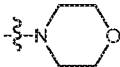
R^8 is independently selected from:



each R^{8A} is independently selected from: C₁-C₄ alkyl substituted with 0-1 OH, and C₁-C₄ haloalkyl;

R^a is independently selected from: H, C₁-C₄ alkyl substituted with 0-1 R^b ,

C₃-C₆ cycloalkyl, , and ; and

R^b is independently selected from: OH and .

12. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11, wherein:

5 R^1 is F.

13. A compound or a pharmaceutically acceptable salt thereof, according to claim 1, wherein said compound is selected from Examples 1 to 374.

10 14. A pharmaceutical composition, comprising one or more pharmaceutically acceptable carriers and a compound of any one of claims 1 to 13.

15. The pharmaceutical composition of Claim 14 further comprising at least one additional therapeutic agent.

15

16. The pharmaceutical composition of Claim 15 where said at least one additional therapeutic agent is selected from other anti-cancer agents, immunomodulators, anti-allergic agents, anti-emetics, pain relievers, cytoprotective agents, and combinations thereof.

20

17. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 13, for use in therapy.

25 18. Use of a compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 13, in the manufacture of a medicament for treating a disease or disorder mediated by mediated by EED and/or PRC2.

19. The use of Claim 18, wherein said disease or disorder is selected from diffused large B cell lymphoma, follicular lymphoma, other lymphomas, leukemia, multiple myeloma, mesothelioma, gastric cancer, malignant rhabdoid tumor, hepatocellular carcinoma, prostate cancer, breast carcinoma, bile duct and gallbladder cancers, bladder carcinoma, brain tumors including neuroblastoma, schwannoma, glioma, glioblastoma and astrocytoma, cervical cancer, colon cancer, melanoma, endometrial cancer, esophageal cancer, head and neck cancer, lung cancer, nasopharyngeal carcinoma, ovarian cancer, pancreatic cancer, renal cell carcinoma, rectal cancer, thyroid cancers, parathyroid tumors, uterine tumors, and soft tissue sarcomas.
20. A method for treating a disease or disorder mediated by mediated by EED and/or PRC2, comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of a compound according to Claims 1 through 13.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053335

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/103155 A1 (NOVARTIS AG [CH]; CHAN HO MAN [US]; GU XIANG-JU JUSTIN [CN]; HUANG YIN) 30 June 2016 (2016-06-30) claim 1 -----	1-20
X,P	HUANG Y.: "Discovery of first-in class, potent, and orally bioavailable embryonic ectoderm development (EED) inhibitor with robust anticancer efficacy", JOURNAL OF MEDICINAL CHEMISTRY, vol. 60, 16 January 2017 (2017-01-16), pages 2215-2226, XP002772151, the whole document -----	1-20
A	WO 2010/022076 A1 (ARRAY BIOPHARMA INC [US]; ALLEN SHELLEY [US]; CELESTE LAURA L [US]; DA) 25 February 2010 (2010-02-25) claim 1 ----- -/-	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2017

Date of mailing of the international search report

21/08/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053335

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 2015/103137 A1 (ARRAY BIOPHARMA INC [US]; GENENTECH INC [US]) 9 July 2015 (2015-07-09) claim 1</p> <p>-----</p>	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/053335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016103155 A1	30-06-2016	AU 2015370524 A1 TW 201629065 A US 2016176882 A1 UY 36462 A WO 2016103155 A1	01-06-2017 16-08-2016 23-06-2016 29-07-2016 30-06-2016
WO 2010022076 A1	25-02-2010	AR 073079 A1 CA 2734831 A1 CN 102186851 A DK 2334677 T3 EP 2334677 A1 ES 2439501 T3 HR P20131140 T1 JP 5518072 B2 JP 2012500277 A JP 2014129409 A PT 2334677 E RS 53079 B SI 2334677 T1 SM T201400154 B TW 201008940 A US 2011144085 A1 UY 32057 A WO 2010022076 A1	13-10-2010 25-02-2010 14-09-2011 18-11-2013 22-06-2011 23-01-2014 03-01-2014 11-06-2014 05-01-2012 10-07-2014 26-11-2013 30-06-2014 31-12-2013 15-01-2015 01-03-2010 16-06-2011 31-01-2011 25-02-2010
WO 2015103137 A1	09-07-2015	CA 2934709 A1 CN 105980387 A EP 3089980 A1 JP 2017502049 A KR 20160104036 A US 2016304519 A1 WO 2015103137 A1	09-07-2015 28-09-2016 09-11-2016 19-01-2017 02-09-2016 20-10-2016 09-07-2015