IN 01503 66

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 June 2014 (12.06.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/089379 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/495 (2006.01)

(21) International Application Number:
PCT/US2013/073457

(22) International Filing Date:
6 December 2013 (06.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/734,726 7 December 2012 (07.12.2012) US
61/787,568 15 March 2013 (15.03.2013) US
61/868,132 21 August 2013 (21.08.2013) US

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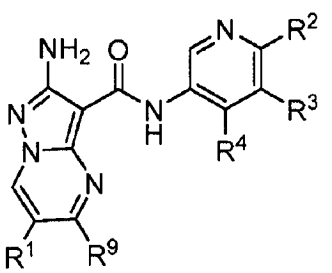
[Continued on next page]

(54) Title: COMPOUNDS USEFUL AS INHIBITORS OF ATR KINASE



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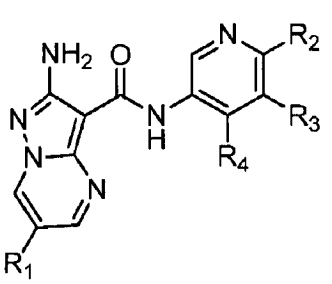

(I-A)

(57) Abstract: The present invention relates to compounds useful as inhibitors of ATR protein kinase. The invention also relates to pharmaceutically acceptable compositions comprising the compounds of this invention; methods of treating of various diseases, disorders, and conditions using the compounds of this invention; processes for preparing the compounds of this invention; intermediates for the preparation of the compounds of this invention; and methods of using the compounds in *in vitro* applications, such as the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors. The compounds of this invention have formula (I) or a pharmaceutically acceptable salt, wherein the variables are as devined herein. Moreover, The compounds of this invention have formula (I-A) or a pharmaceutically acceptable salt, wherein the variables are as defined herein.

WO 2014/089379 A1

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

COMPOUNDS USEFUL AS INHIBITORS OF ATR KINASE

BACKGROUND OF THE INVENTION

[0001] ATR ("ATM and Rad3 related") kinase is a protein kinase involved in cellular responses to certain forms of DNA damage (e.g., double strand breaks and replication stress). ATR kinase acts with ATM ("ataxia telangiectasia mutated") kinase and many other proteins to regulate a cell's response to double strand DNA breaks and replication stress, commonly referred to as the DNA Damage Response ("DDR"). The DDR stimulates DNA repair, promotes survival and stalls cell cycle progression by activating cell cycle checkpoints, which provide time for repair. Without the DDR, cells are much more sensitive to DNA damage and readily die from DNA lesions induced by endogenous cellular processes such as DNA replication or exogenous DNA damaging agents commonly used in cancer therapy.

[0002] Healthy cells can rely on a host of different proteins for DNA repair including the DDR kinases ATR and ATM. In some cases these proteins can compensate for one another by activating functionally redundant DNA repair processes. On the contrary, many cancer cells harbour defects in some of their DNA repair processes, such as ATM signaling, and therefore display a greater reliance on their remaining intact DNA repair proteins which include ATR.

[0003] In addition, many cancer cells express activated oncogenes or lack key tumour suppressors, and this can make these cancer cells prone to dysregulated phases of DNA replication which in turn cause DNA damage. ATR has been implicated as a critical component of the DDR in response to disrupted DNA replication. As a result, these cancer cells are more dependent on ATR activity for survival than healthy cells. Accordingly, ATR inhibitors may be useful for cancer treatment, either used alone or in combination with DNA damaging agents, because they shut down a DNA repair mechanism that is more important for cellular survival in many cancer cells than in healthy normal cells.

[0004] In fact, disruption of ATR function (e.g. by gene deletion) has been shown to promote cancer cell death both in the absence and presence of DNA damaging agents. This suggests that ATR inhibitors may be effective both as single agents and as potent sensitizers to radiotherapy or genotoxic chemotherapy.

[0005] ATR peptide can be expressed and isolated using a variety of methods known in the literature (see e.g., Ünsal-Kaçmaz et al, *PNAS* 99: 10, pp6673-6678, May 14, 2002; see also Kumagai et al. Cell 124, pp943-955, March 10, 2006; Unsal-Kacmaz et al. Molecular and Cellular Biology, Feb 2004, p1292-1300; and Hall-Jackson et al. Oncogene 1999, 18, 6707-6713).

[0006] For all of these reasons, there is a need for the development of potent and selective ATR inhibitors for the treatment of cancer, either as single agents or as combination therapies with radiotherapy or genotoxic chemotherapy.

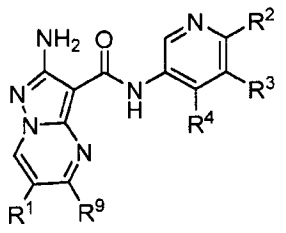
SUMMARY OF THE INVENTION

[0007] The present invention relates to compounds useful as inhibitors of ATR protein kinase. The invention also relates to pharmaceutically acceptable compositions comprising the compounds of this invention; methods of treating of various diseases, disorders, and conditions using the compounds of this invention; processes for preparing the compounds of this invention; intermediates for the preparation of the compounds of this invention; and methods of using the compounds in *in vitro* applications, such as the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

[0008] The compounds of the invention are very potent ATR inhibitors. These compounds also show surprising synergy with other cancer agents, such as cisplatin and gemcitabine, in combination therapies.

DETAILED DESCRIPTION OF THE INVENTION

[0009] One aspect of the invention provides a compound of Formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

R^9 is independently selected from H, $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

k is 0 or 1;

M and L are a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$, each M and L^1 is optionally substituted with 0-3 occurrences of J^{LM};

J^{LM} is independently selected from halo, -CN, or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$;

W is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein W is optionally substituted with 0-5 occurrences of J^W;

J^W is independently selected from -CN, halo, $-CF_3$; a C_{1-4}aliphatic wherein up to two methylene units are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

two occurrences of J^W on the same atom, together with atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

two occurrences of J^W, together with W, form a 6-10 membered saturated or partially unsaturated bridged ring system;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; 3-4 membered heterocyclyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or →O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; →O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from-CN; =O; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$;

J^T is independently selected from halo, -CN; →O; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

[0010] In another embodiment, the present invention is a compound of formula **I**, wherein R^9 is H.

[0011] In one or more aspects, the present invention is a compound of formula **I**, wherein R^9 is M. In another aspect, the present invention is a compound of formula **I**, wherein M is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-. In some aspects, the present invention is a compound of formula **I**, wherein M is C_{1-4}alkyl, -(C_{1-4}alkyl)O(C_{1-3}aliphatic), -(C_{1-3}alkyl)OH, -O(C_{1-4}alkyl)N(C_{1-2}alkyl)$_2$, -NH(C_{1-4}alkyl), or -(C_{1-4}alkyl)NH(C_{1-4}alkyl). In yet another aspect, the present invention is a compound of formula **I**, wherein M is C_{1-4}alkyl.

[0012] In one or more embodiments, the present invention is a compound of formula **I**, wherein J^{LM} is halo.

[0013] In some embodiments, the present invention is a compound of formula **I**, wherein R^9 is -$(L)_k$-W.

[0014] In another example, the present invention is a compound of formula **I**, wherein k is 1. In other examples, the present invention is a compound of formula **I**, wherein k is 0.

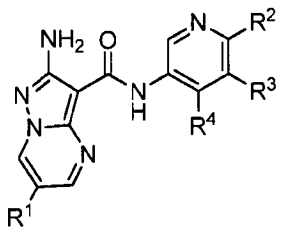
[0015] In one or more aspects, the present invention is a compound of formula **I**, wherein L is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-. In other aspects of the invention, the present invention is a compound of formula **I**, wherein L is -O-, -O(C1-4aliphatic)-, or -NR(C_{1-3}alkyl)-.

[0016] In one or more embodiments, the present invention is a compound of formula **I**, wherein W is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur. In some embodiments, the present invention is a compound of formula **I**, wherein W is a 3-7 membered heterocyclyl. In another embodiment, the present invention is a compound of formula **I**, wherein W is independently selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or azetidinyl.

[0017] In other embodiments, the present invention is a compound of formula **I**, wherein W is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In yet another embodiment, the present invention is a compound of formula **I**, wherein W is octahydropyrrolo[1,2-a]pyrazine.

[0018] In some aspects, the present invention is a compound of formula **I**, wherein J^W is selected form $C_{1\text{-}3}$alkyl or CF_3. In other aspects, the present invention is a compound of formula **I**, wherein two occurrences of J^W on the same atom, together with atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In yet another aspect, the present invention is a compound of formula **I**, wherein the ring formed by the two occurrences of J^W on the same atom is oxetanyl.

[0019] Another aspect of the invention provides a compound of Formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or $C_{1\text{-}2}$alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; $\rightarrow$O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from-CN; =O; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-;

J^T is independently selected from halo, -CN; →O; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

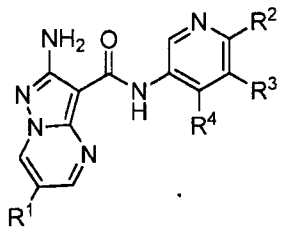
two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

[0020] Another aspect of the invention provides a compound of Formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur;

or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; →O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from -CN; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-;

J^T is independently selected from -CN; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

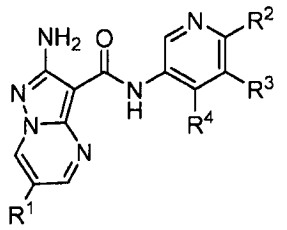
two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

[0021] Another aspect of the invention provides a compound of formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^2 is independently selected from H; chloro; NH_2; or a C_{1-2}alkyl optionally substituted with fluoro;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; or -CN;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -S-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring; having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from halo; =O; →O; a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^X is independently selected from halo or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; or

J^T is independently selected from a C_{1-6}aliphatic or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

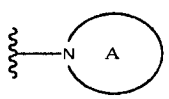
[0022] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^1 is fluoro. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^1 is $-CH_2CN$. In another embodiment R^1 is $-CH(C_{1-2}alkyl)CN$. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^1 is $C(CH_3)_2CN$. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^1 is chloro.

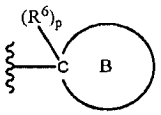
[0023] In one example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^2 is independently selected from $-CF_3$, -$NH(C_{1-2}alkyl)$, chloro, or

H. In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^2 is H. In other examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^2 is -chloro.

[0024] In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is independently selected from H, chloro, fluoro, CHF_2, -CN, cyclopropyl, or C_{1-4}alkyl. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is independently selected from H, chloro, or fluoro. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is H. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is –$O(C_{1-2}alkyl)$. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is chloro. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 is fluoro.

[0025] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^4 is independently selected from:

-O-; 

; 

; or -CH_2-R^7, wherein:

-O- is substituted with one J^Q;

Ring A is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

Ring B is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^6 is H;

R^7 is independently selected from H or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; and

p is 0 or 1.

[0026] In one example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^4 is -O-. In some examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^Q is independently selected from -(C_{1-4}alkyl), -(C_{1-4}alkyl)N(C_{1-4}alkyl)$_2$, -(C_{1-3}alkyl)O(C_{1-2}alkyl)N(C_{1-3}alkyl)$_2$, (C_{1-4}alkyl)OH, -(C_{1-4}alkyl)NH_2, or -(C_{1-4}alkyl)O(C_{1-4}alkyl).

[0027] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^Q is Q^2. In yet another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen.

[0028] In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is independently selected from a 5-6 membered aryl, a 5-6 membered heteroaryl, a 4-6 membered cycloaliphatic, or a 4-7 membered heterocyclyl. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is a 4-7 membered heterocyclyl. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is independently selected from pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, and oxetanyl. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is independently selected from tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, or azetidinyl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is piperidinyl.

[0029] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is a 5-6 membered heteroaryl. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is independently selected from imidazolyl, pyrrolyl,

pyridinyl, pyrazinyl, pyrimidinyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is pyridinyl.

[0030] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is a 4-6 membered cycloaliphatic. In yet another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is independently selected from cyclobutyl or cyclohexyl. In other examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is phenyl.

[0031] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^2 is 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole.

[0032] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or $-S(O)_n-$. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is independently selected from C_{1-4}alkyl, $-N(C_{1-4}alkyl)_2$, -C(O)OH, $-C(O)O(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)_2$, $-(C_{1-4}alkyl)O(C_{1-4}alkyl)$, or -C(O)-. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is C_{1-4}alkyl.

[0033] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is a 3-6 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur. In another

embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is independently independently selected from oxetanyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is oxetanyl. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is cyclopropyl.

[0034] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is Q^3. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Q^3 is a 3-6 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^3 is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur. In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^3 is independently independently selected from oxetanyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl. In other embodiments, when R^4 is -O-, Q^3 is oxetanyl. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, Q^3 is cyclopropyl.

[0035] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^R is =O or halo.

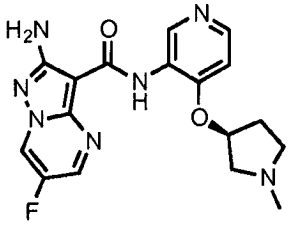
[0036] In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, two occurrences of J^R on the same atom, taken together with the atom to which they are joined, form a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, the ring formed by the two occurrences of J^R on the same atom, taken together with the atom to which they are joined, is selected from oxetanyl, cyclobutyl, or azetidinyl.

[0037] In other examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is -O-, J^T is a 4-6 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In some examples, the present

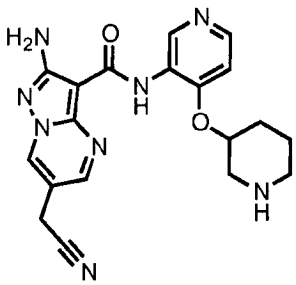
invention is a compound represented by structural formula I or **I-A**, wherein when R^4 is -O-, J^T is piperazinyl.

[0038] In another example, the compounds of formula I and **I-A** of this invention are represented in Table 1. It will be appreciated by those skilled in the art that the compounds of the present invention may be represented in varying tautomeric forms.

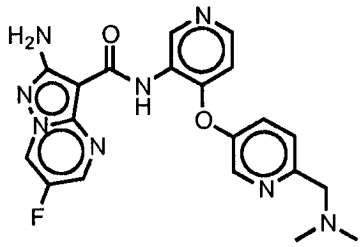
Table 1



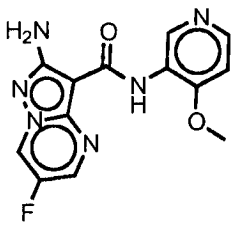
I-O-1



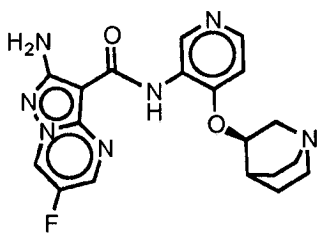
I-O-2



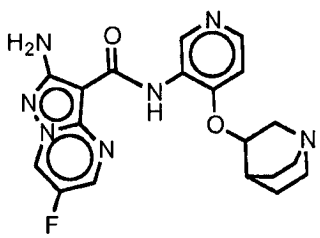
I-O-3



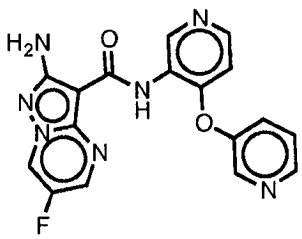
I-O-4



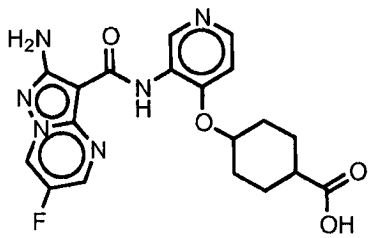
I-O-5



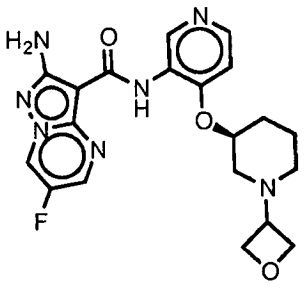
I-O-6



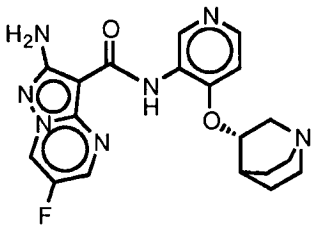
I-O-7



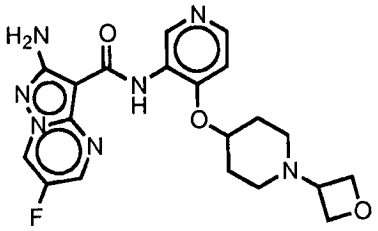
I-O-8



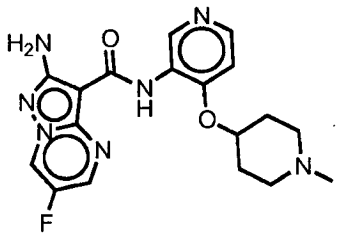
I-O-9



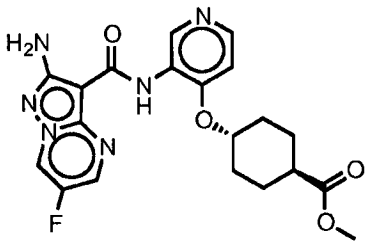
I-O-10



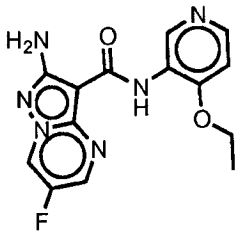
I-O-11



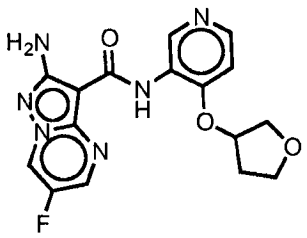
I-O-12



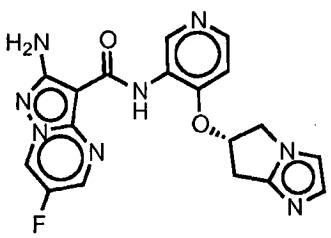
I-O-13



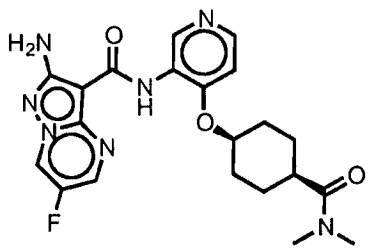
I-O-14



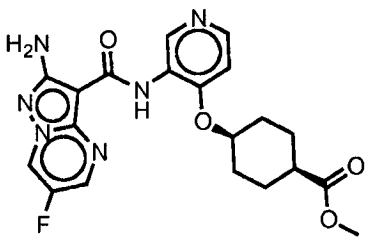
I-O-15



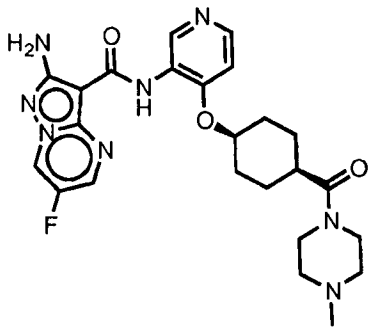
I-O-16



I-O-17



I-O-18



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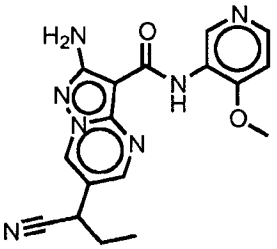

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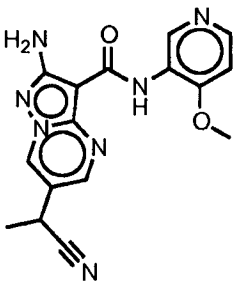

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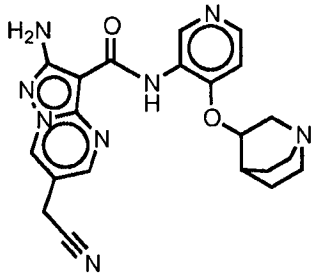

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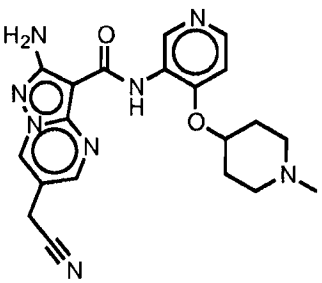

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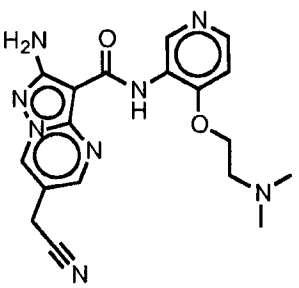

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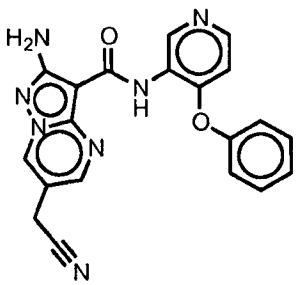

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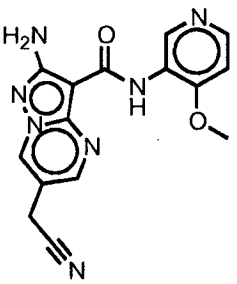

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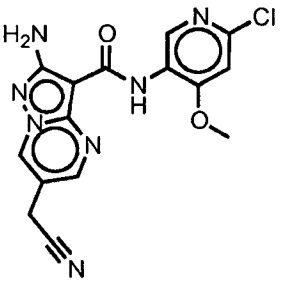

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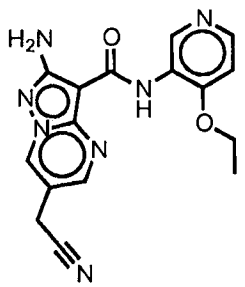

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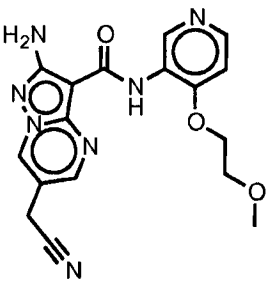

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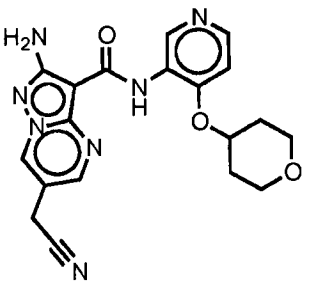

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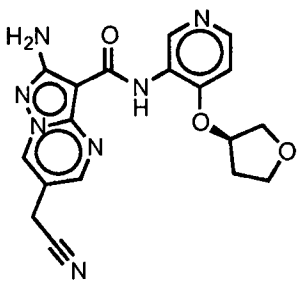

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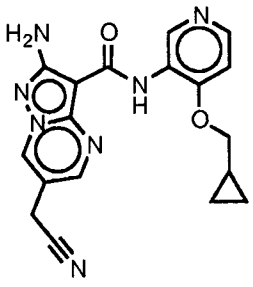

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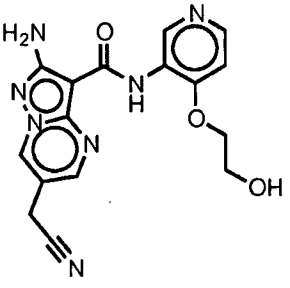

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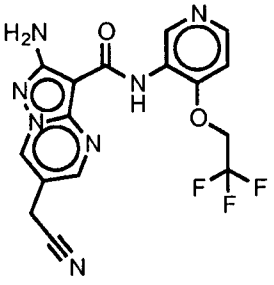

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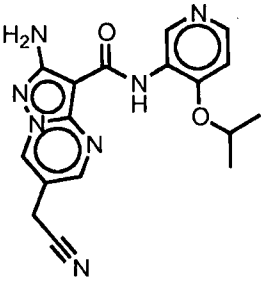

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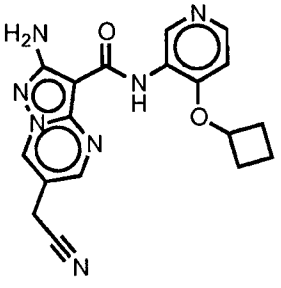

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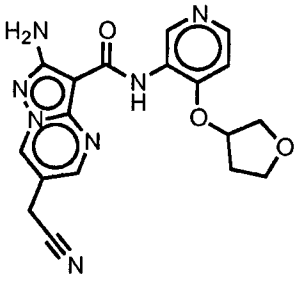

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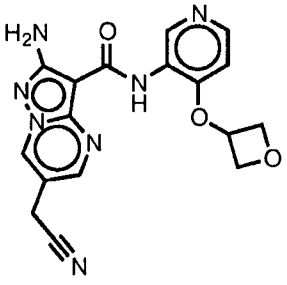

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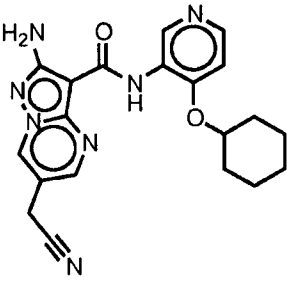

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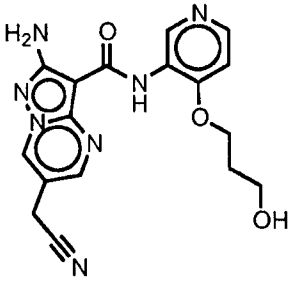

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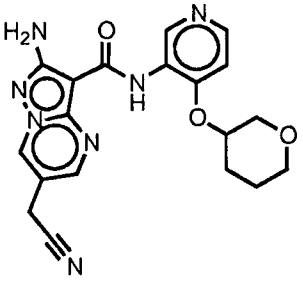

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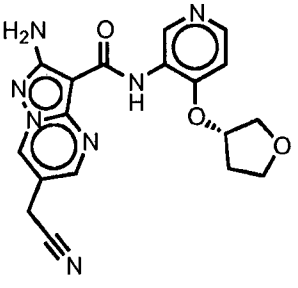

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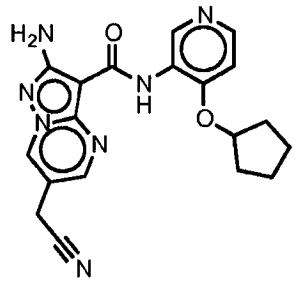

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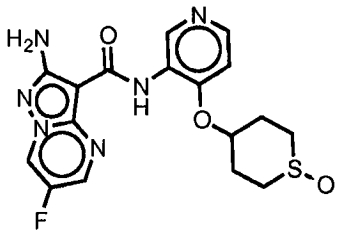

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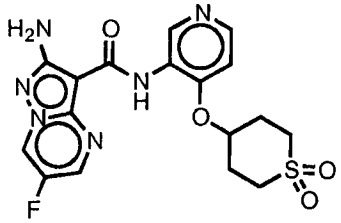

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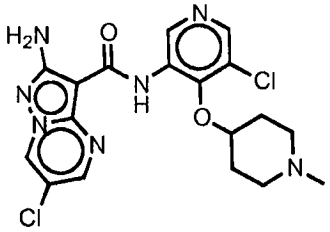

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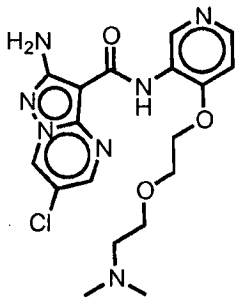

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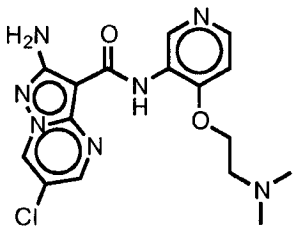

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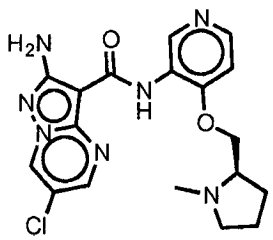

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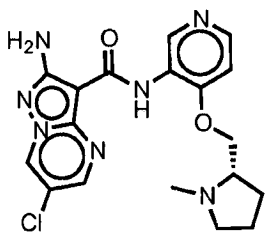

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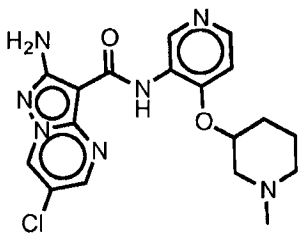

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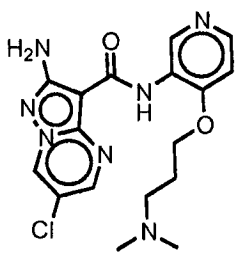

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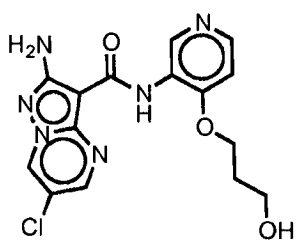

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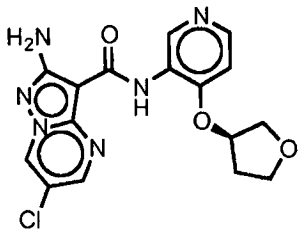

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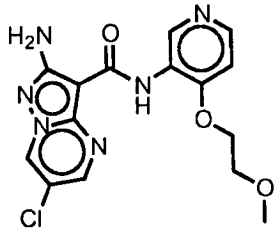

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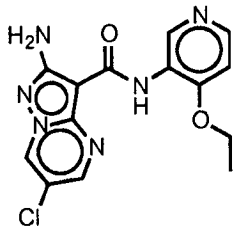
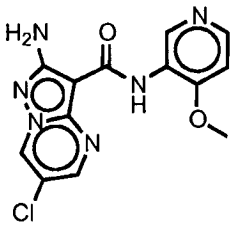


I-O-56



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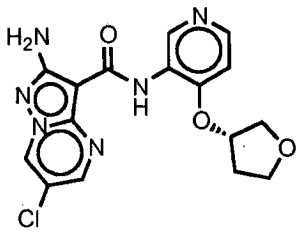

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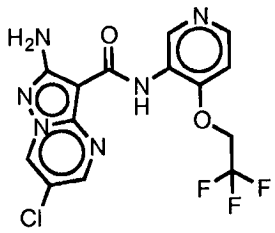

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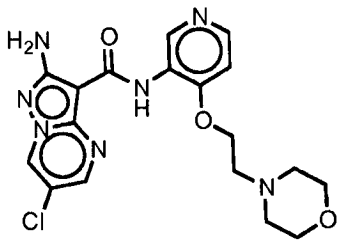

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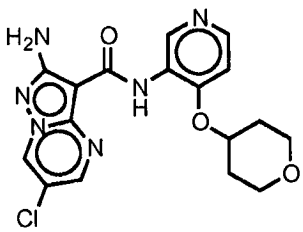

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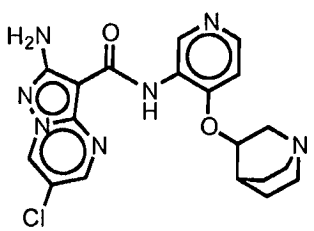
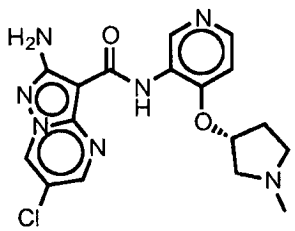


I-O-62



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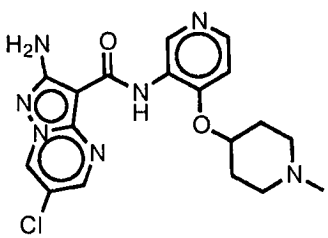
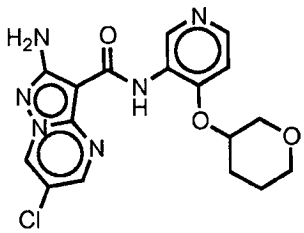
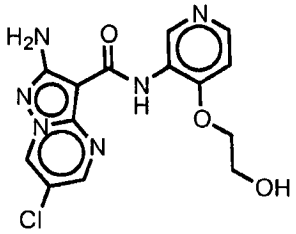


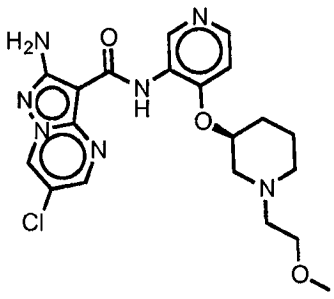
I-O-64



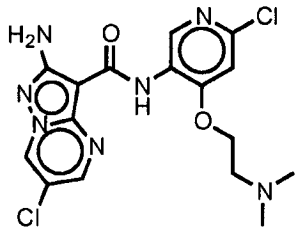
I-O-65



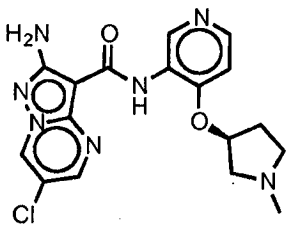
I-O-66



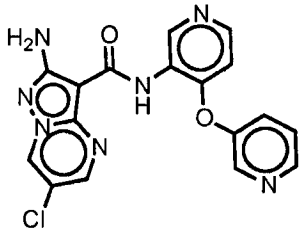
I-O-67



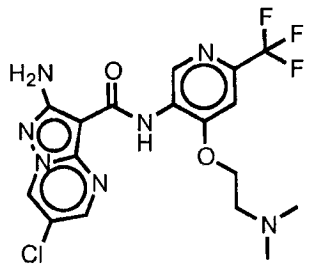
I-O-68



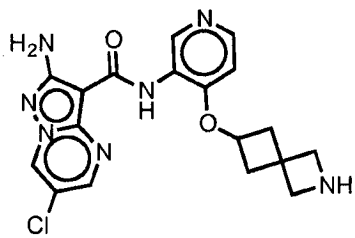
I-O-69



I-O-70



I-O-71



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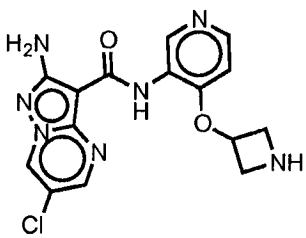

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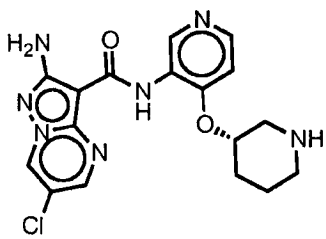
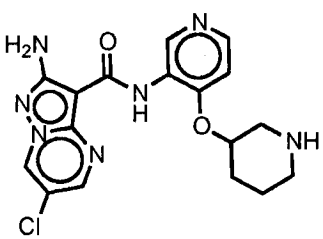
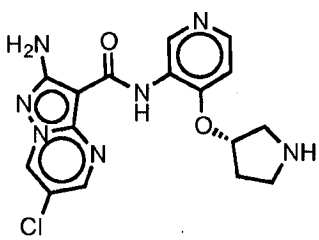


I-O74



I-O-75



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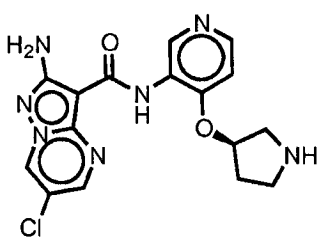

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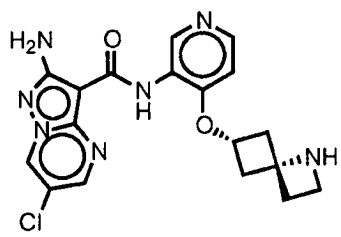

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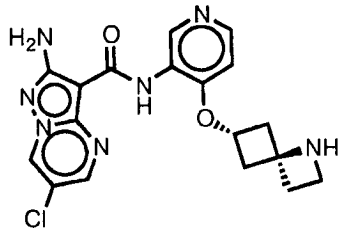

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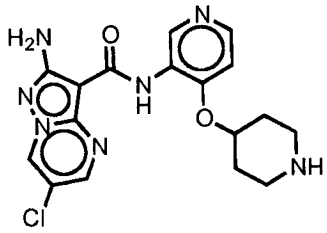
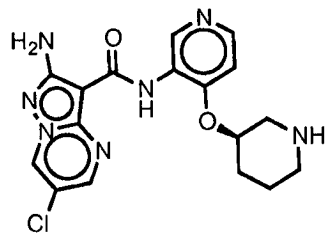


I-O-80



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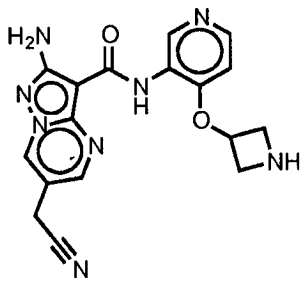

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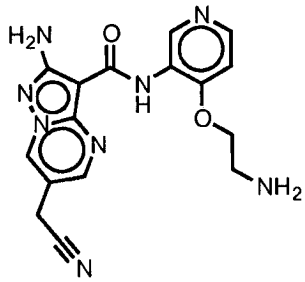
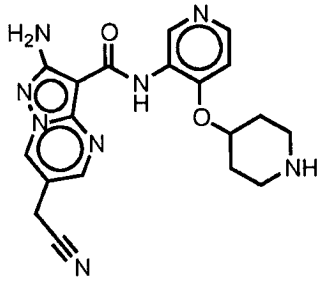


I-O-83



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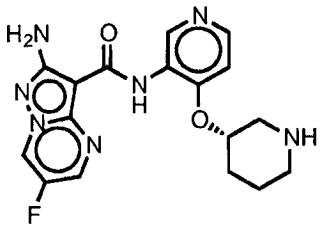
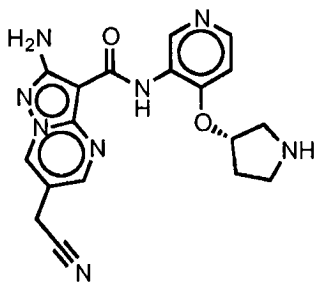
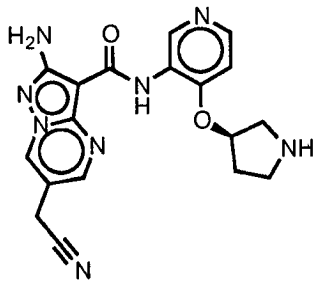


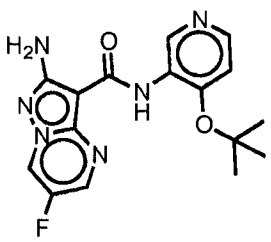
I-O-85



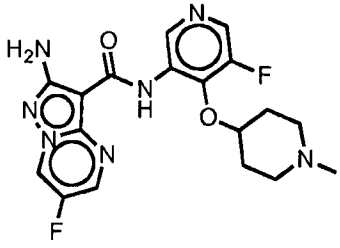
I-O-86



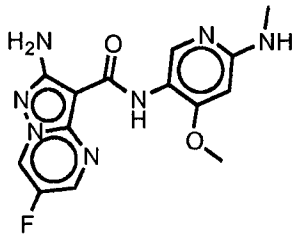
I-O-87



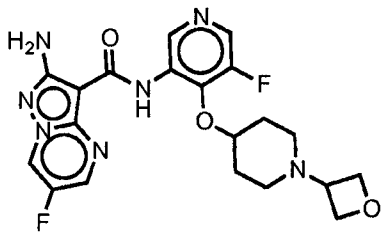
I-O-88



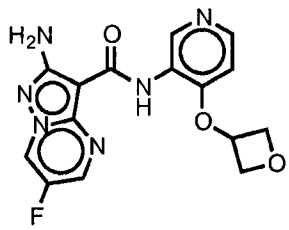
I-O-89



I-O-90

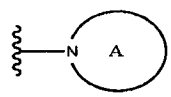


I-O-91



I-O-92.

[0039] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^4 is Ring A, which is represented by the structure:



[0040] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is a is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is a 4-6 membered heterocyclyl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is a 3-7 membered heterocyclyl. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is independently selected from pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, and azetidinyl. In yet another embodiment, the present invention is a compound represented by structural formula **I**

or **I-A**, wherein Ring A is independently selected from piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, and morpholinyl. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is independently selected from piperazinyl or piperidinyl.

[0041] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is a 5 membered heteroaryl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is independently selected from pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is independently selected from pyrazolyl or imidazolyl.

[0042] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring A is independently selected from octahydropyrrolo[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, octahydro-1H-pyrazino[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl, 2,5-diazabicyclo[4.1.0], or octahydropyrazino[2,1-c][1,4]oxazinyl.

[0043] In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is C_{1-8}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -C(O)-. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -C(O)-. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is independently selected from -O-, -C(O)-, $-S(O)_2-$, C_{1-4}alkyl, $-(C_{0-4}alkyl)NH_2$, $-(C_{0-4}alkyl)NH(C_{1-4}alkyl)$, $-(C_{0-4}alkyl)N(C_{1-4}alkyl)_2$, $-(C_{0-4}alkyl)OH$, $-(C_{0-4}alkyl)O(C_{1-4}alkyl)$, -C(O)OH, $-S(O)_2N(C_{1-3}alkyl)-$, $-C(O)(C_{1-4}alkyl)-$, $-(O)C(C_{1-4}alkyl)N(C_{1-2}alkyl)_2$ or $-C(O)O(C_{1-4}alkyl)$. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is independently selected from -C(O)-, C_{1-4}alkyl, $-(C_{0-4}alkyl)NH_2$, $-(C_{0-4}alkyl)NH(C_{1-4}alkyl)$, $-(C_{0-4}alkyl)N(C_{1-4}alkyl)_2$, $-(C_{0-4}alkyl)OH$, $-(C_{0-4}alkyl)O(C_{1-4}alkyl)$, -C(O)OH, -

$C(O)O(C_{1-4}alkyl)$. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is $C_{1-4}alkyl$. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is $C_{1-4}alkyl$, -O-, or -C(O)-.

[0044] In one or more examples, when R^4 is Ring A, J^Q is Q^2.

[0045] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is a 3-7 membered heterocyclyl or carbocyclyl; the heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur. In other examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is independently selected from selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidinyl, pyrrolidinyl, piperazinyl, cyclobutyl, thiomorpholinyl, or morpholinyl. In yet other examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is independently selected from oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl. In some examples, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is oxetanyl.

[0046] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, Q^2 is independently selected from 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl or 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl.

[0047] In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein two occurrences of J^Q, together with Ring A, form a bridged ring system.

[0048] In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^Q is =O.

[0049] In another embodiment, the present invention is a compound represented by

structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^R is independently selected from oxetanyl, piperadinyl, azetidinyl, piperazinyl, pyrrolidinyl, or morpholinyl. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^R is a piperazinyl.

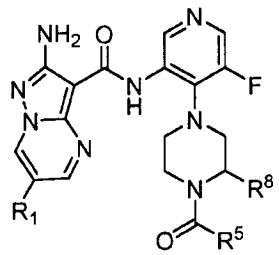
[0050] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^R is independently selected from halo, =O, -OH, C_{1-4}alkyl, -(C_{0-4}alkyl)N(C_{1-4}alkyl)$_2$, or -(C_{0-4}alkyl)O(C_{1-4}alkyl).

[0051] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring A, J^R is independently selected from oxetanyl or azetidinyl.

[0052] In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein two occurrences of J^R, together with Ring A, form a bridged ring system.

[0053] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein J^T is a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein J^T is oxytanyl. In another embodiment, J^T is a C_{1-6}aliphatic. In another embodiment, J^T is methyl.

[0054] Another aspect of the present invention provides a compound of formula **I-A-1**:



I-A-1 ;

wherein:

R^5 is selected from C_{1-4}aliphatic, a 3-6 membered cycloalkyl, or a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur;

R^8 is selected from H or C_{1-3} alkyl; or

R^5 and R^8, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

[0055] In another embodiment, the present invention is a compound represented by structural formula **I-A-1**, wherein R^1 in formula **I-A-1** is fluoro.

[0056] In another example, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is C_{1-4}aliphatic. In yet other embodiments, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is independently selected from methyl or ethyl.

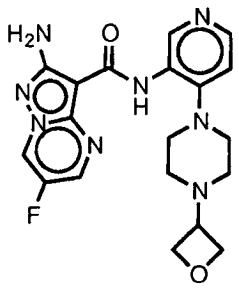
[0057] In some embodiments, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is a 3-6 membered cycloalkyl. In other embodiments, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is cyclopropyl.

[0058] In yet another embodiment, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur. In some embodiments, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 is tetrahydrofuranyl or oxetanyl.

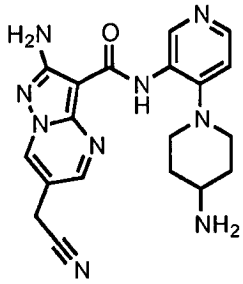
[0059] In other embodiments, the present invention is a compound represented by structural formula **I-A-1**, wherein R^5 and R^8, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected form oxygen, nitrogen or sulfur. In another embodiment, the present invention is a compound represented by structural formula **I-A-1**, wherein the ring formed by R^5 and R^8 is a five-membered ring. In yet another embodiment, the present invention is a compound represented by structural formula **I-A-1**, wherein the ring formed by R^5 and R^8 is a six-membered ring.

[0060] In another example, the compounds of formula **I**, **I-A**, and **I-A-1**of this invention are represented in Table 2.

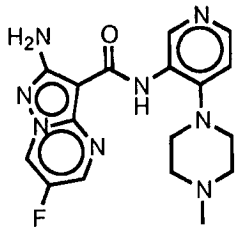
Table 2



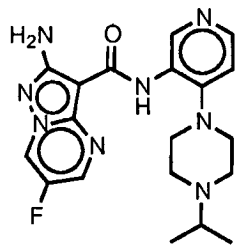
I-N-1



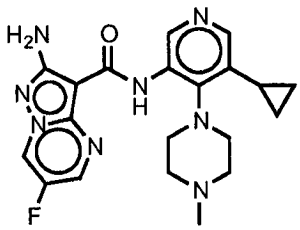
I-N-2



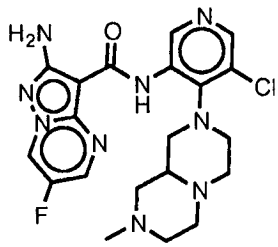
I-N-3



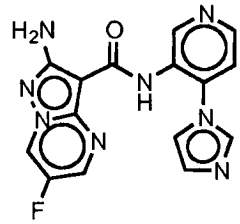
I-N-4



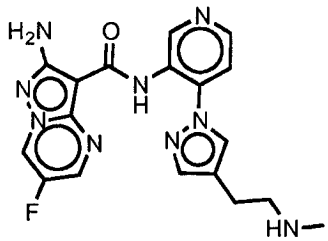
I-N-5



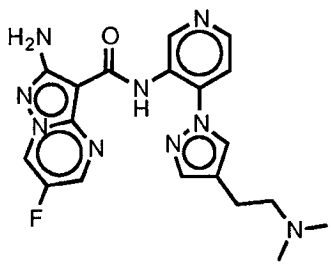
I-N-6



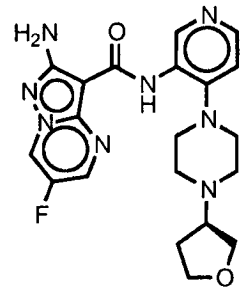
I-N-7



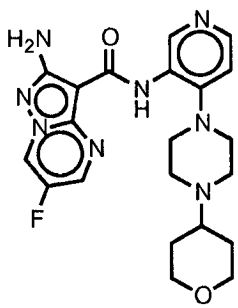
I-N-8



I-N-9



I-N-10



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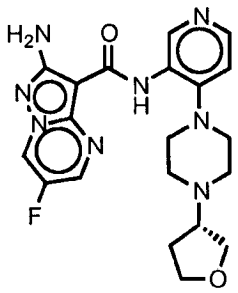
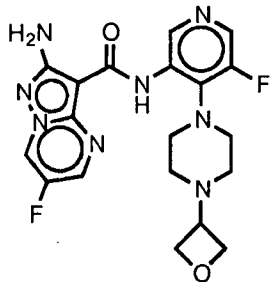


I-N-12



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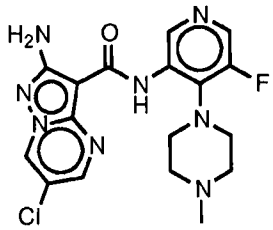

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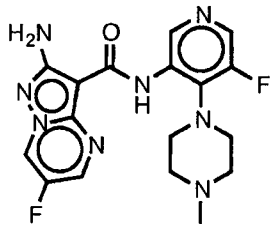

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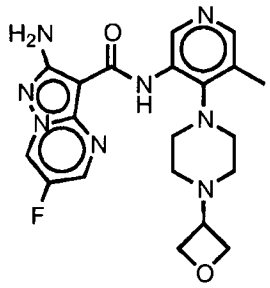

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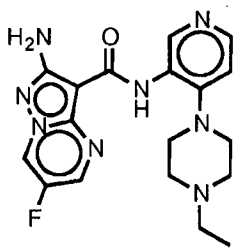

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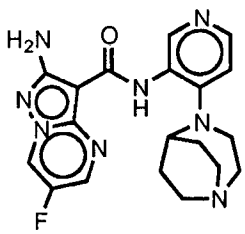

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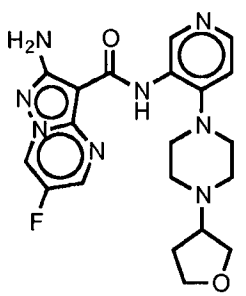

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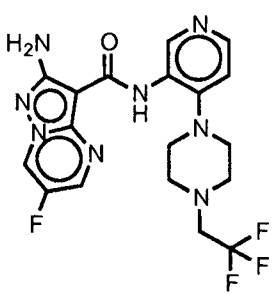

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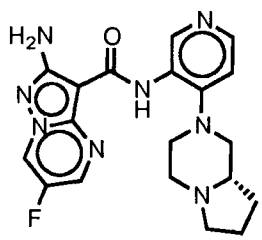

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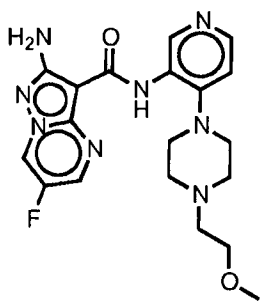

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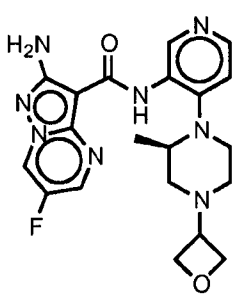

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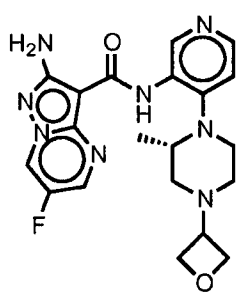

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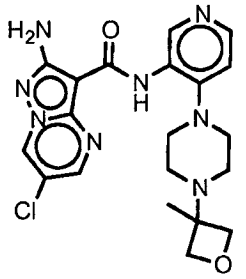

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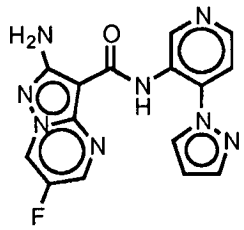

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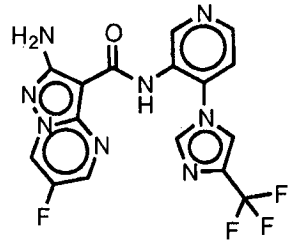

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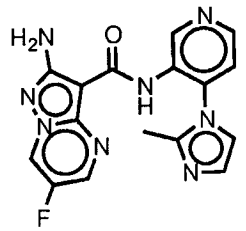

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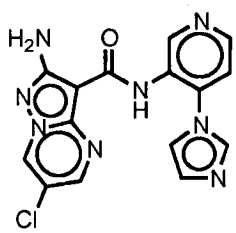

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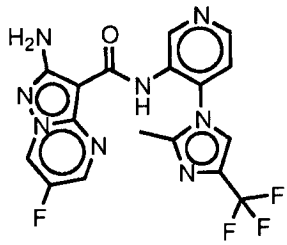

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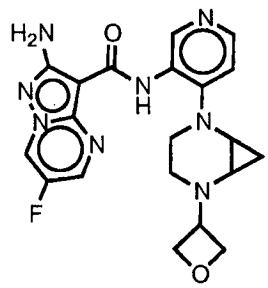

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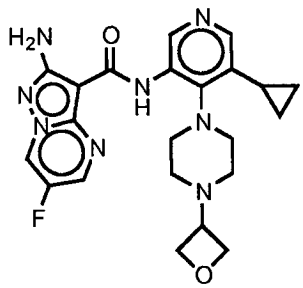

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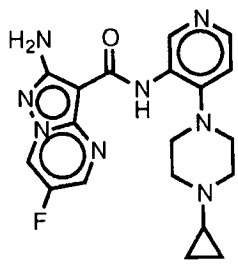

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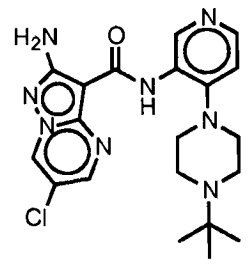

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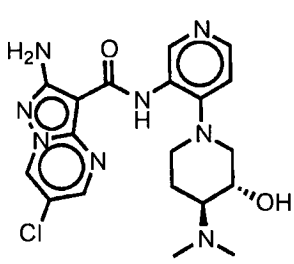

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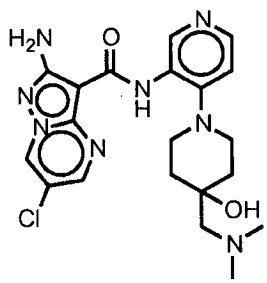

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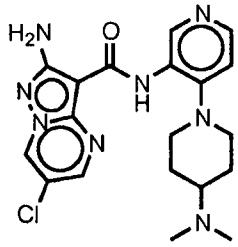

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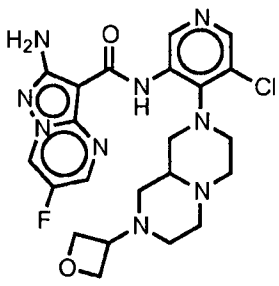

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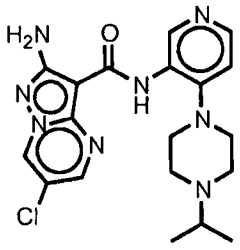

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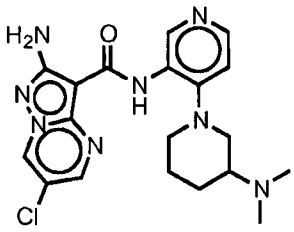

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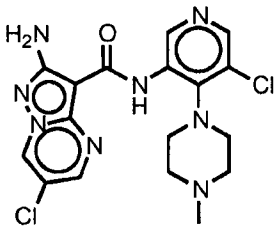
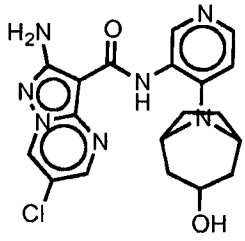
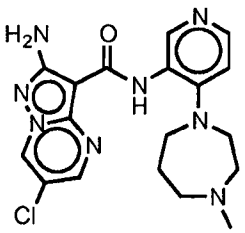


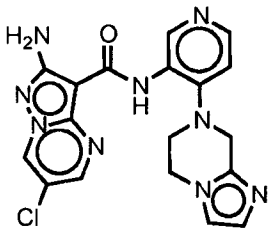
I-N-41



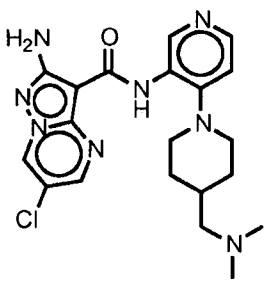
I-N-42



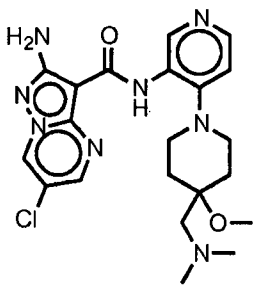
I-N-43



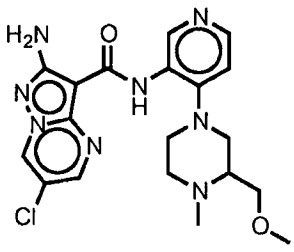
I-N-44



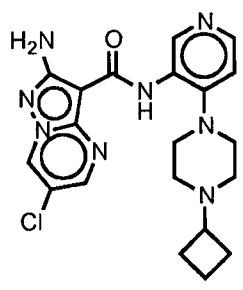
I-N-45



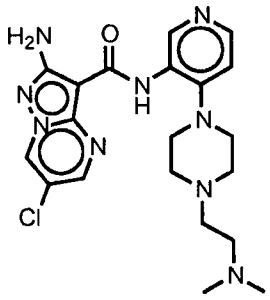
I-N-46



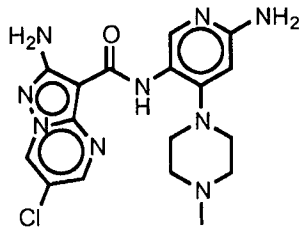
I-N-47



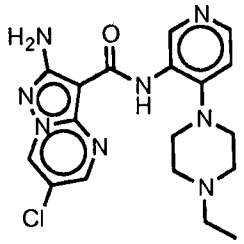
I-N-48



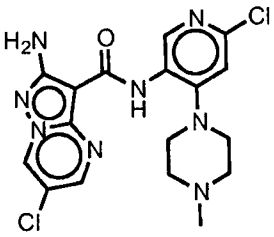
I-N-49



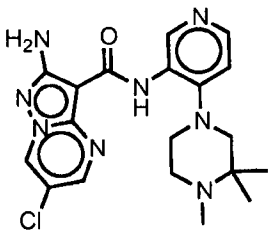
I-N-50



I-N-51



I-N-52



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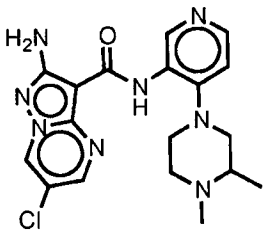
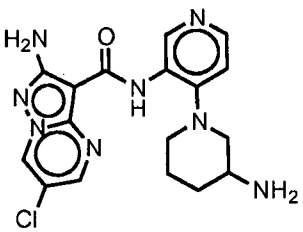
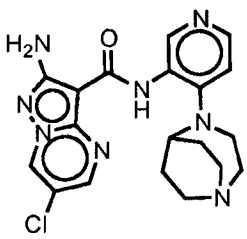


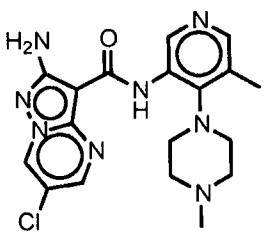
I-N-54



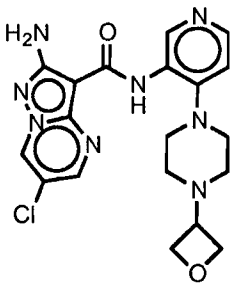
I-N-55



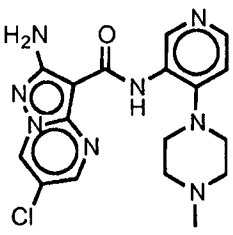
I-N-56



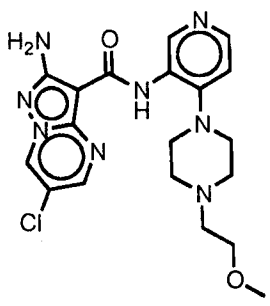
I-N-57



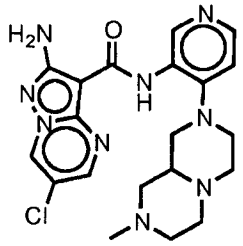
I-N-58



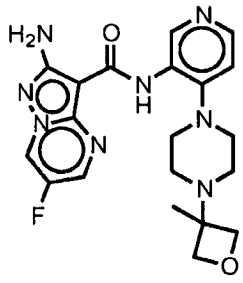
I-N-59



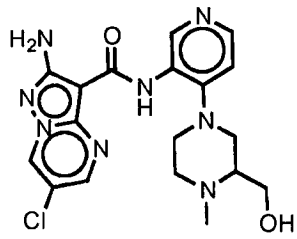
I-N-60



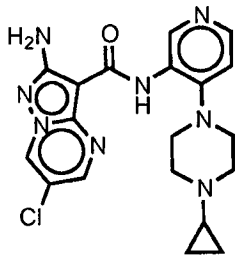
I-N-61



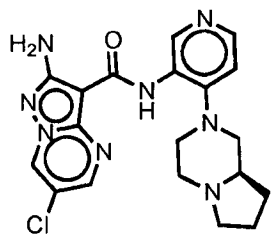
I-N-62



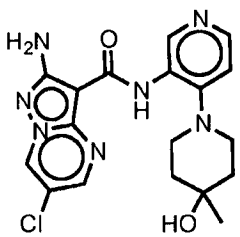
I-N-63



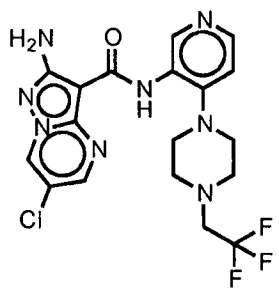
I-N-64



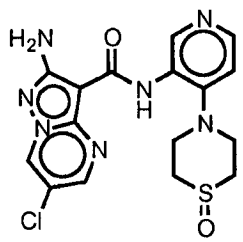
I-N-65



I-N-66



I-N-67



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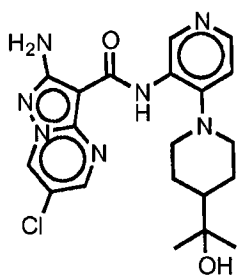

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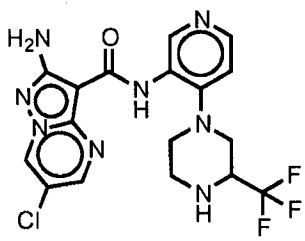
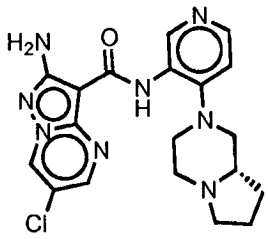
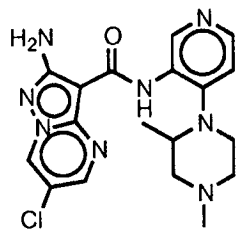


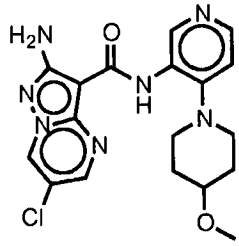
I-N-70



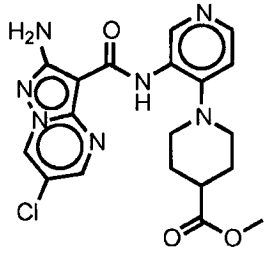
I-N-71



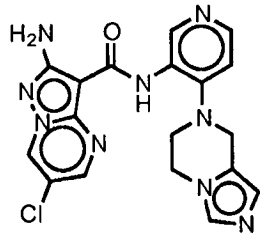
I-N-72



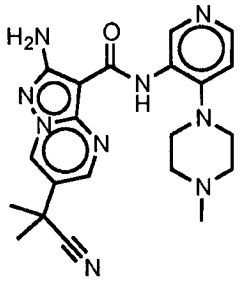
I-N-73



I-N-74



I-N-75



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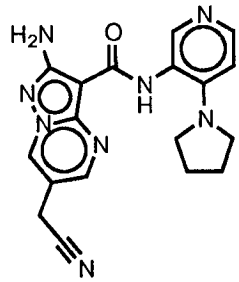
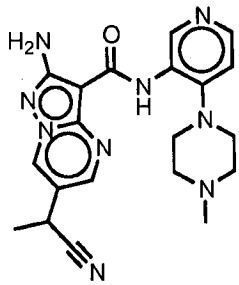


I-N-77



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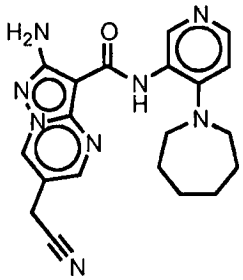

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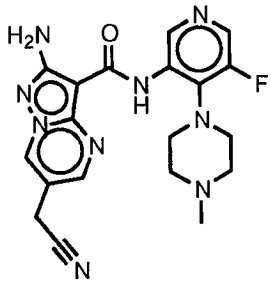

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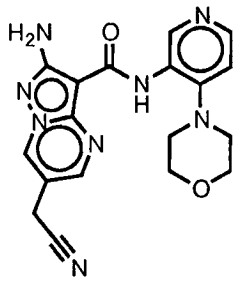

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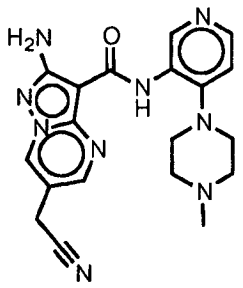
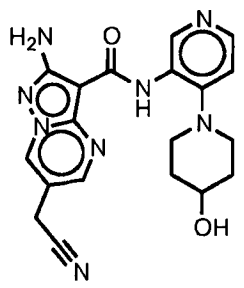


I-N-82



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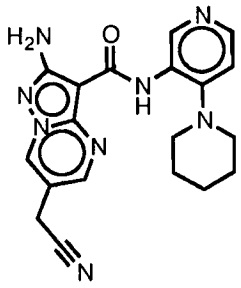

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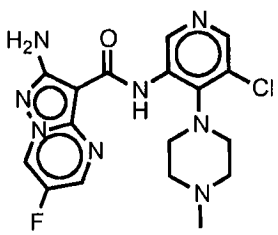

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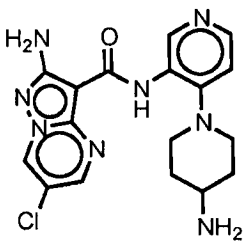

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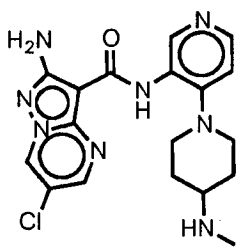

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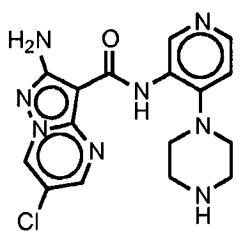

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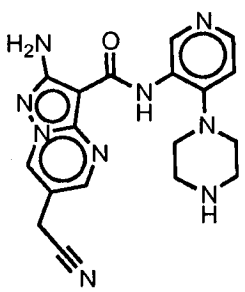

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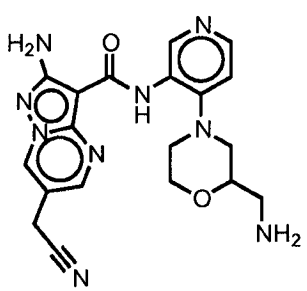

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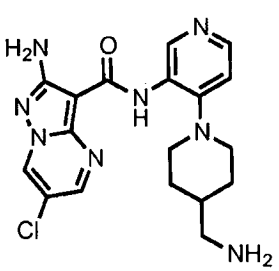

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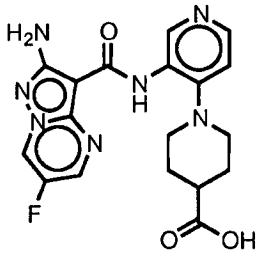

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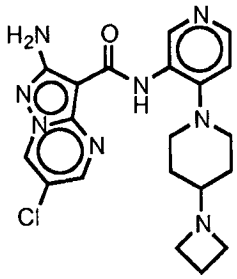

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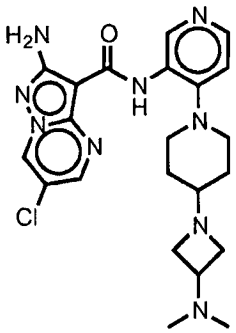

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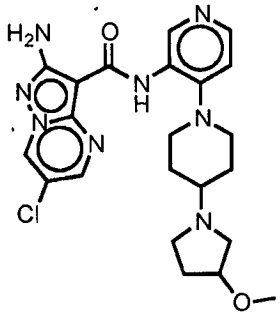

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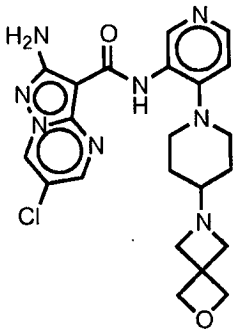
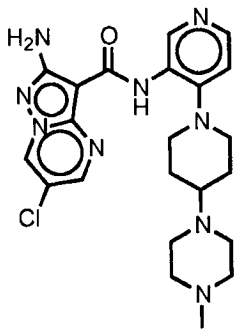
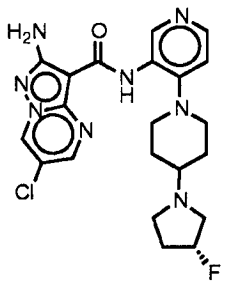


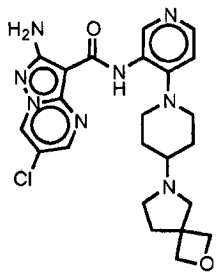
I-N-96



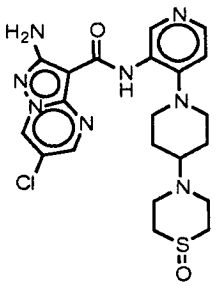
I-N-97



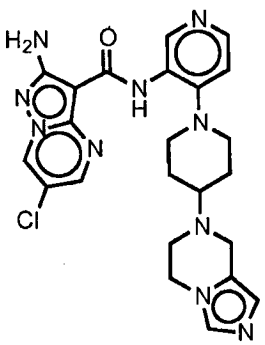
I-N-98

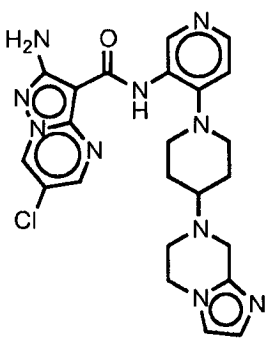


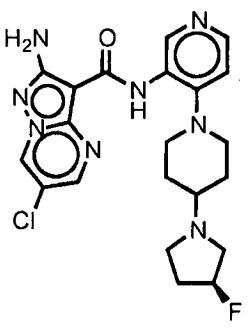
I-N-99



I-N-100







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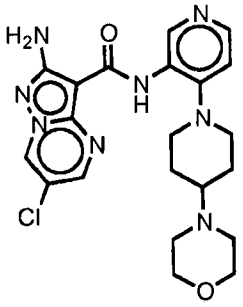
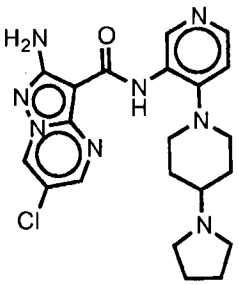
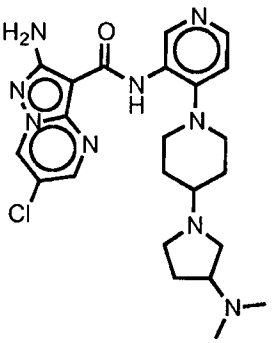


I-N-102



I-N-103



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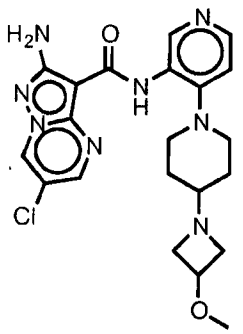

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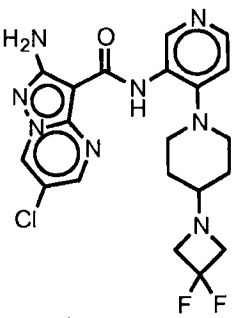
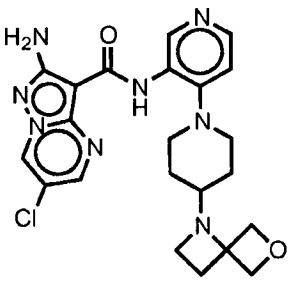
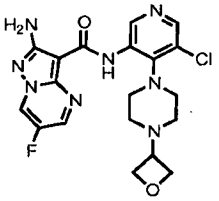


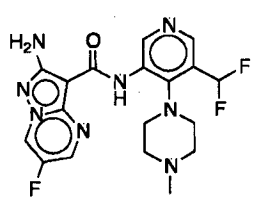
I-N-106



I-N-107



I-N-108



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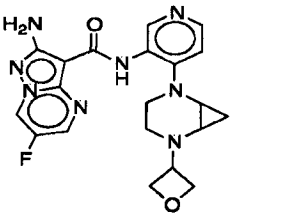

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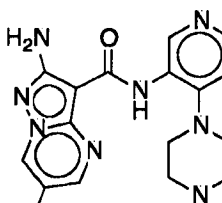
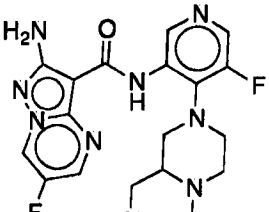
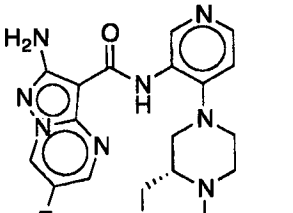


I-N-111

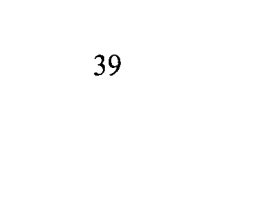


I-N-112

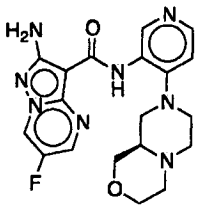


I-N-113

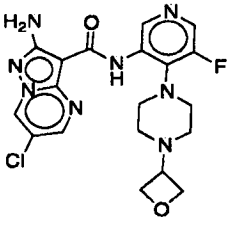
I-N-114



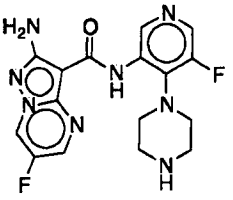
I-N-115



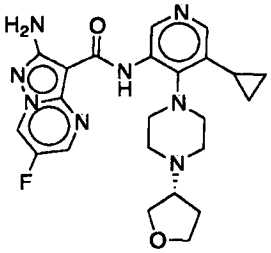
I-N-116



I-N-117



I-N-118



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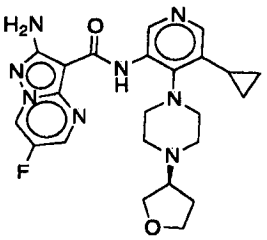
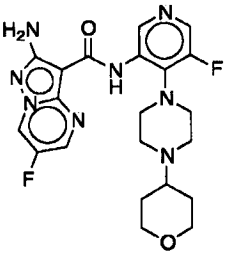


I-N-120



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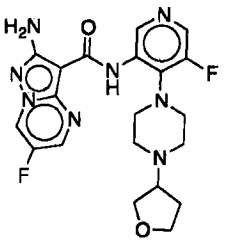

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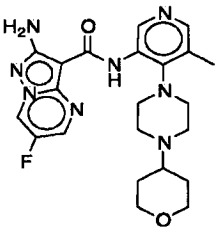

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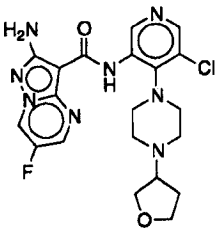

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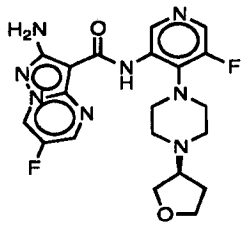

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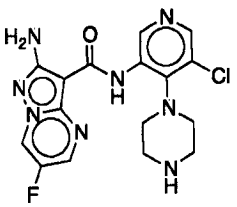

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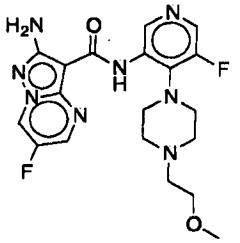

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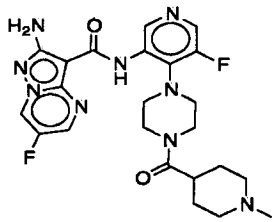

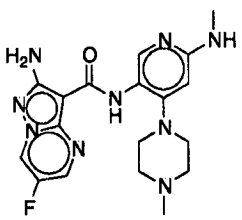

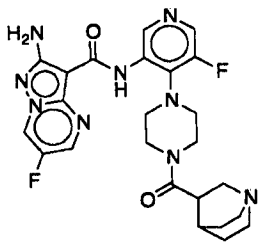

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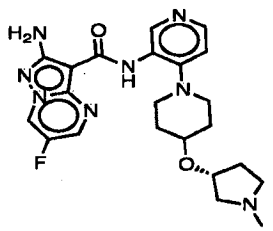

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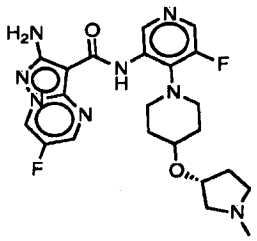

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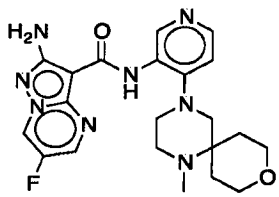

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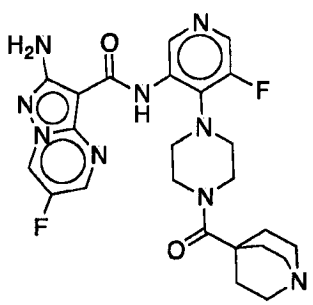

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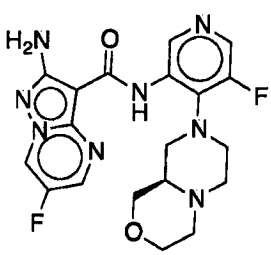

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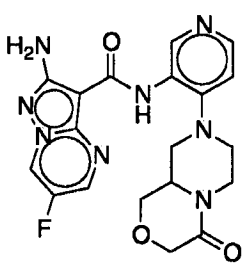

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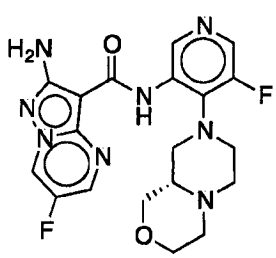

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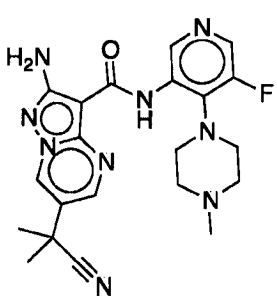

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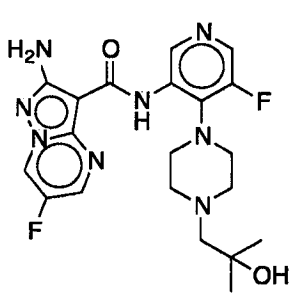

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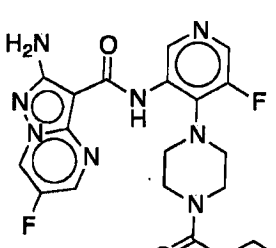

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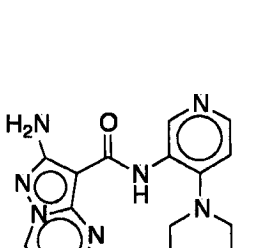

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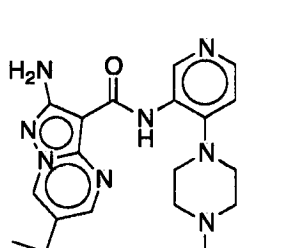
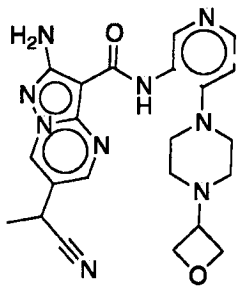


I-N-140

I-N-141

I-N-142



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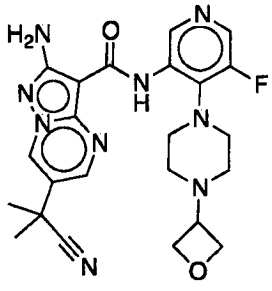

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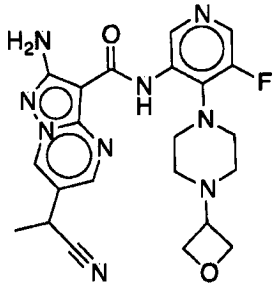

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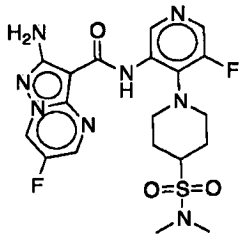

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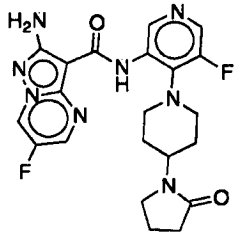

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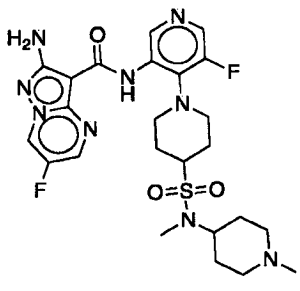

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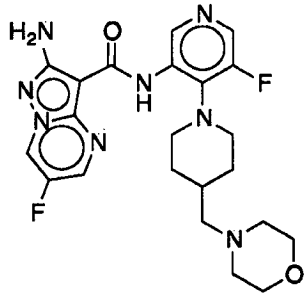

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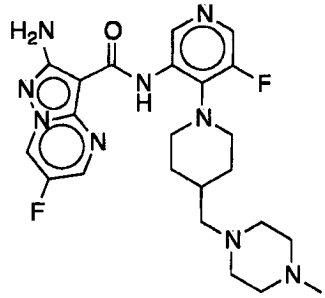

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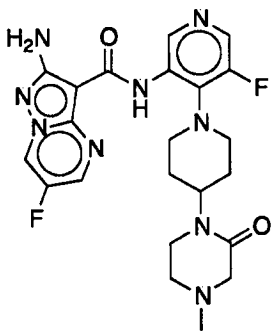

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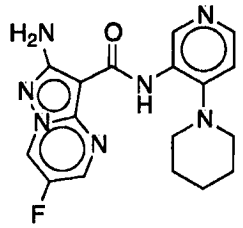

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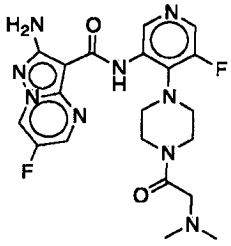

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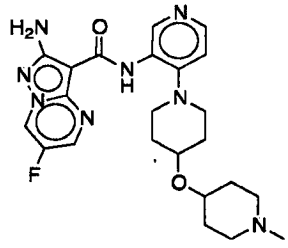

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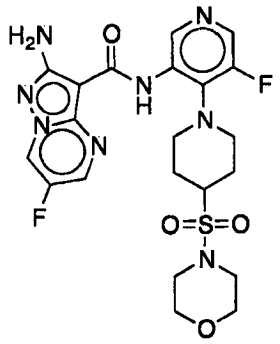

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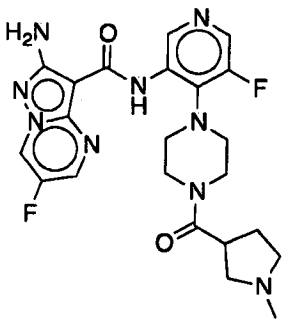

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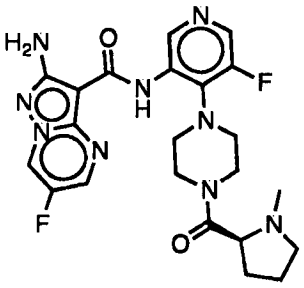

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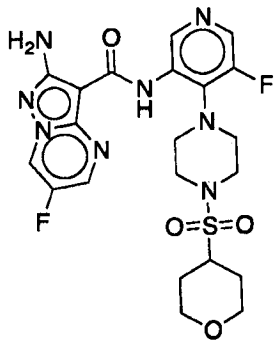

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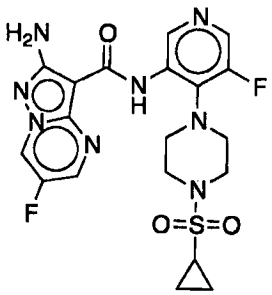

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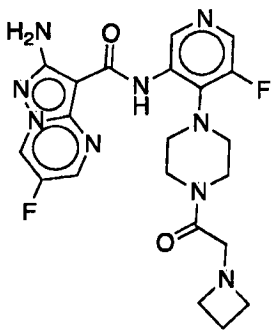

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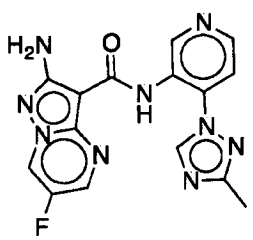

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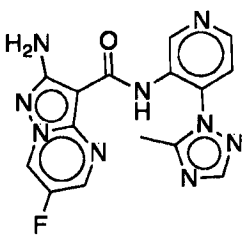

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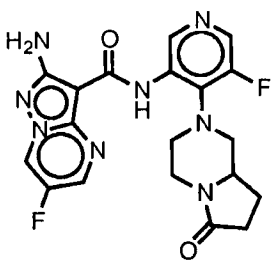

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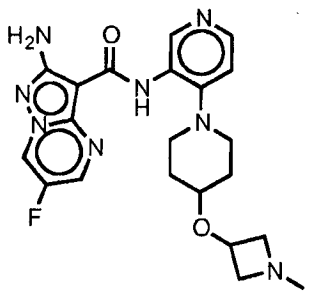

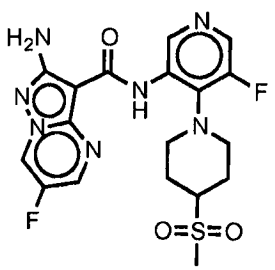

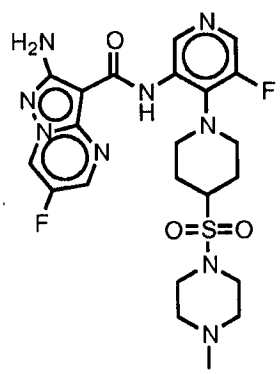

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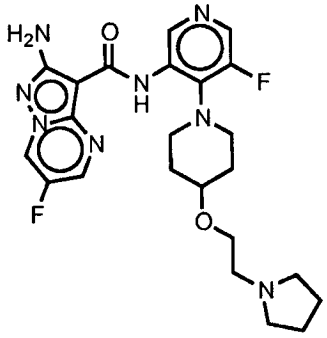

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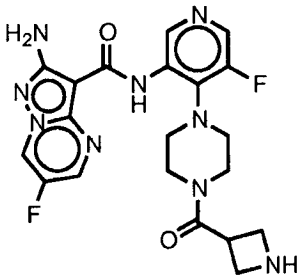

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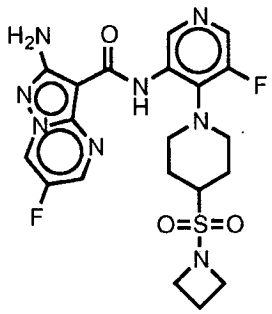

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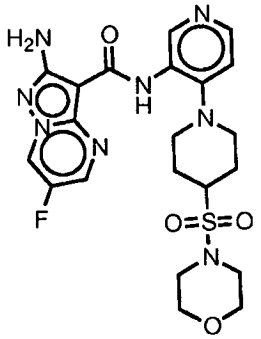
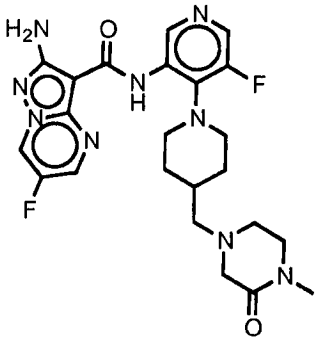
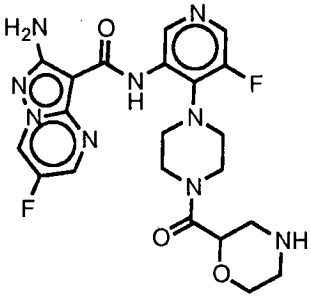


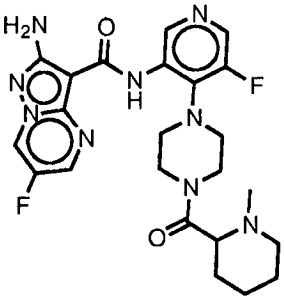
I-N-168



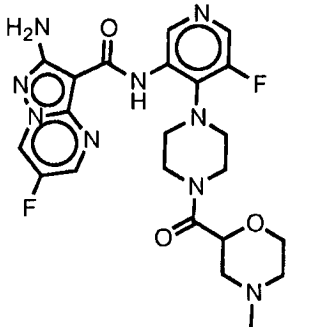
I-N-169



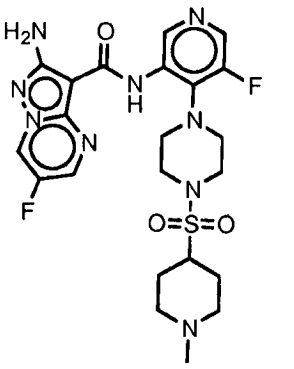
I-N-170



I-N-171



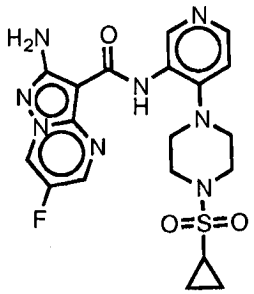
I-N-172



I-N-173

I-N-174

I-N-175



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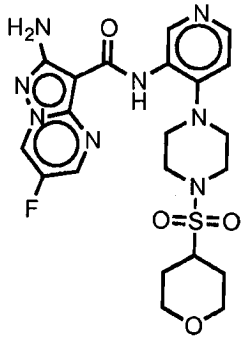

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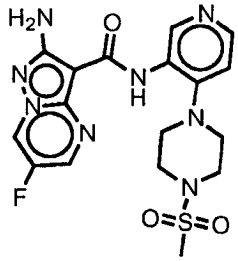

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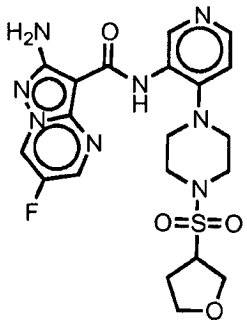

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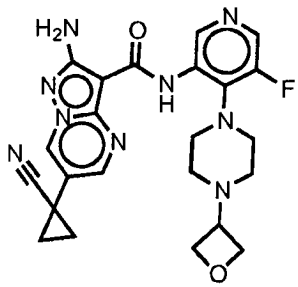

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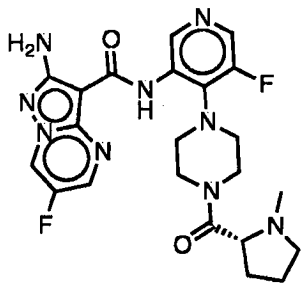
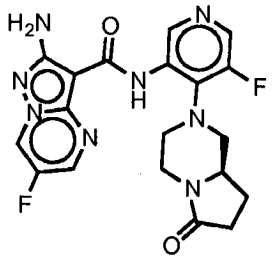
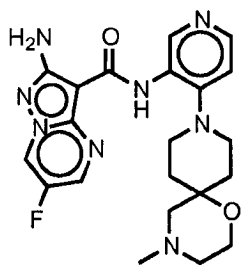


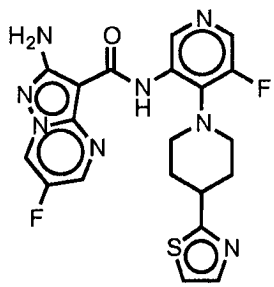
I-N-181



I-N-182



I-N-183



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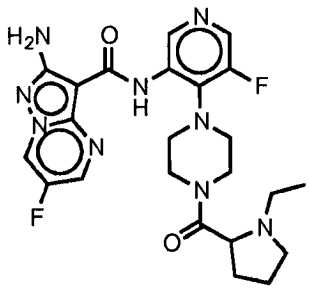

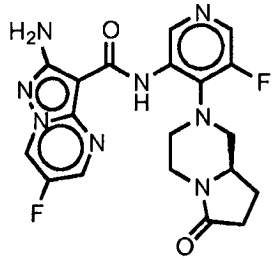

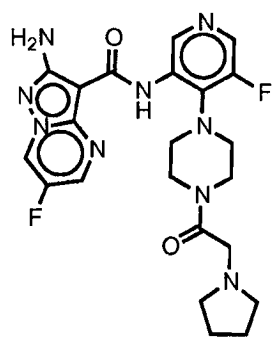

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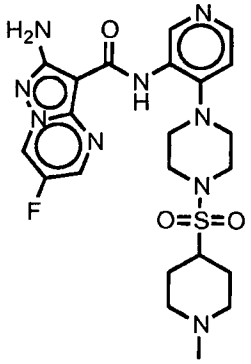
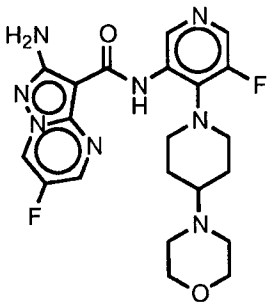


I-N-186



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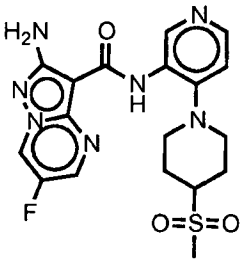

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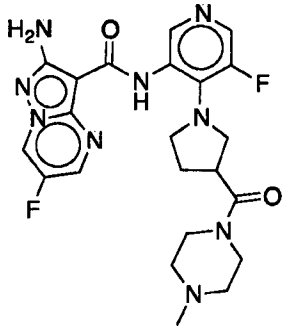

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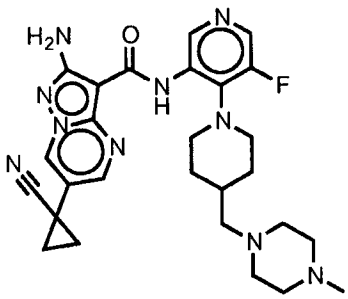

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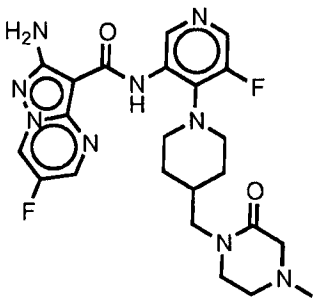

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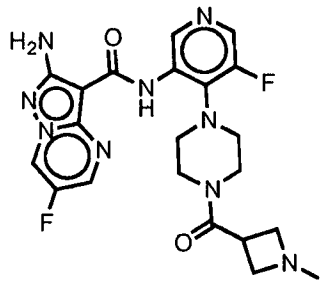

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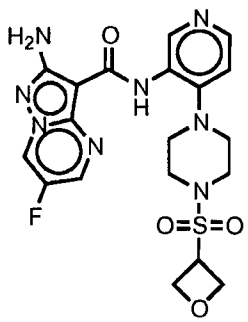

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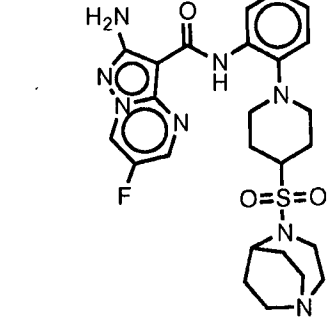
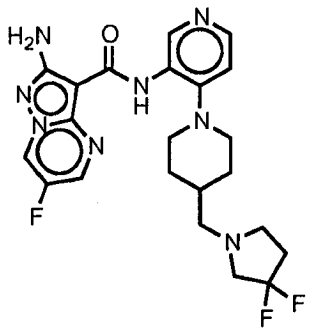


I-N-194

I-N-195

I-N-196



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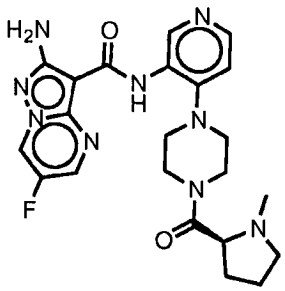

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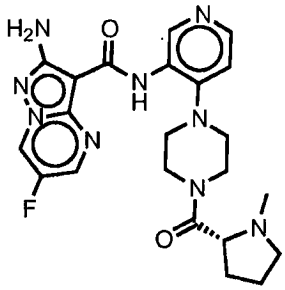

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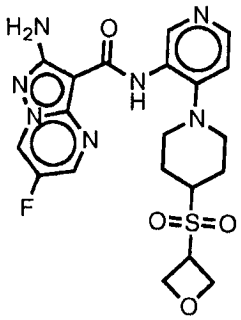

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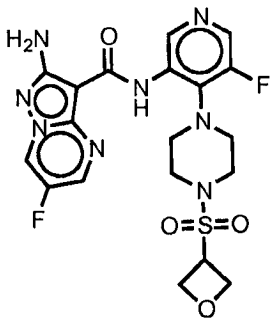

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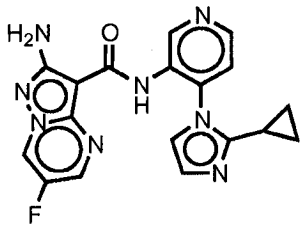
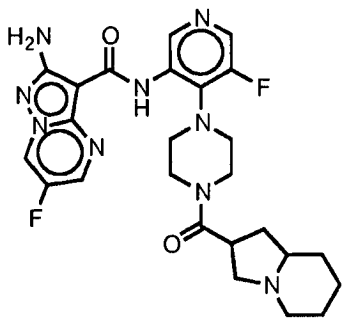
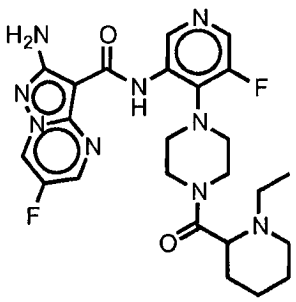


I-N-202



I-N-203



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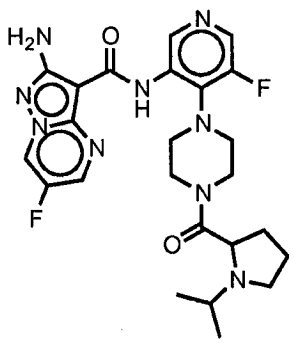

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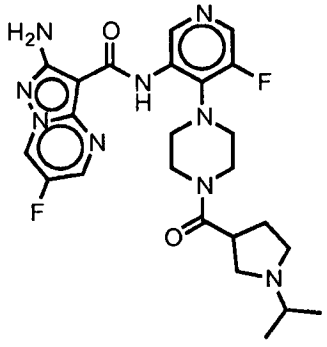

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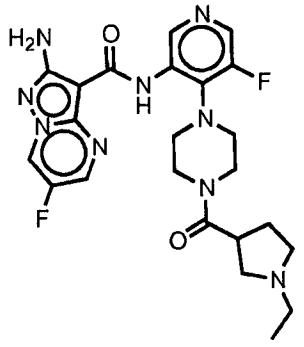

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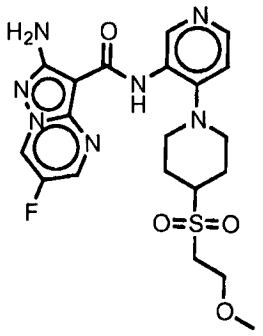
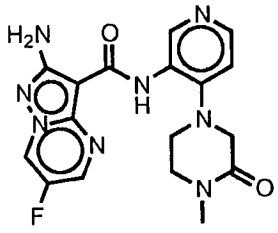
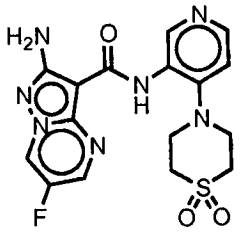


I-N-208



I-N-209



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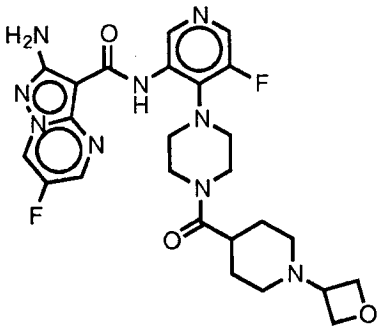

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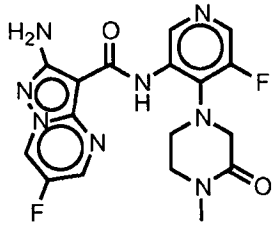
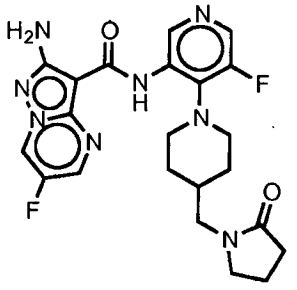


I-N-212



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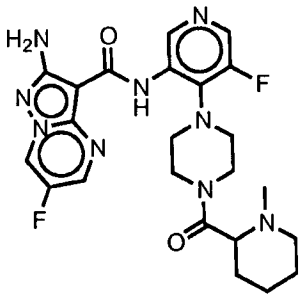
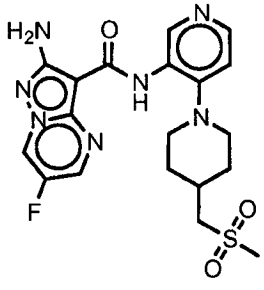
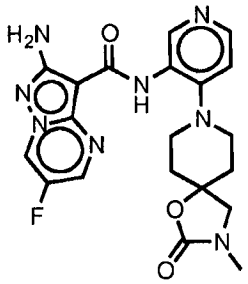


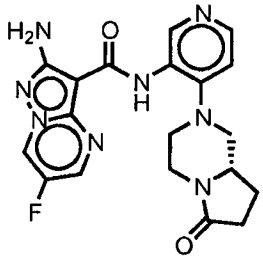
I-N-214



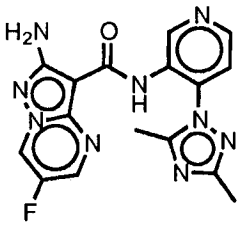
I-N-215



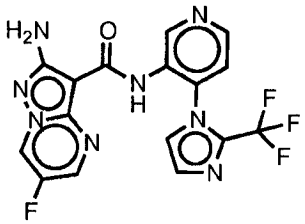
I-N-216



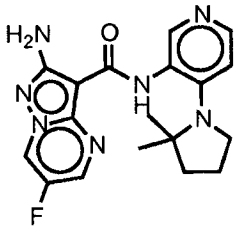
I-N-217



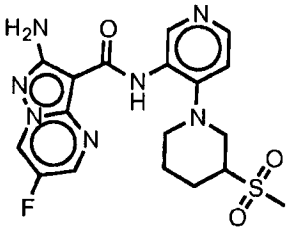
I-N-218



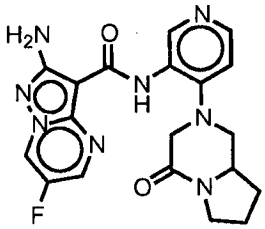
I-N-219



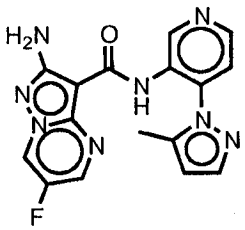
I-N-220



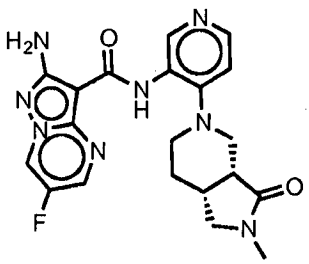
I-N-221



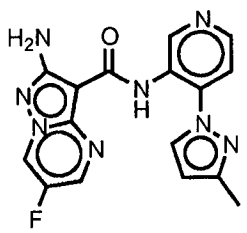
I-N-222



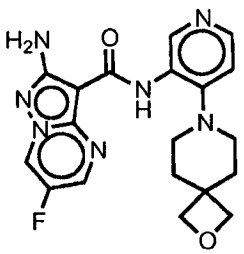
I-N-223



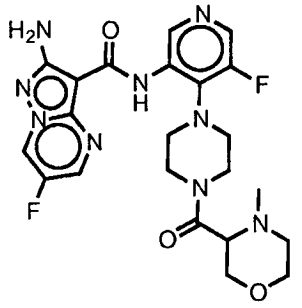
I-N-224



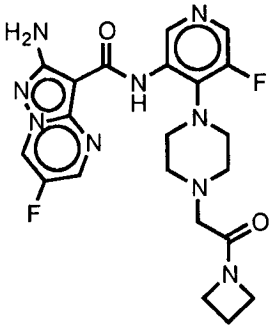
I-N-225



I-N-226



I-N-227



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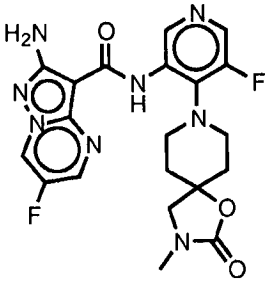

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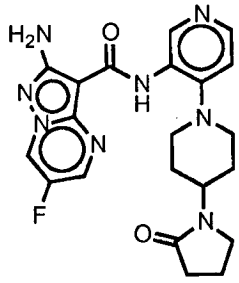

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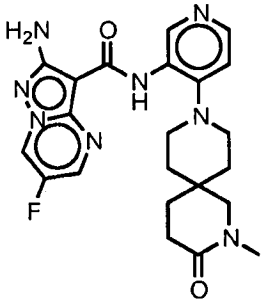

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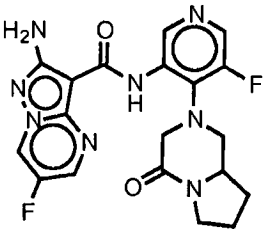

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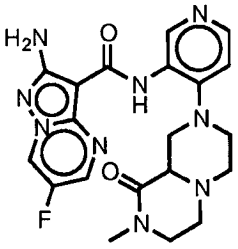

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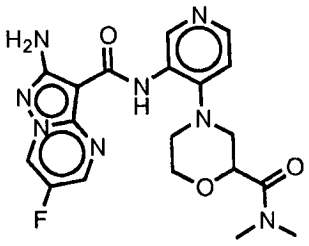

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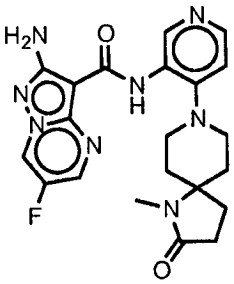

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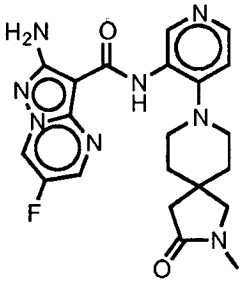

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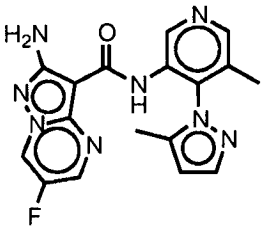

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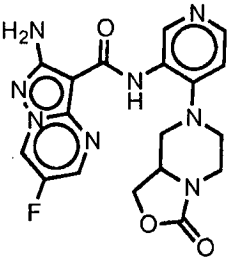

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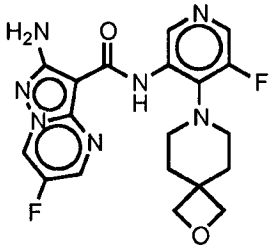

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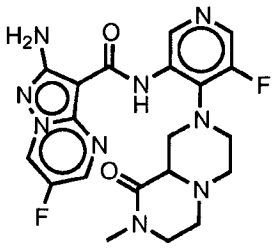

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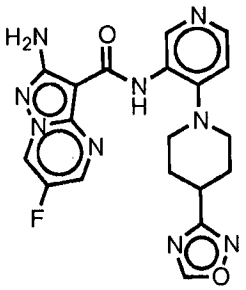

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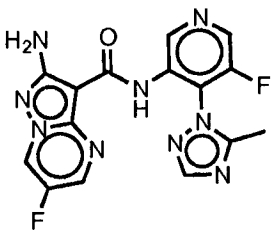

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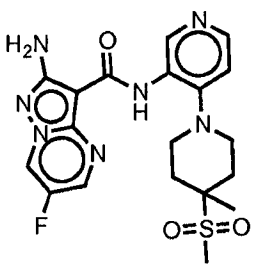

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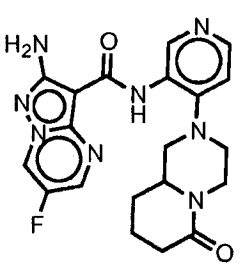

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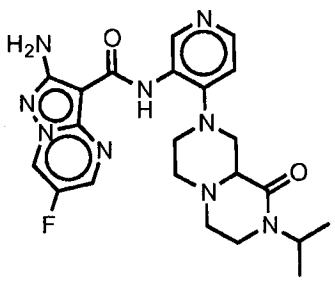

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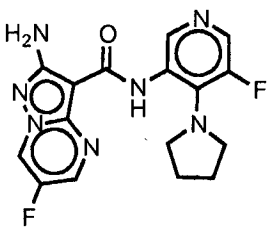

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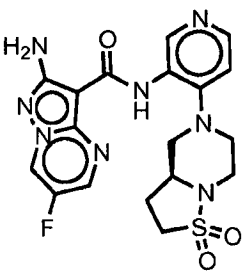

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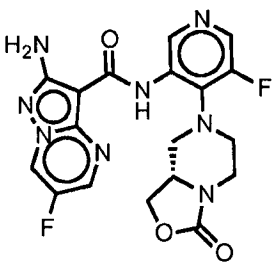

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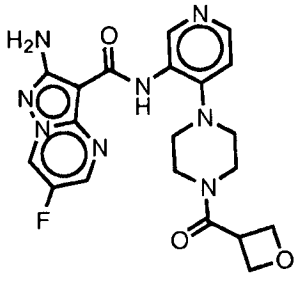

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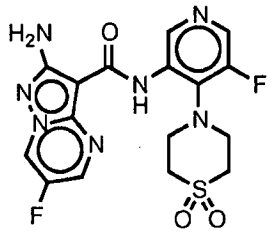

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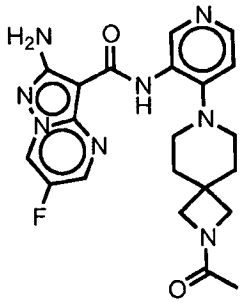

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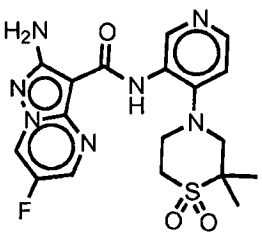

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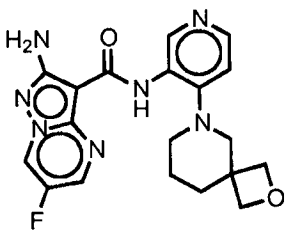

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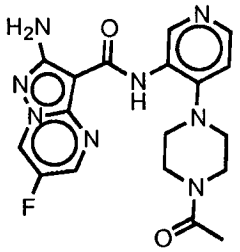

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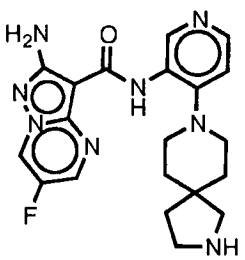

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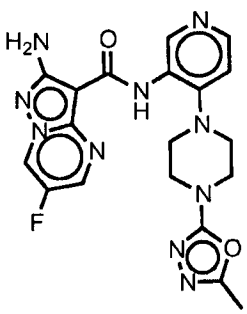

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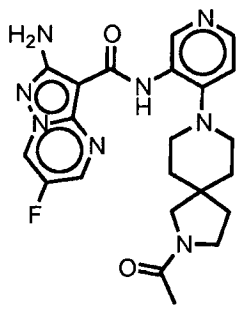

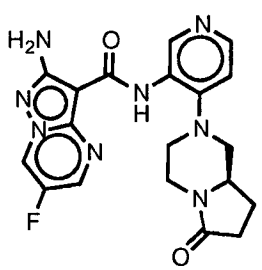

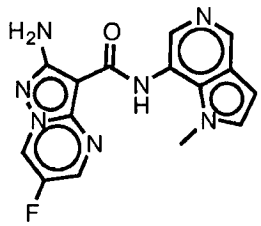

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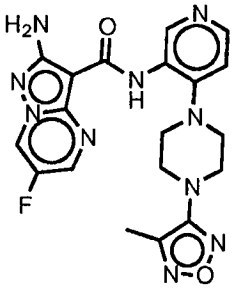

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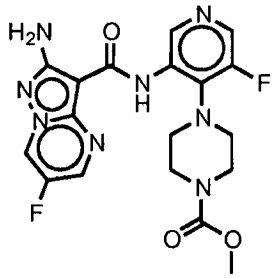

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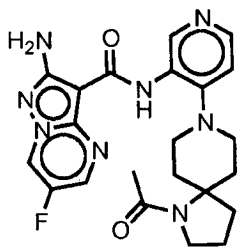

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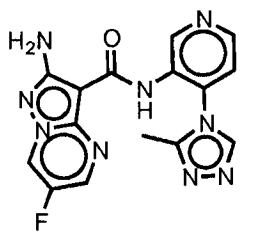
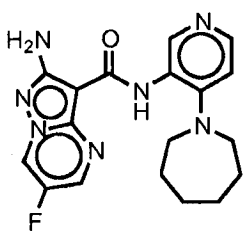


I-N-261

I-N-262

I-N-263



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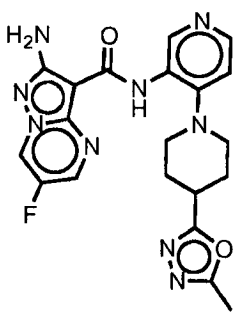

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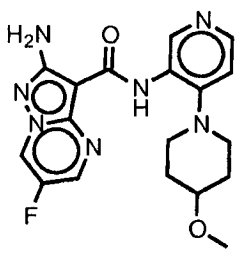

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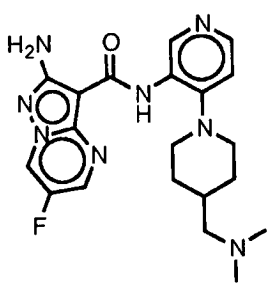

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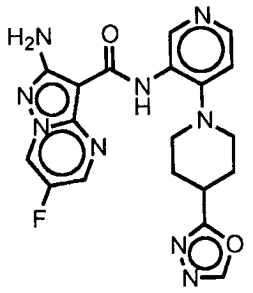

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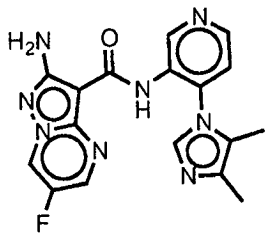

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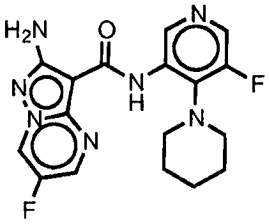

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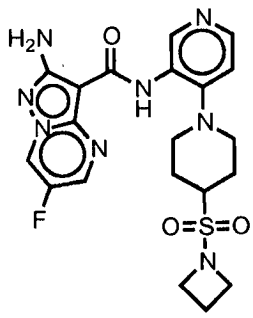

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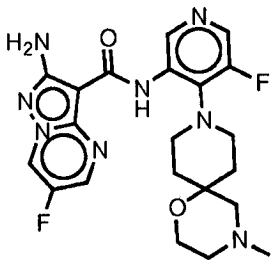

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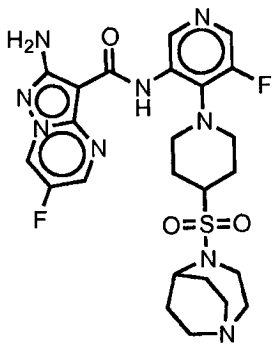

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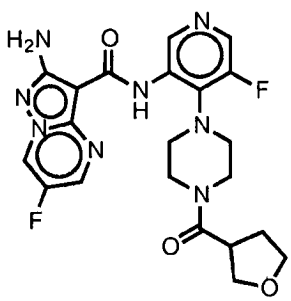

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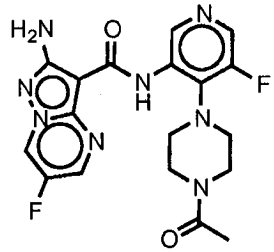

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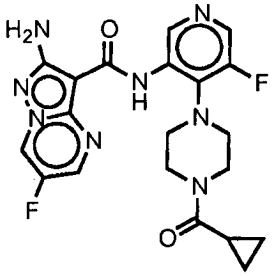

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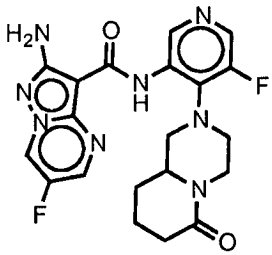

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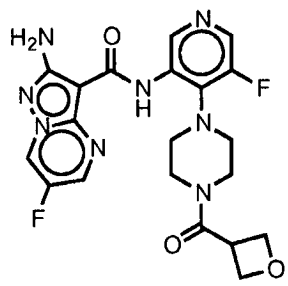

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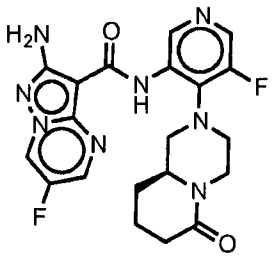
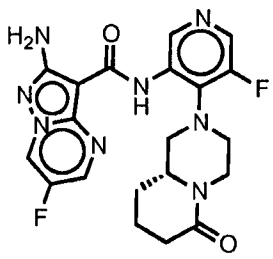
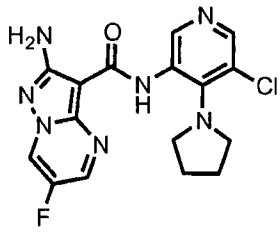


I-N-279



I-N-280



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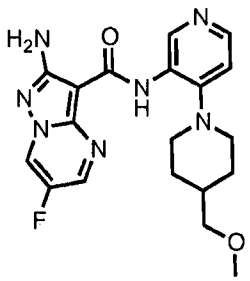

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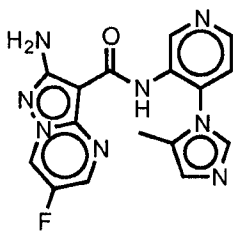

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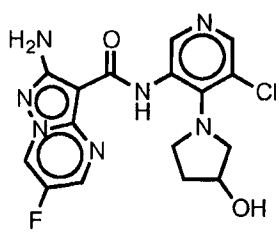
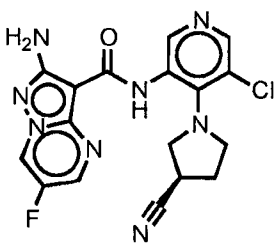


I-N-284



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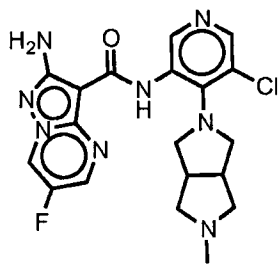

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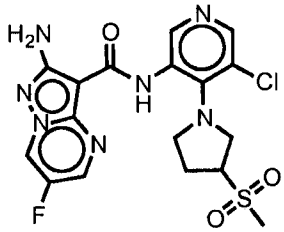

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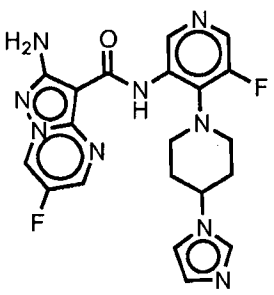

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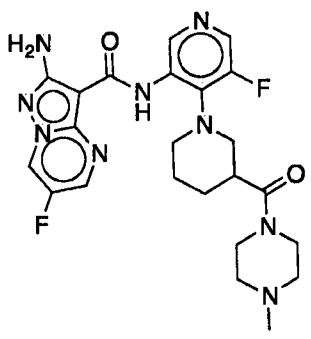

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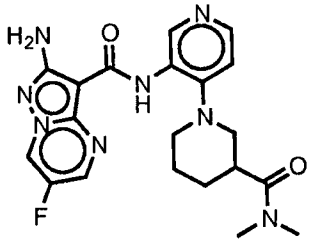
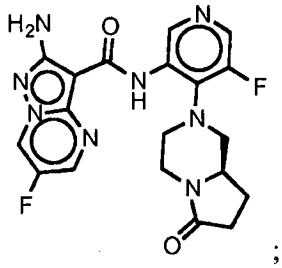


I-N-290.

[0061] In other embodiments, the compounds of the present invention are selected from one of the followin: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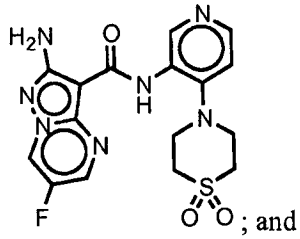
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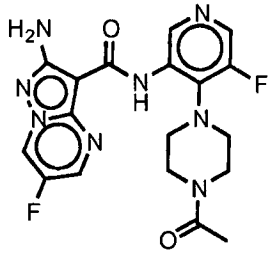
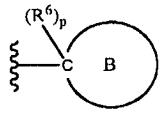


I-N-182 **I-N-210** **I-N-275** .

[0062] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^4 is Ring B, which is respresented by the structure:



[0063] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein p is 1.

[0064] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when p is 1, Ring B is a 3-7 membered cycloaliphatic or heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when p is 1, Ring B is independently selected from selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, 1,2,3,6-tetrahydropyridine, and azetidinyl. In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Ring B is piperidinyl.

[0065] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring B, J^Q is -C(O)- or C_{1-4}alkyl. In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring B, J^Q is C_{1-4}alkyl.

[0066] In yet another embodiment, the present invention is a compound represented by

structural formula **I** or **I-A**, wherein when R^4 is Ring B, J^Q is Q^2. In some embodiments, when R^4 is Ring B, the present invention is a compound represented by structural formula **I** or **I-A**, wherein Q^2 is independently selected from Q^2 is independently selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidinyl, pyrrolidinyl, piperazinyl, piperidinyl, cyclobutyl, thiomorpholinyl, or morpholinyl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when R^4 is Ring B, Q^2 is oxetanyl.

[0067] In one embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein p is 0.

[0068] In some embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when p is 0, Ring B is independently selected from phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydropyridinyl, pyridizinyl, or pyrazolyl. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when p is 0, Ring B is imidazolyl. In other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein when p is 0, Ring B is independently selected from phenyl or pyridinyl.

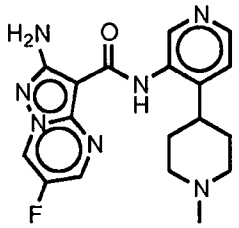
[0069] In another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^4 is $-CH_2-(R^7)$. In yet another embodiment, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^7 is H.

[0070] In still other embodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen.

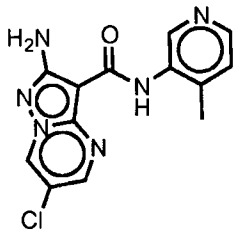
[0071] In some emodiments, the present invention is a compound represented by structural formula **I** or **I-A**, wherein J^Z is independently selected from $\rightarrow O$ or C_{1-4}alkyl.

[0072] In another example, the present invention is a compound represented by structural formula **I** or **I-A**, wherein the compounds of this invention are represented in Table 3.

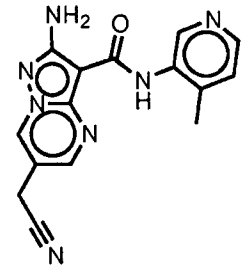
Table 3



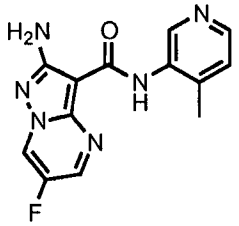
I-C-1



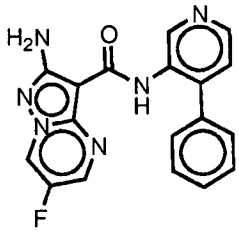
I-C-2



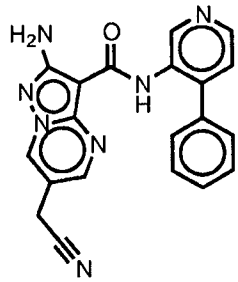
I-C-3



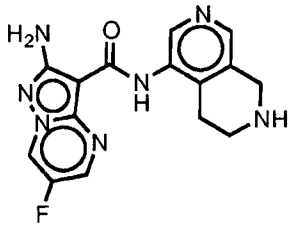
I-C-4



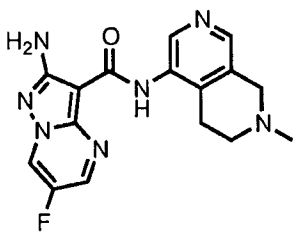
I-C-5



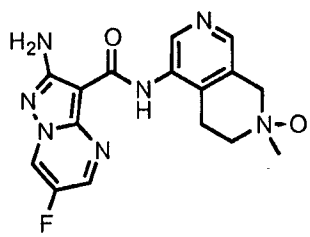
I-C-6



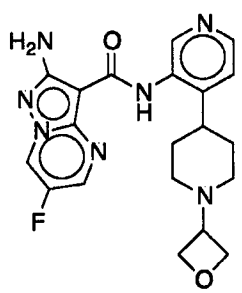
I-C-7



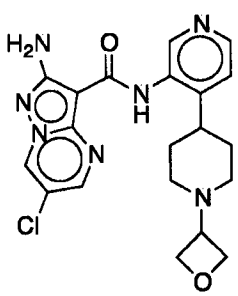
I-C-8



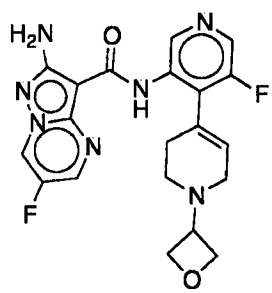
I-C-9



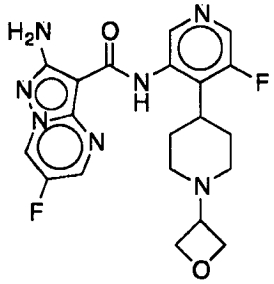
I-C-10



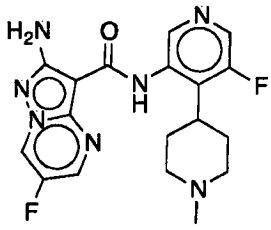
I-C-11



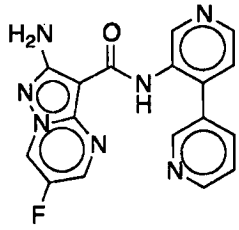
I-C-12



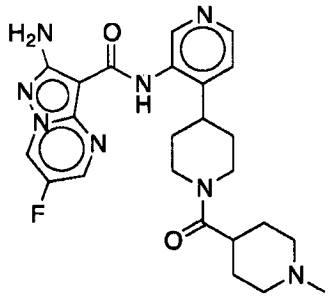
I-C-13



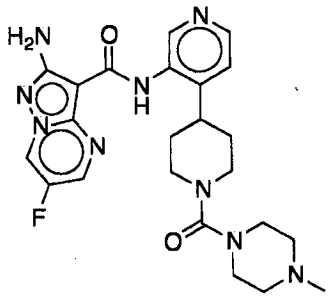
I-C-14



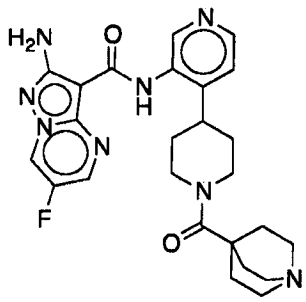
I-C-15



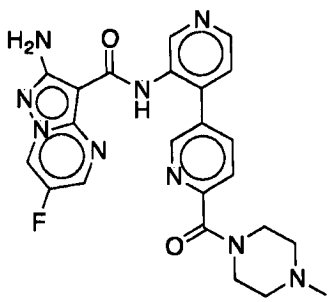
I-C-16



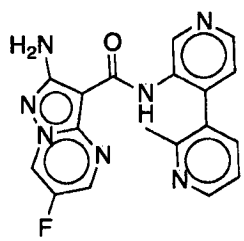
I-C-17



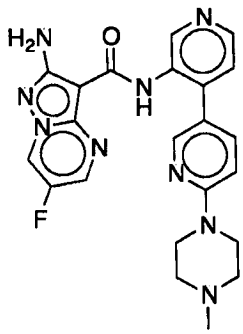
I-C-18



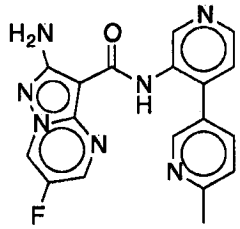
I-C-19

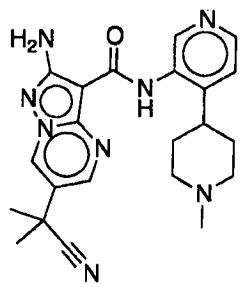


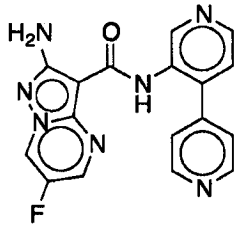
I-C-20



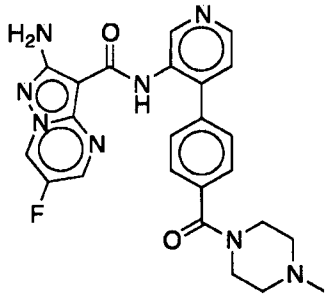
I-C-21



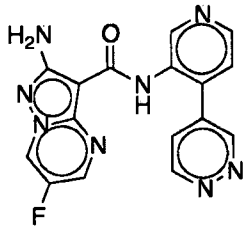




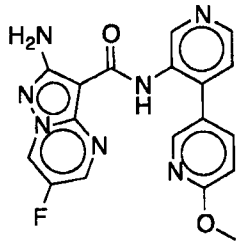
I-C-22



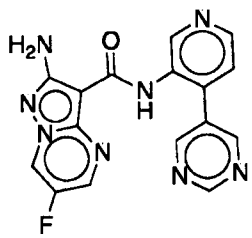
I-C-23



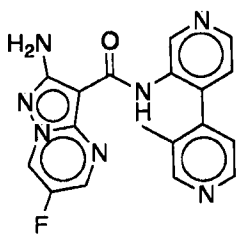
I-C-24



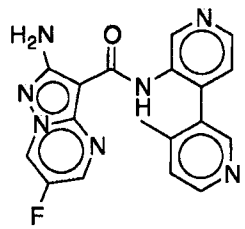
I-C-25



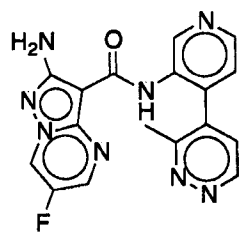
I-C-26



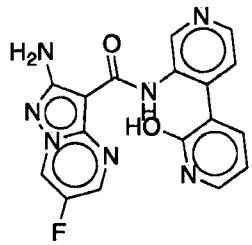
I-C-27



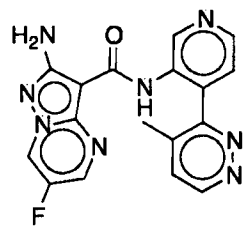
I-C-28



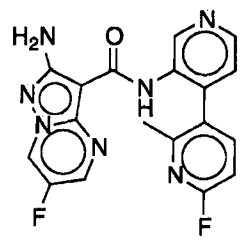
I-C-29



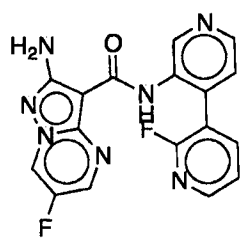
I-C-30



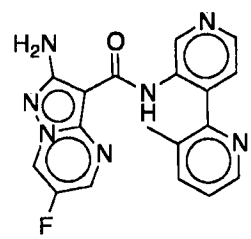
I-C-31



I-C-32



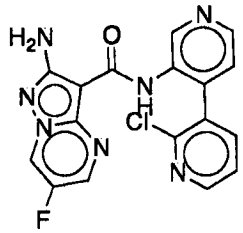
I-C-33



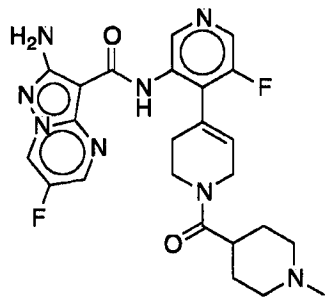
I-C-34

I-C-35

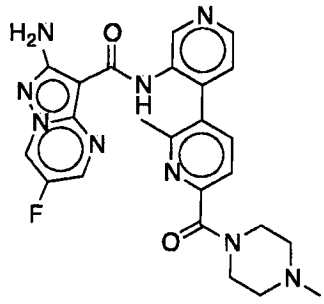
I-C-36



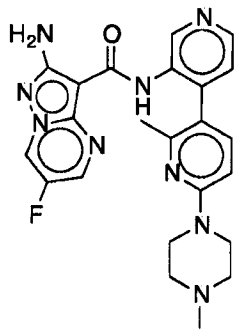
I-C-37



I-C-38



I-C-39



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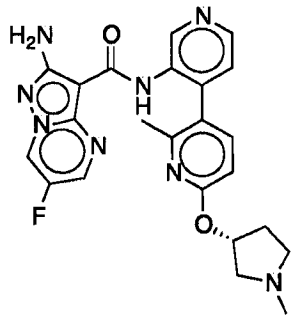

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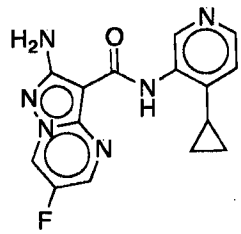

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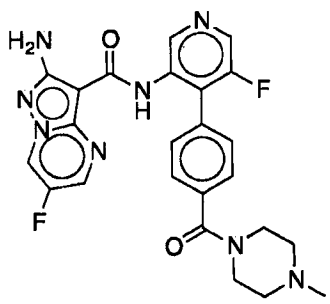

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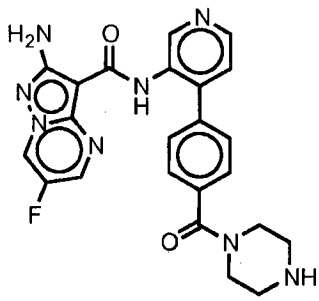

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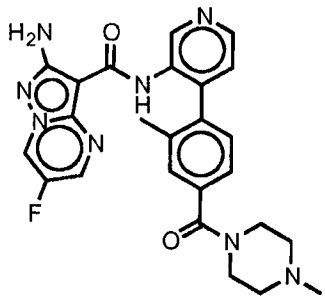
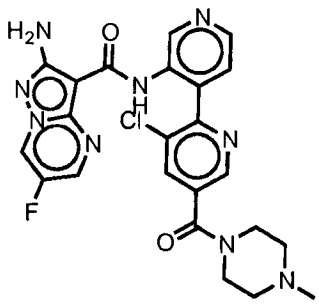
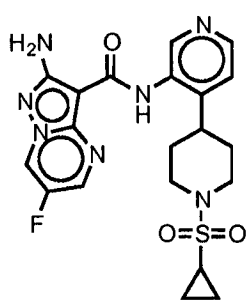
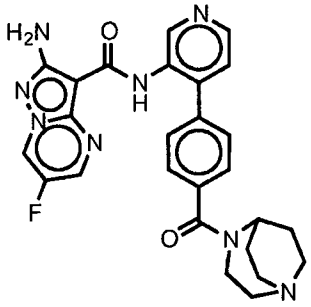


I-C-45

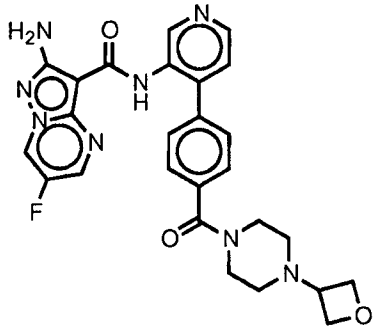




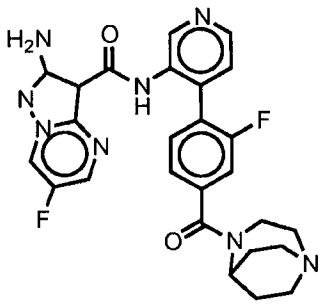
I-C-46



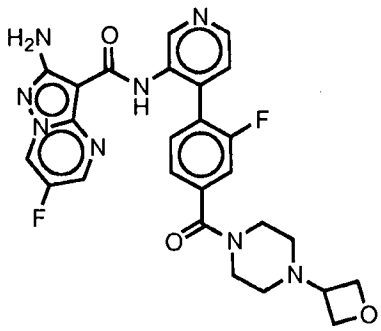
I-C-47



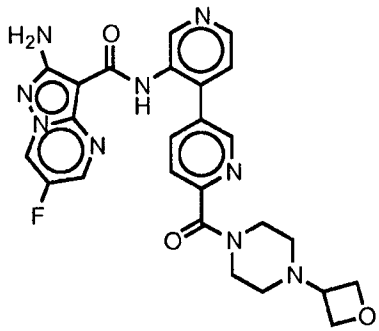
I-C-48



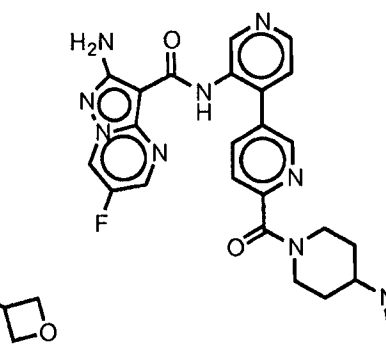
I-C-49



I-C-50



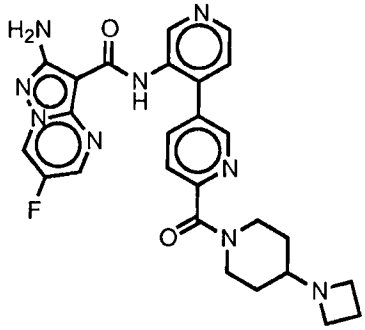
I-C-51



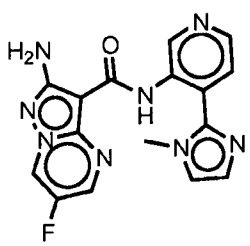
I-C-52

I-C-53

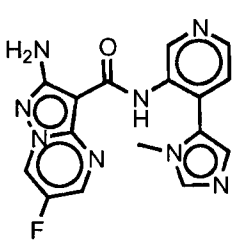
I-C-54

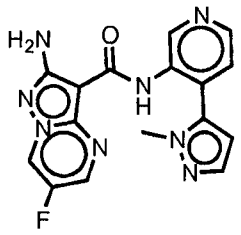


I-C-55

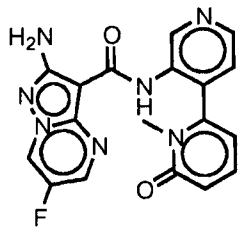


I-C-56

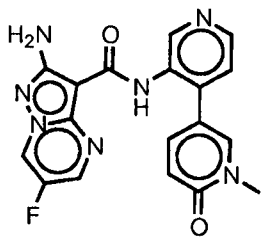




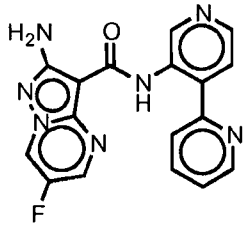
I-C-57



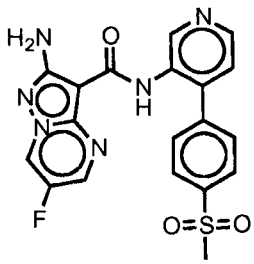
I-C-58



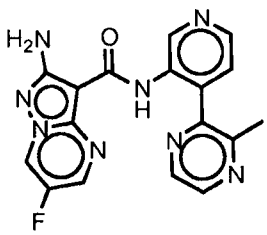
I-C-59



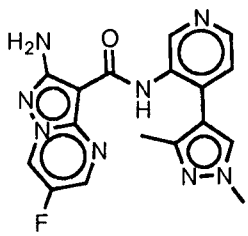
I-C-60



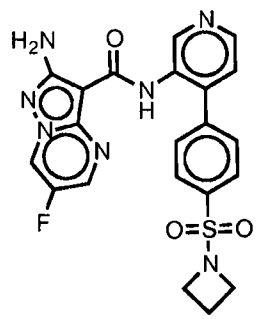
I-C-61



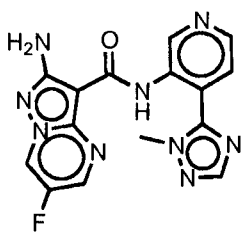
I-C-62



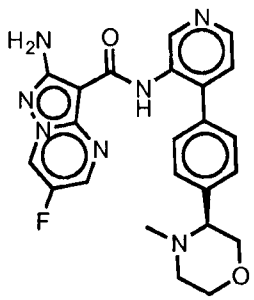
I-C-63



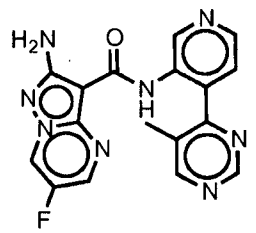
I-C-64



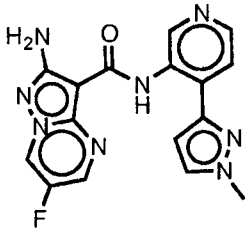
I-C-65

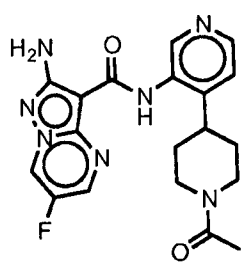


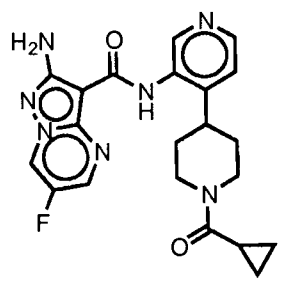
I-C-66



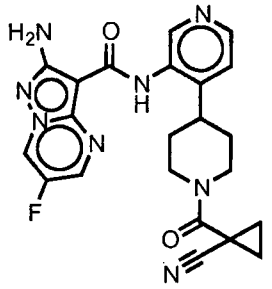
I-C-67



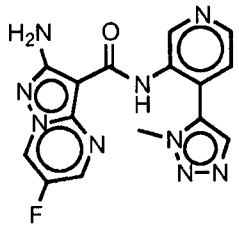




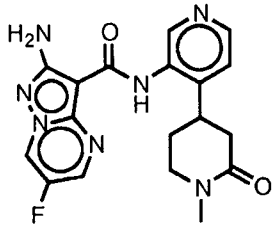
I-C-68



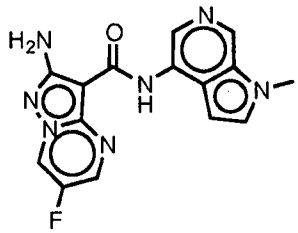
I-C-69



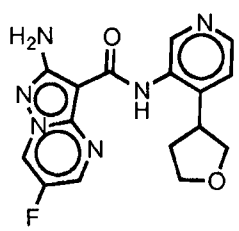
I-C-70



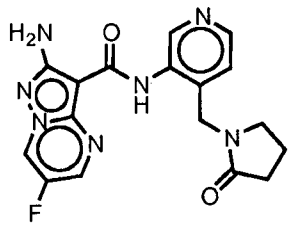
I-C-71



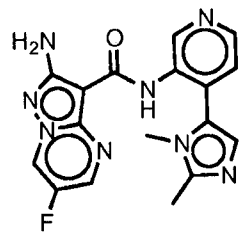
I-C-72



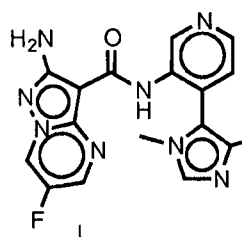
I-C-73



I-C-74



I-C-75

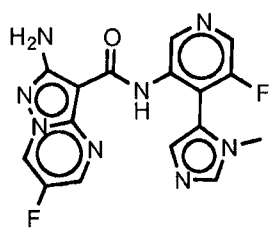


I-C-76

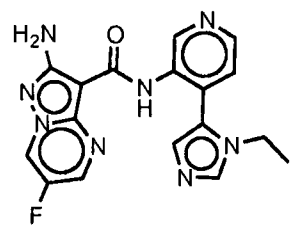
I-C-77

I-C-78

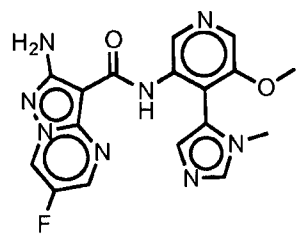
I-C-79



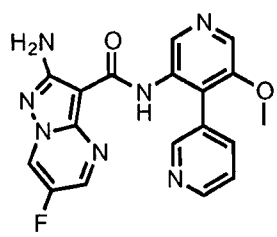
I-C-80



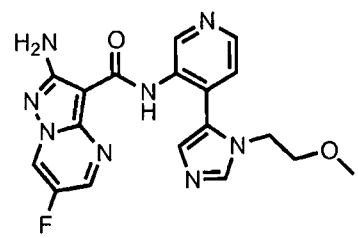
I-C-81



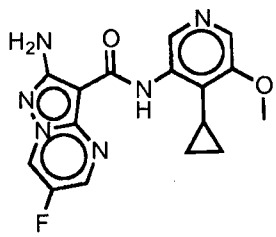
I-C-82



I-C-83

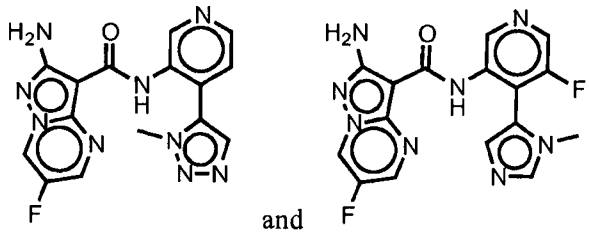


I-C-84.



[0073] In another embodiment, the compounds of the present invention are selected from

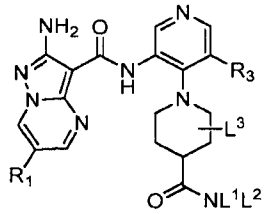
one of the following:



and

I-C-72 **I-C-79.**

[0074] A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is

optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

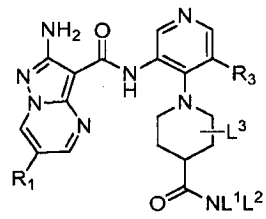
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

[0075] Another aspect of the present invention provides a compound of Formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; -CN; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

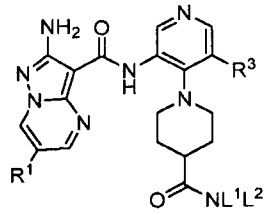
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

[0076] Another aspect of the present invention provides a compound of Formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or

partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; =O; -CN; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

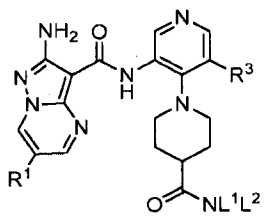
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

[0077] Another aspect of the present invention provides a compound of Formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

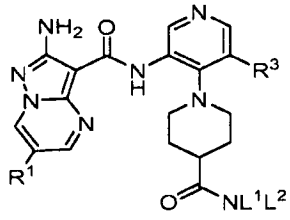
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

[0078] Another aspect of the present invention provides a compound of Formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; or -CN;

L^1 is an optionally substituted C_{1-6}aliphatic;

L^2 is an optionally substituted C_{1-6}aliphatic; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from C_{1-4}alkyl , $-N(R°)_2$, or a 3-5 membered carbocycyl; or

two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system; and

R° is H or C_{1-4}alkyl.

[0079] In another example, R^1 of formula **I-B** is fluoro. In yet another example, R^1 of formula **I-B** is $-CH_2CN$. In still other examples, R^1 of formula **I-B** is chloro.

[0080] In some embodiments, R^3 of formula **I-B** is independently selected from H, chloro, fluoro, cyclopropyl, or C_{1-4}alkyl. In one or more embodiments, R^3 of formula **I-B** is independently selected from H, chloro, or fluoro. In yet another embodiment, R^3 of formula **I-B** is H. In other embodiments, R^3 of formula **I-B** is chloro. In still other embodiments, R^3 of formula **I-B** is fluoro.

[0081] In another embodiment, the present invention is a compound represented by structural formula **I-B**, wherein L^1 and L^2 are independently selected from H; $-(C_{1-3}alkyl)O(C_{1-2}alkyl)$; $-(C_{1-3}alkyl)N(C_{1-2}alkyl)_2$; C_{1-4}alkyl; azetidinyl; piperidinyl; oxytanyl; or pyrrolidinyl. In another embodiment, the present invention is a compound represented by

structural formula **I-B**, wherein L^1 and L^2 are C_{1-3}alkyl.

[0082] In other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein L^1 and L^2, together with the nitrogen to which they are attached, form Ring D. In yet another embodiment, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In some embodiments, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is independently selected from piperazinyl, piperidinyl, morpholinyl, tetrahydopyranyl, azetidinyl, pyrrolidinyl, or 1,4-diazepanyl. In another embodiment, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is piperazinyl, piperidinyl, 1,4-diazepanyl, pyrrolidinyl or azetidinyl. In still other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is piperidinyl or piperazinyl. In still other embodiments, Ring D is piperazinyl.

[0083] In one or more aspects, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In other examples, the present invention is a compound represented by structural formula **I-B**, wherein Ring D is octahydropyrrolo[1,2-a]pyrazine or octahydropyrrolo[3,4-c]pyrrole. In another example, Ring D is octahydropyrrolo[1,2-a]pyrazine.

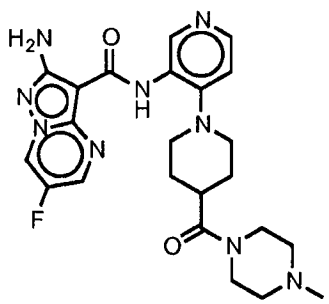
[0084] In yet another example, the present invention is a compound represented by structural formula **I-B**, wherein J^G is halo, C_{1-4}alkyl, -O(C_{1-3}alkyl), C_{3-6}cycloalkyl, a 3-6 membered heterocyclyl, -NH(C_{1-3}alkyl), -OH, or -N(C_{1-4}alkyl)$_2$. In other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein J^G is methyl, -N(C_{1-4}alkyl)$_2$, ethyl, -O(C_{1-3}alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidinyl. In still other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein J^G is methyl, -O(C_{1-3}alkyl), oxetanyl, pyrrolidinyl, piperidinyl, or azetidinyl. In yet another example, the present invention is a compound represented by structural formula **I-B**, wherein J^G is C_{1-4}alkyl, C_{3-5}cycloalkyl, or -N(C_{1-4}alkyl)$_2$. In other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein J^G is methyl, ethyl, or cyclopropyl. In some embodiments, the present invention is a compound represented by structural formula **I-B**, wherein J^G is methyl. In still other embodiments, the present invention is a compound represented by structural formula **I-B**, wherein J^G is oxetanyl.

[0085] In another example, the present invention is a compound represented by structural formula **I-B**, wherein two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system. In some examples, the present invention is a compound represented by structural formula **I-B**, wherein the bridged ring system is 1,4- diazabicyclo[3.2.2]nonane, 1,4-diazabicyclo[3.2.1]octane, or 2,5-diazabicyclo[2.2.1]heptane. In some examples, the present invention is a compound represented by structural formula **I-B**, wherein the bridged ring system is 1,4-diazabicyclo[3.2.2]nonane.

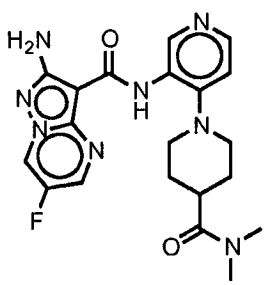
[0086] In some embodiments, the present invention is a compound represented by structural formula **I-B**, wherein two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur. the present invention is a compound represented by structural formula **I-B**, wherein In other embodiments, the ring formed by the two occurrences of J^G on the same atom is selected from oxetanyl or cyclopropyl

[0087] In another example, the present invention is a compound represented by structural formula **I**, **I-A**, and **I-B**, wherein the compounds of this invention are represented in Table 4.

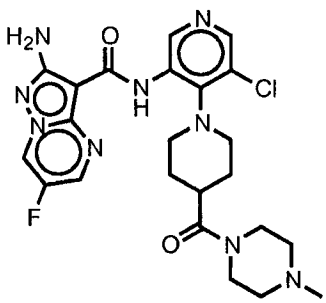
Table 4



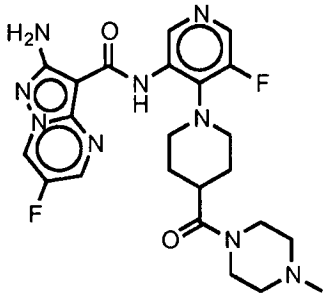
I-G-1



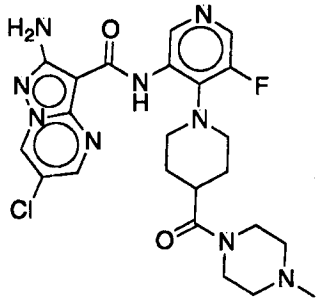
I-G-2



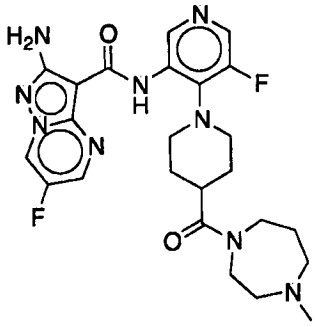
I-G-3



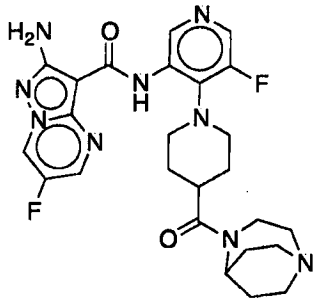
I-G-4



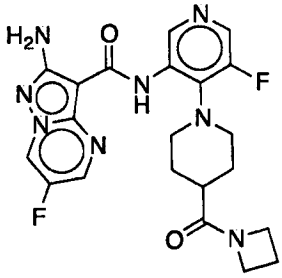
I-G-5



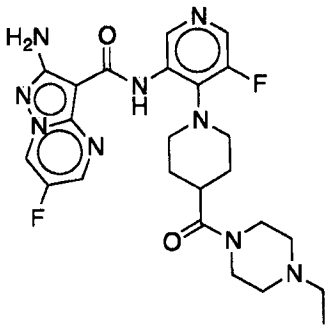
I-G-6



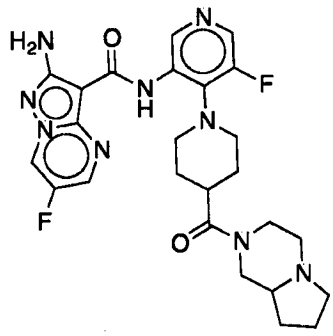
I-G-7



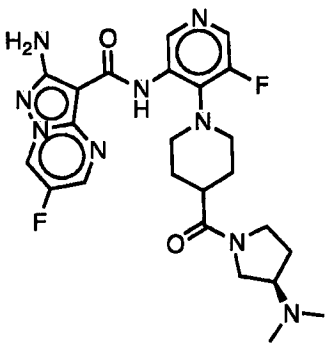
I-G-8



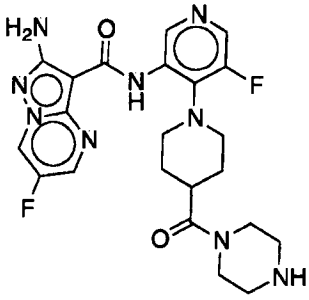
I-G-9



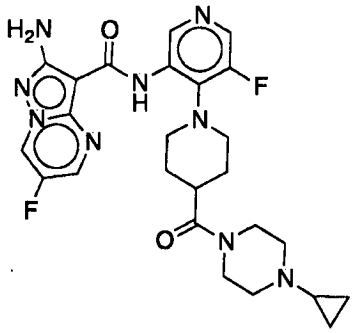
I-G-10



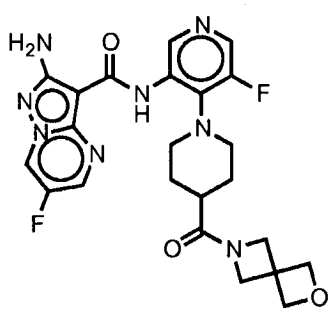
I-G-11



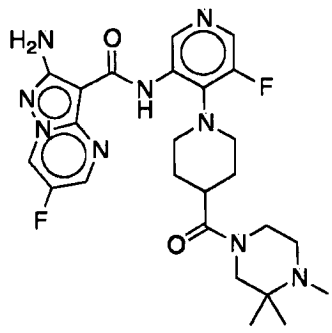
I-G-12



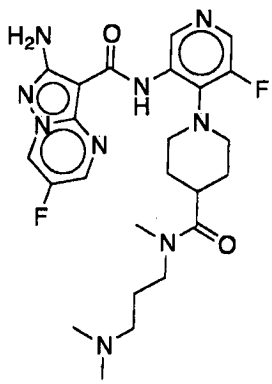
I-G-13



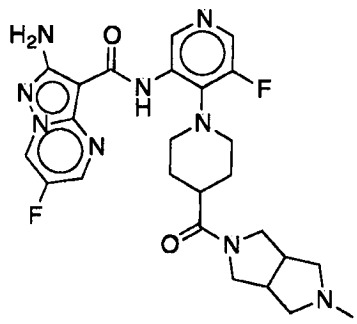
I-G-14



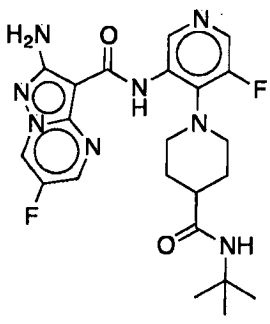
I-G-15



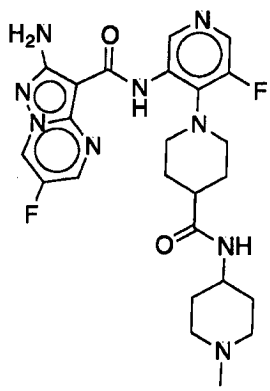
I-G-16



I-G-18



I-G-19



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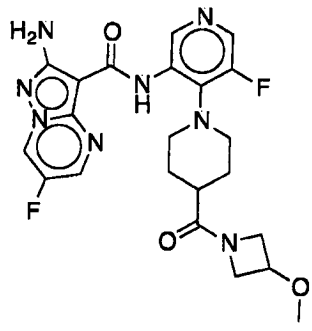

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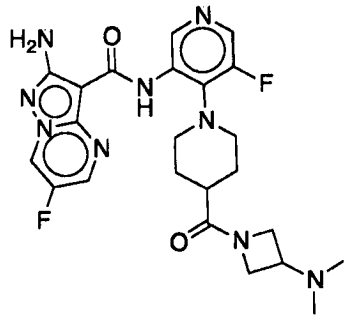
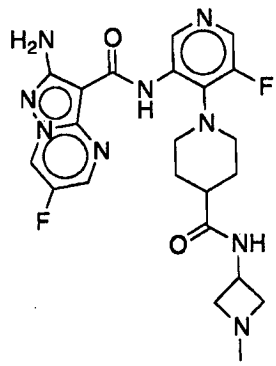


I-G-22



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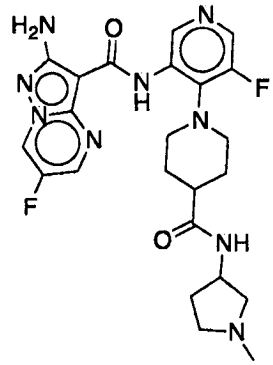

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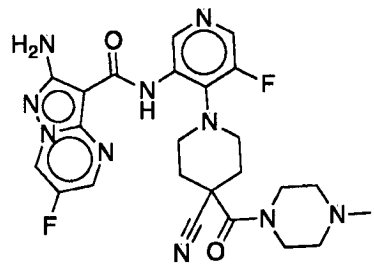

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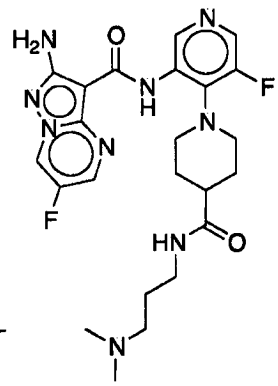

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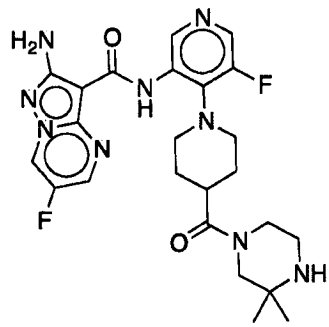

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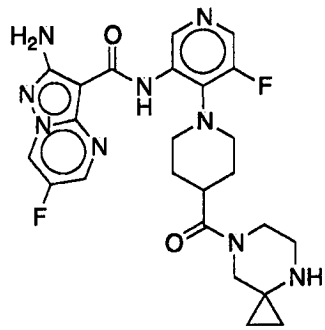

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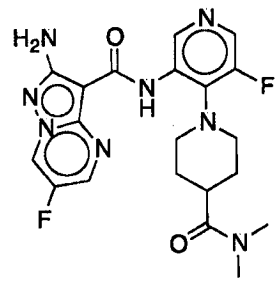

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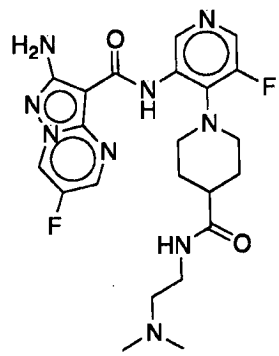

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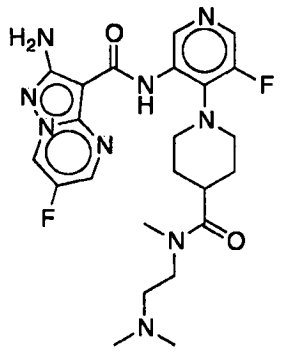
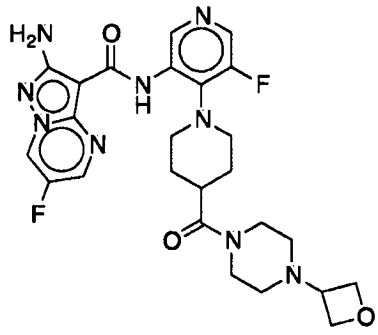
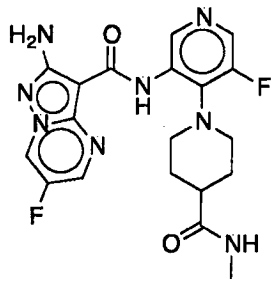


I-G-31



I-G-32



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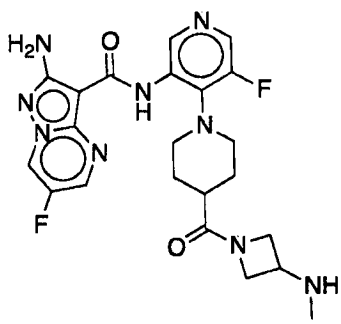

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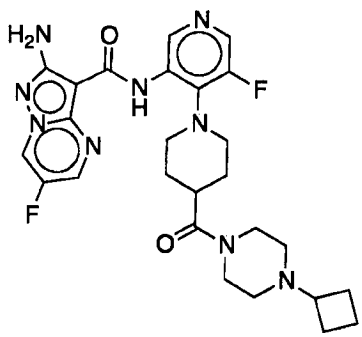

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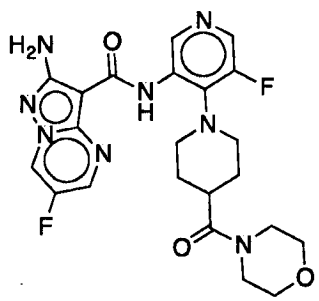

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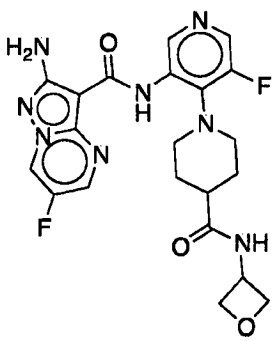

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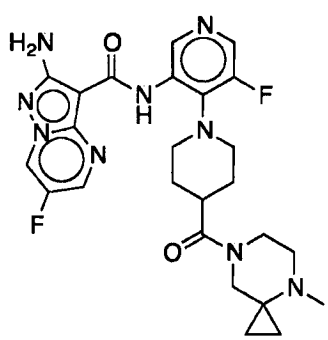

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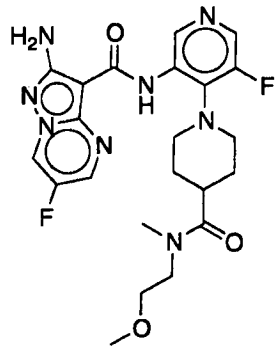

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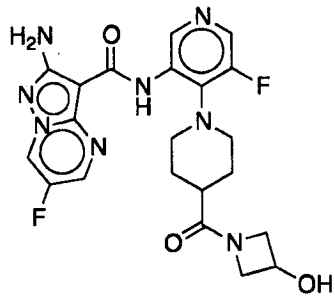

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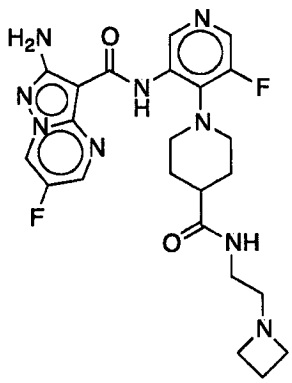

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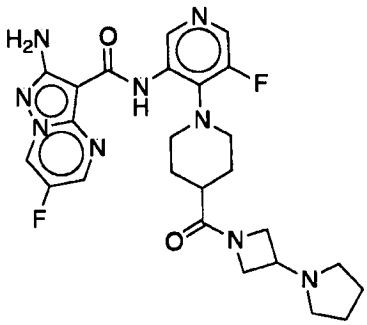

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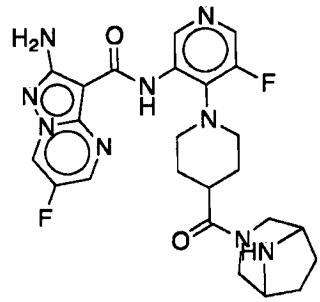

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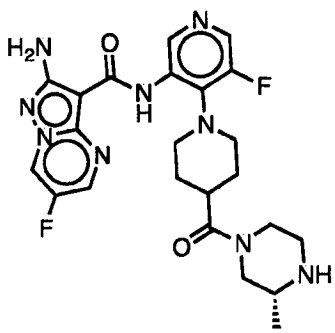

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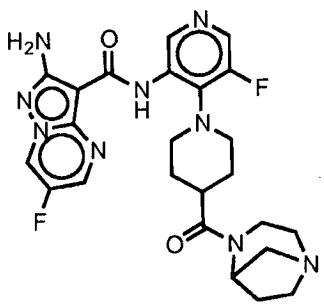

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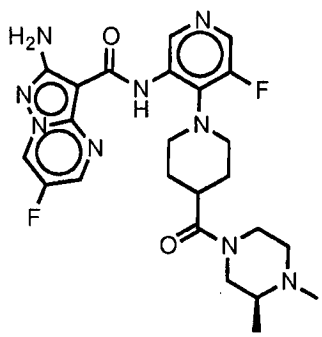

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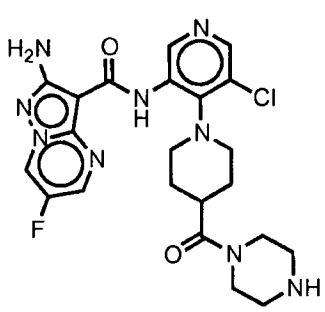

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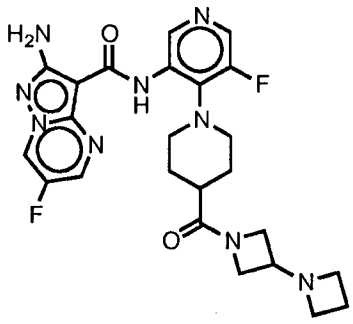

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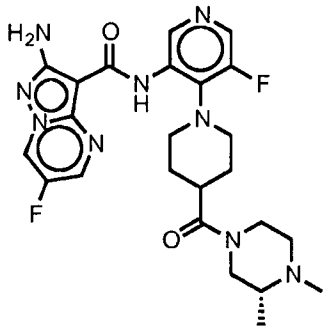
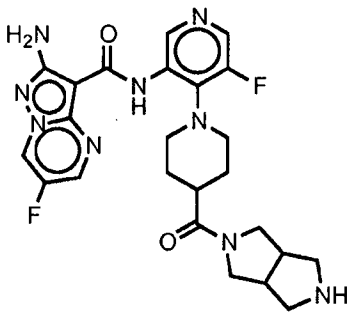


I-G-50



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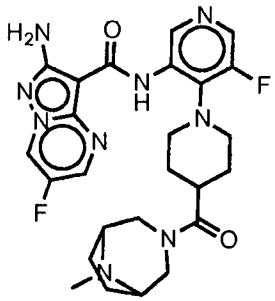

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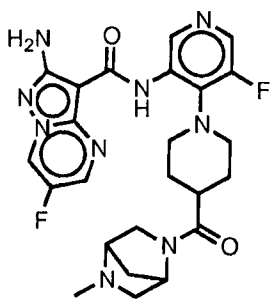

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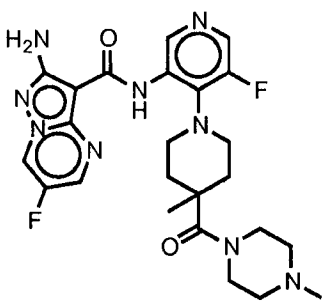

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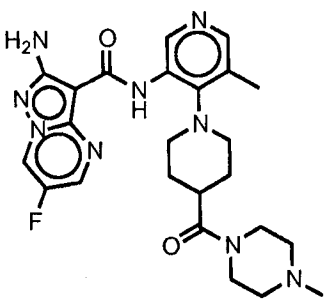
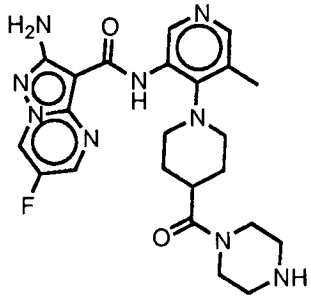
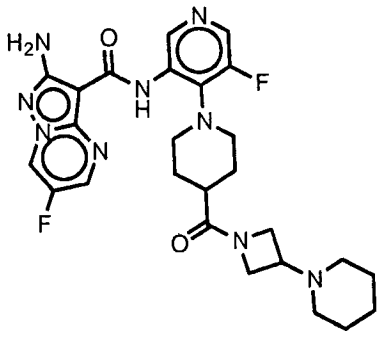


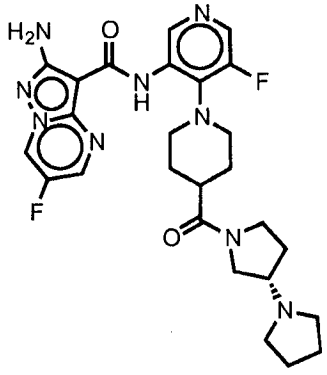
I-G-55



I-G-56



I-G-57



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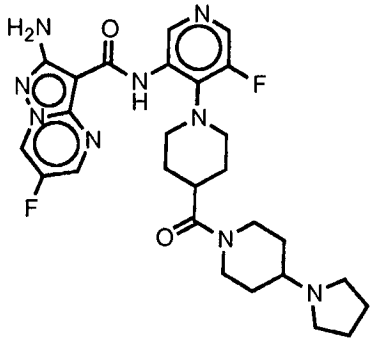

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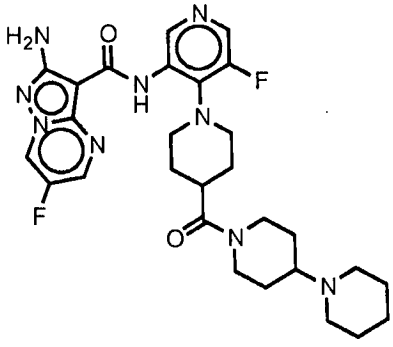

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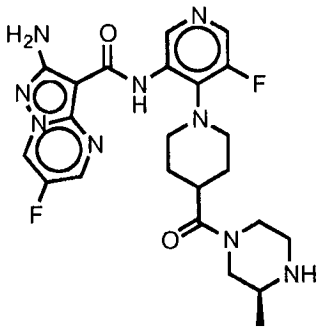
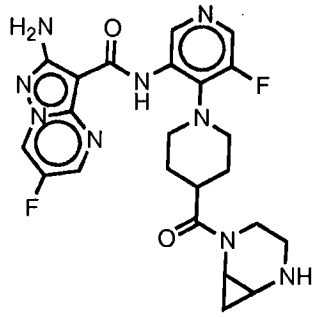
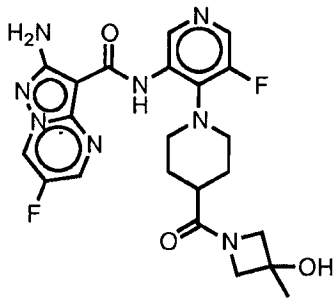


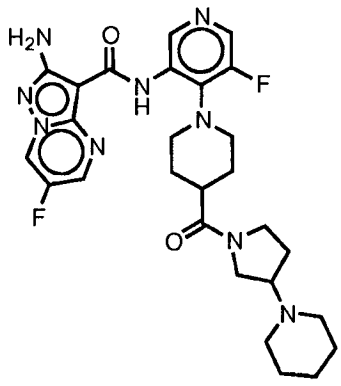
I-G-61



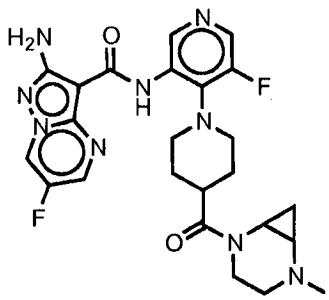
I-G-62



I-G-63



I-G-64



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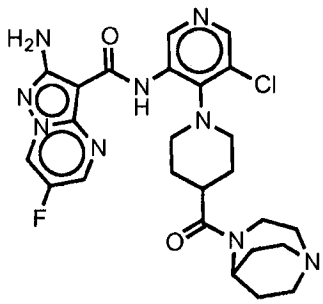
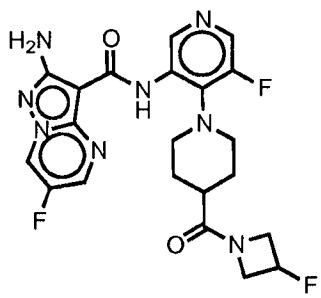
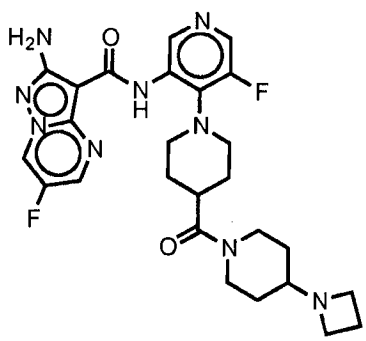


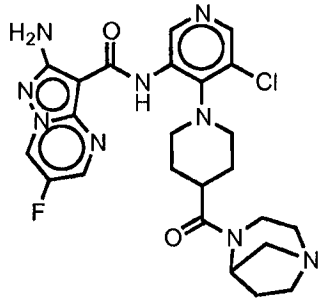
I-G-66



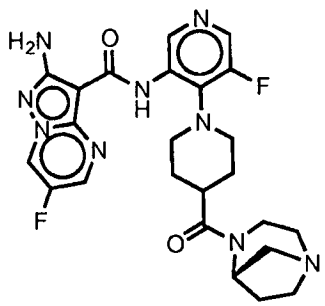
I-G-67



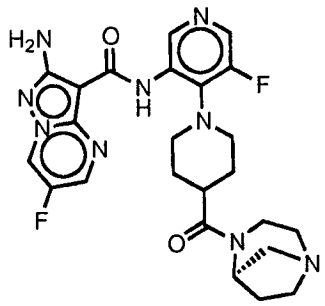
I-G-68



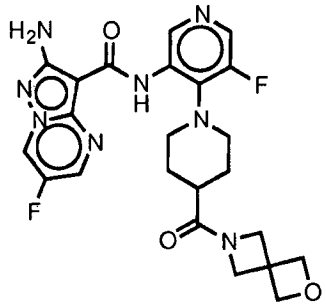
I-G-69



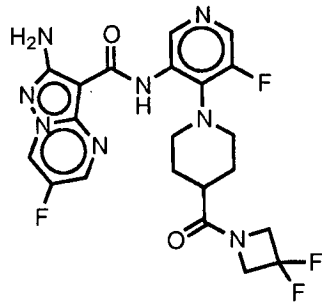
I-G-70



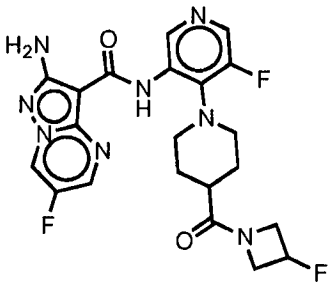
I-G-71



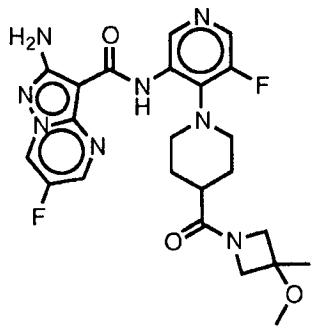
I-G-72



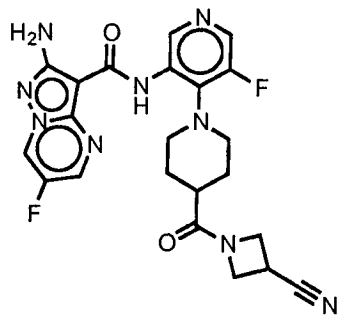
I-G-73



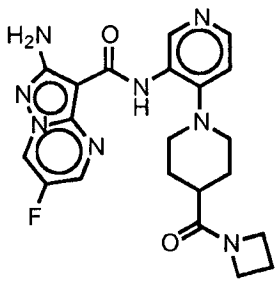
I-G-74



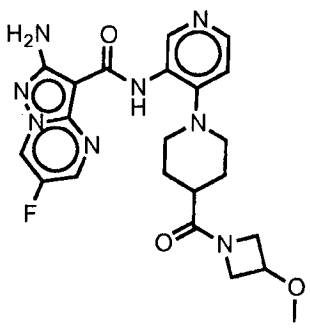
I-G-75



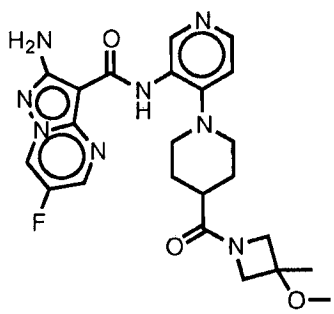
I-G-76



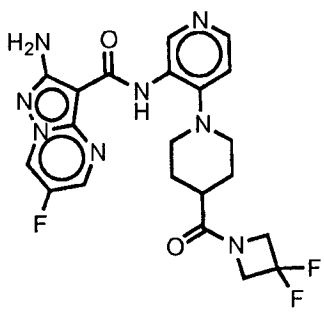
I-G-77



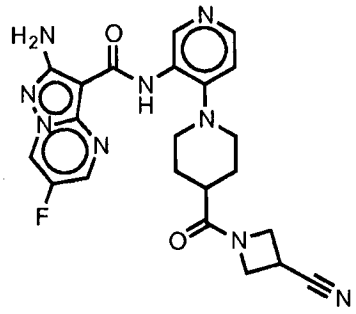
I-G-78



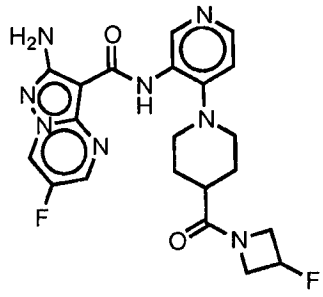
I-G-79



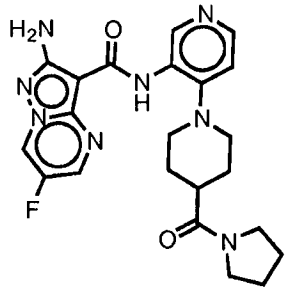
I-G-80



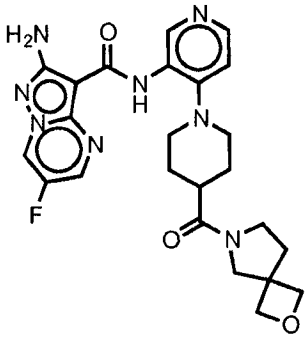
I-G-81



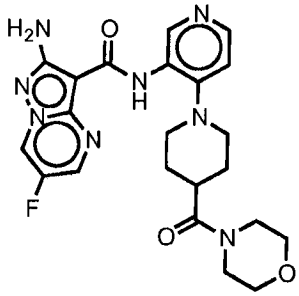
I-G-82



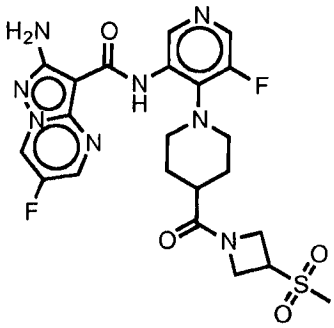
I-G-83



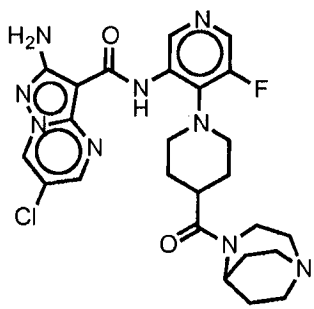
I-G-84



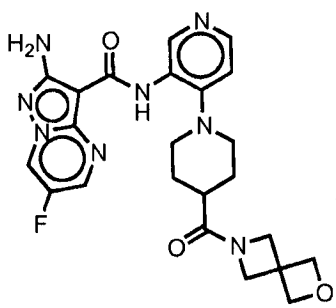
I-G-85



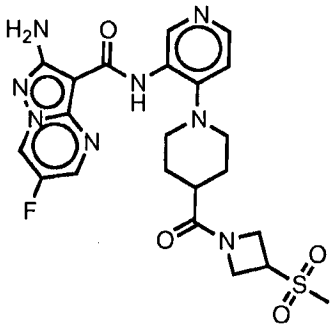
I-G-86

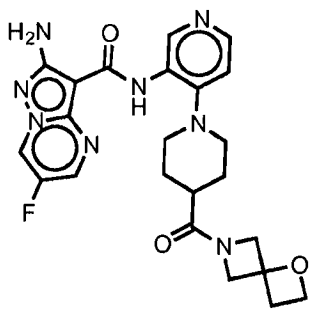


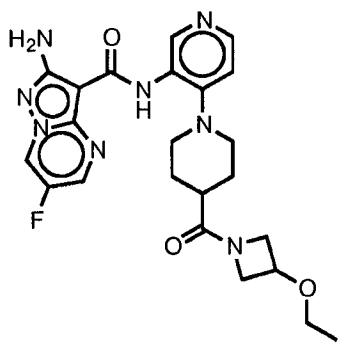
I-G-87



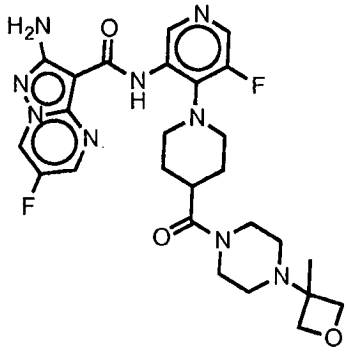
I-G-88



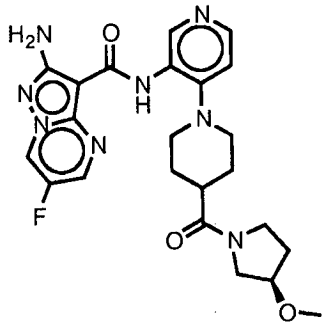




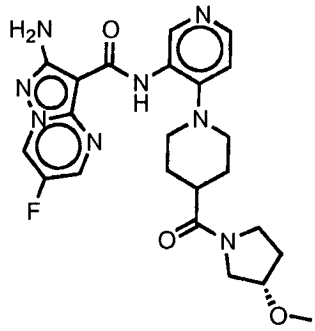
I-G-89



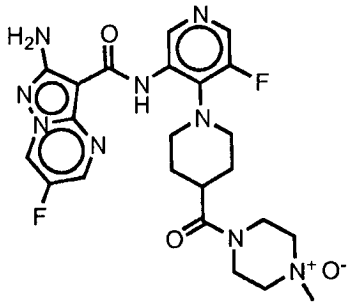
I-G-90



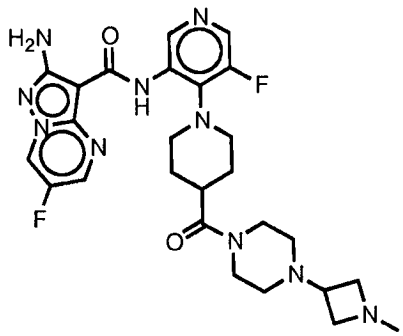
I-G-91



I-G-92



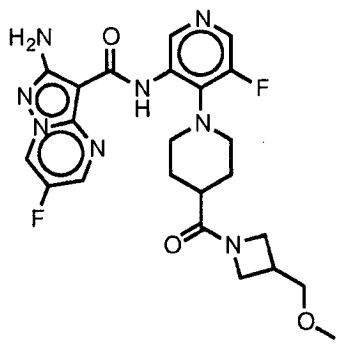
I-G-93

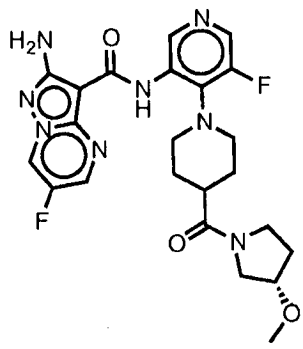


I-G-94

I-G-95

I-G-96

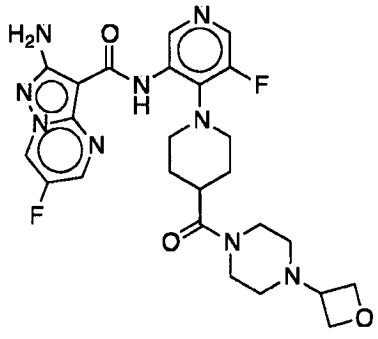




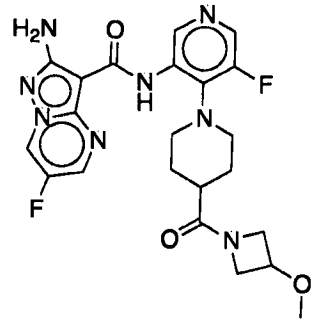
I-G-98

I-G-99.

[0088] In another embodiment, the compound of the present invention is selected from one of the following:

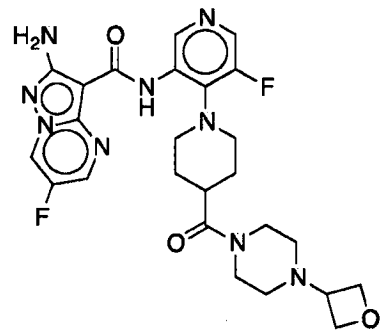


and



I-G-32 **I-G-21.**

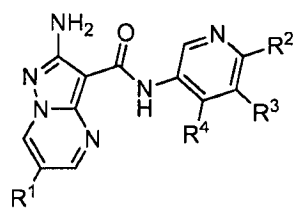
[0089] Preferably, the compound has the structure **I-G-32**:



I-G-32

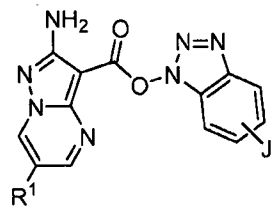
or a pharmaceutically acceptable salt.

[0090] Another aspect of the present invention comprises a process for preparing a compound of formula **I-A**:



I-A

comprising reacting a compound of formula **6**:

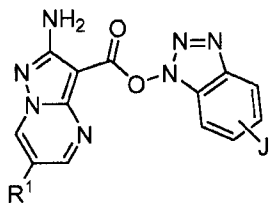


6

under suitable conditions to form an amide bond, wherein J, R^1, R^2, R^3, and R^4 are as defined herein.

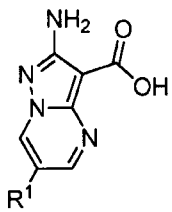
[0091] In some examples, the suitable conditions for forming the amide bond comprises reacting the compound of formula **6** with a substituted 3-amino pyridine in an aprotic solvent under heat. In other examples, the aprotic solvent is selected from NMP, optionally substituted pyridine, or DMF. In another embodiment, the aprotic solvent is optionally substituted pyridine. In still other embodiments, the reaction temperature is at least 80°C. In another embodiment, the reaction temperature is at least 100°C

[0092] In another embodiment, the process, described above, further comprises preparing a compound of formula **6**:



6

by reacting a compound of formula **5**:

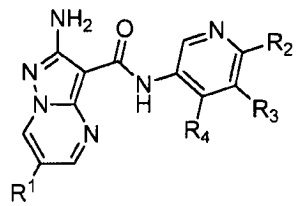


5

under suitable conditions to form an activated ester, wherein J and R^1 is as defined herein.

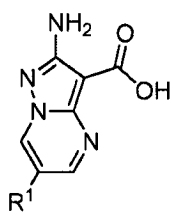
[0093] In some embodiments, suitable conditions for forming the activated ester comprises reacting the compound of formula **5** with an amide coupling agent in the presence of an organic base. In other embodiments, the organic base is an aliphatic amine. In still other embodiments, the organic base is independently selected from triethylamine or DIPEA. In one or more embodminets, the amide coupling agent is independently selected from EDCI, TBTU, TCTU, HATU, T3P, or COMU. In yet another embodiment, the amide coupling agent is independently selected from TBTU or TCTU. In another embodiment, the amide coupling agent is TCTU.

[0094] Another aspect of the invention comprises a process for preparing a compound of formula **I-A**:



I-A

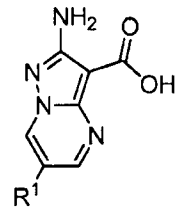
comprising reacting a compound of formula **5**:



5

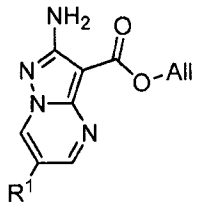
under suitable conditions to form an amide bond, wherein R^1, R^2, R^3, and R^4 are as defined herein.

[0095] Yet another apect of the present invention comprises a process for preparing a compound of formula **5**:



5

by reacting a compound of formula 4:



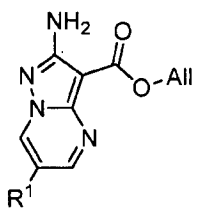
4

under suitable hydrolytic conditions, wherein R^1 is as defined herein.

[0096] In some embodiments, suitable hydrolytic conditions comprise reacting the compound of formula **4** with a silane in the presence of a metal catalyst. In other embodiments, the silane is a phenylsilane. In another embodiment, the metal catalyst is a palladium catalyst. In yet another embodiment, the palladium catalyst is $Pd(PPh_3)_4$. In another embodiment suitable hydrolytic conditions comprise reacting the compound of formula **4** with 4-methylbenzenesulfinate in the presence of a metal catalyst.

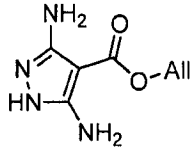
[0097] In still other embodiments, suitable hydrolytic conditions comprise reacting the compound of formula **4** with an aqueous alkali. In some embodiments, the aqueous alkali is selected from LiOH, NaOH or KOH.

[0098] Another aspect of the present invention comprises a process for preparing a compound of formula **4**:



4

by reacting a compound of formula **3**:

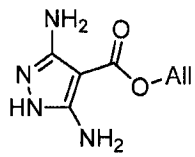


3

under suitable condensation conditions to form a pyrimidine ring.

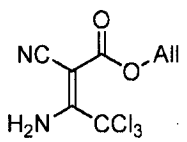
[0099] In some embodiments, suitable condensation conditions to form a pyrimidine ring comprise reacting the compound of formula **3** with a 1,3-dielectrophilic species in the presence of a solvent. In another embodiment, the 1,3-dielectrophilic species is selected from 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal. In still other embodiments, the solvent is selected from DMF or DMSO in water. In other embodiments, the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species. In another embodiment the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid. In yet another embodiment, the sulfonic acid is PTSA.

[00100] Another aspect of the present invention comprises a process for preparing the compound of formula **3**:



3

by reacting a compound of formula **2**:



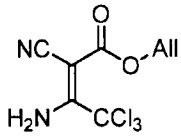
2

under suitable condensation conditions to form a pyrazole ring.

[00101] In some embodiments, suitable condensation conditions to form a pyrazole ring comprise reacting the compound of formula **2** with a hydrazine or hydrazine hydrate in the

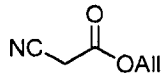
presence of an aprotic solvent under basic conditions. In another embodiment, the aprotic solvent is DMF. In yet another embodiment, the basic conditions comprise reacting the compound of formula **2** in the presence of potassium acetate or sodium acetate.

[00102] Yet another aspect of the present invention comprises a process for preparing a compound of formula **2**:



2

by reacting a compound of formula **1**:

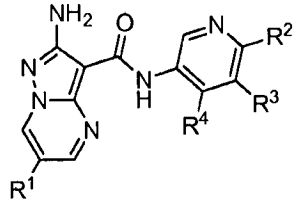


1

under suitable anion condensation conditions.

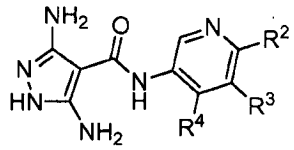
[00103] In some embodiments, suitable anion condensation conditions comprise 1) reacting the compound of formula **1** with a base, in the presence of a solvent, to generate the anion of the compound of formula **1**; and 2) reacting the anion of the compound of formula **1** with trichloroacetonitrile. In still other embodiments, the base is potassium acetate. In yet another embodiment, the solvent is an alcohol. In other embodiments, the solvent is isopropylalcohol.

[00104] One embodiment of the present invention comprises a process for preparing a compound of formula **I-A**:



I-A

comprising reacting a compound of formula **9**:

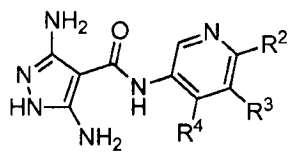


9

under suitable condensation conditions to form a pyrimidine ring, wherein R^1, R^2, R^3 and R^4 are as defined herein.

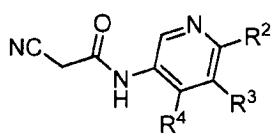
[00105] In some embodiments, suitable condensation conditions to form a pyrimidine ring comprise reacting the compound of formula **9** with a 1,3-dielectrophilic species in the presence of a solvent. In another embodiment, the 1,3-dielectrophilic species is selected from 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal. In still other embodiments, the solvent is selected from DMF or DMSO in water. In other embodiments, the 1,3-dielectrophilic species is generated in situ from a protected 1,3-dielectrophlic species. In another embodiment the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid. In yet another embodiment, the sulfonic acid is PTSA.

[00106] Another embodiment of the present invention comprises a process for preparing a compound of formula **9**:



9

by reacting a compound of formula **8**:



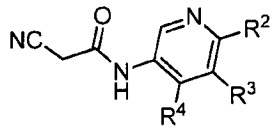
8

under suitable condensation conditions to form a pyrazole ring.

[00107] In some embodiments, suitable condensation conditions to form a pyrazole ring comprise 1) reacting the compound of formula **8** with a base, in the presence of a solvent, to generate the anion of the compound of formula **I**; 2) reacting the anion with trichloroacetonitrile; and 3) reacting the product from 2) with a hydrazine or hydrazine

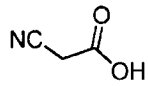
hydrate in the presence of an aprotic solvent. In another embodiment, the aprotic solvent is NMP or DMF. In some embodiments, the base is selected from sodium acetate or potassium acetate.

[00108] Yet another embodiment comprises a process for preparing a compound of formula **8**:



8

by reacting a compound of formula **7**:

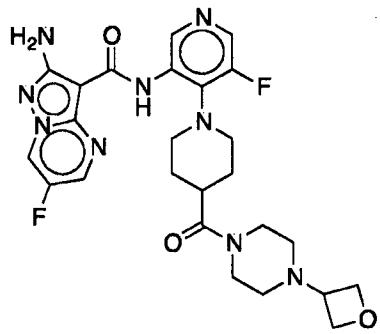


7

under suitable conditions to form an amide bond.

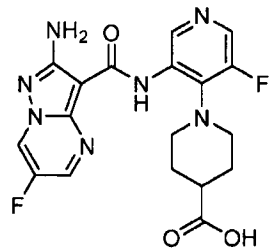
[00109] In some examples, the suitable conditions for forming the amide bond comprises reacting the compound of formula **7** with a substituted 3-amino pyridine with an amide coupling agent in the presence of an aprotic solvent and an organic base. In other examples, the aprotic solvent is selected from NMP or DMF. In another embodiment, the organic base is an aliphatic amine. In still other embodiments, the organic base is independently selected from triethylamine or DIPEA. In yet another embodiment, the amide coupling agent is independently selected from TBTU or TCTU.

[00110] Another aspect of the present invention provides a process of preparing a compound of formula **I-G-32**:



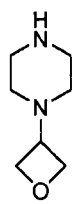
I-G-32

comprising the step of reacting the compound of formula **29**:



29

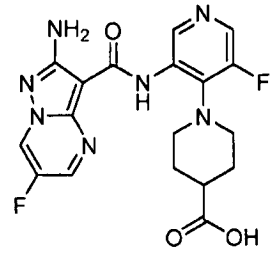
with a compound of formula **25**:



25

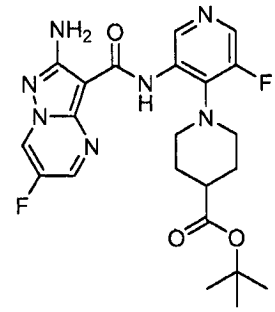
under suitable conditions to form an amide bond.

[00111] Still other embodiments of the present invention comprise provides a process for preparing the compound of formula **29**:



29

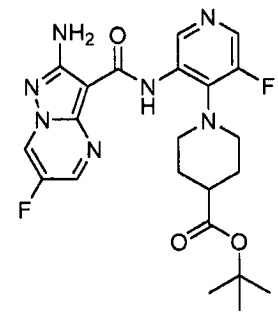
by reacting the compound of formula **28**:



28

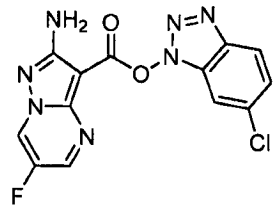
under suitable deprotection conditions to form the carboxylic acid.

[00112] Another embodiment provides a process for preparing a compound of formula **28**:



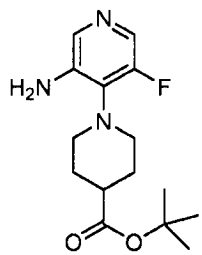
28

by reacting the compound of formula **6a***:



6a*

with a compound of formula **27**:



27

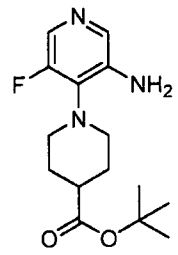
under suitable conditions to form an amide bond.

[00113] In some embodiments, suitable conditions for forming the amide bond comprise reacting the compound of formula **29** with the compound of formula **25** in the presence of an amide coupling partner, an aprotic solvent, and a base. In other embodiments, the aprotic solvent is independently selected from NMP, DMF, or tetrahydrofuran. In still other embodiments, the aprotic solvent is tetrahydrofuran. In another embodiment, the base is an aliphatic amine. In yet another embodiment, the base is DIPEA. In some embodiments, the amide coupling partner is independently selected from TBTU or TCTU. In one or more embodiments, the amide coupling partner is TCTU.

[00114] In other embodiments, suitable deprotection conditions comprise reacting the compound of formula **28** with an acid in the presence of a solvent. In some embodiments, the acid is HCl. In another embodiment, the solvent is 1,4-dioxane.

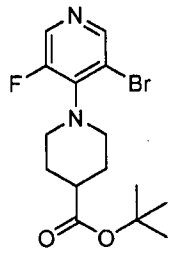
[00115] In yet another embodiment, suitable conditions for forming the amide bond comprise reacting the compound of formula **6a*** with the compound of formula **27** in an aprotic solvent under heat. In still other embodiments, the aprotic solvent is independently selected from NMP, pyridine, or DMF. In another embodiment, the aprotic solvent is pyridine. In some embodiments, the reaction is carried out at a temperature of at least 80°C.

[00116] Another aspect of the present invention provides a process of preparing a compound of formula **27**:



27

comprising the step of reacting a compound of formula **26**:

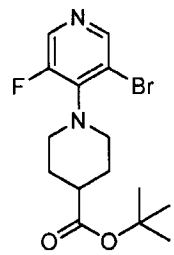


26

under suitable conditions to form an amine.

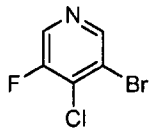
[00117] In some embodiments, suitable conditions to form an amine comprise reacting the compound of formula **27** under Buchwald-Hartwig amination conditions, known to those skilled in the art.

[00118] Yet another embodiment provides a process for preparing a compound of formula **26**:



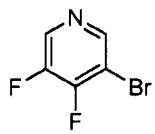
26

by 1) reacting a compound of formula **18**:



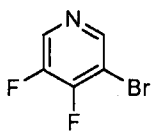
18

under suitable halogen exchange conditions to generate the compound of formula **32**



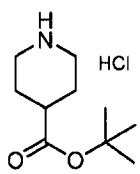
32 , and

2) reacting the compound of formula **32**:



32

with a compound of formula **22**:



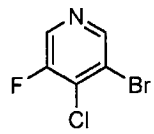
22

under suitable displacement conditions.

[00119] In some embodiments, suitable halogen exchange conditions comprise reacting the compound of formula **18** with potassium fluoride in the presence of an aprotic solvent and a phase transfer catalyst. In other embodiments, the aprotic solvent is independently selected from DMSO, DMF, or sulfolane. In still other embodiments, the phase transfer catalyst is Me_4NCl. In still other embodiments, suitable displacement conditions comprise reacting the compound of formula **32** with a compound of formula **22** in the presence of a base. In another embodiment, the base is an aliphatic amine. In some embodiments, the aliphatic

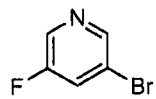
amine is DIPEA.

[00120] Other embodiments of the present invention provides a process for preparing a compound of formula **18**:



18

by reacting the compound of formula **31**:



31

under suitable halogenation conditions.

[00121] In some embodiments, suitable halogenation conditions comprise 1) reacting the compound of formula **31** with a base to generate an anion; and 2) reacting the anion with a chlorinating agent. In yet another embodiment, the base is LDA. In another embodiment, the chlorinating agent is 1,1,1,2,2,2-hexachloroethane.

[00122] For purposes of this application, it will be understood that the terms embodiment, example, and aspect are used interchangeably.

[00123] For purposes of this application, it will be understood that when two occurrences of J^Q, together with Q^1, form a bridged ring system, the two occurrences of J^Q are attached to separate atoms of Q^1. Additionally, when two occurrences of J^R, together with Q^2, form a bridged ring system, the two occurrences of J^R are attached to separate atoms of Q^2. Moreover, when two occurrences of J^T, together with Q^3, form a bridged ring system, the two occurrence of J^T are attached to separate atoms of Q^3. Further, when two occurrences of J^W, together with W, form a bridged ring system, the two occurences of J^W are attached to separate atoms of W. Finally, when two occurrences of J^G, together with Ring D, form a bridged ring system, the two occurrences of J^G are attached to separate atoms of Ring D.

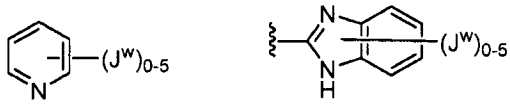
[00124] It will be understood by those skilled in the art that the arrow in $\rightarrow O$ represents a dative bond.

[00125] Compounds of this invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[00126] As described herein, a specified number range of atoms includes any integer therein. For example, a group having from 1-4 atoms could have 1, 2, 3, or 4 atoms.

[00127] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally herein, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

[00128] Unless otherwise indicated, a substituent connected by a bond drawn from the center of a ring means that the substituent can be bonded to any position in the ring. In example **i** below, for instance, J^w can be bonded to any position on the pyridyl ring. For bicyclic rings, a bond drawn through both rings indicates that the substituent can be bonded from any position of the bicyclic ring. In example **ii** below, for instance, J^w can be bonded to the 5-membered ring (on the nitrogen atom, for instance), and to the 6-membered ring.



i **ii**

[00129] The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00130] The term "dative bond", as used herein, is defined as the coordination bond formed upon interaction between molecular species, one of which serves as a donor and the other as an acceptor of the electron pair to be shared in the complex formed.

[00131] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched), branched, or cyclic, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation that has a single point of attachment to the rest of the molecule.

[00132] Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. Aliphatic groups may be linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Specific examples include, but are not limited to, methyl, ethyl, isopropyl, n-propyl, sec-butyl, vinyl, n-butenyl, ethynyl, and tert-butyl. Aliphatic groups may also be cyclic, or have a combination of linear or branched and cyclic groups. Examples of such types of aliphatic groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, -CH_2-cyclopropyl, $CH_2CH_2CH(CH_3)$-cyclohexyl.

[00133] The term "cycloaliphatic" (or "carbocycle" or "carbocyclyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Examples of cycloaliphatic groups include, but are not limited to, cycloalkyl and cycloalkenyl groups. Specific examples include, but are not limited to, cyclohexyl, cyclopropyl, and cyclobutyl.

[00134] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means

non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[00135] Examples of heterocycles include, but are not limited to, 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydro-imidazol-2-one.

[00136] Cyclic groups, (e.g. cycloaliphatic and heterocycles), can be linearly fused, bridged, or spirocyclic.

[00137] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[00138] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation. As would be known by one of skill in the art, unsaturated groups can be partially unsaturated or fully unsaturated. Examples of partially unsaturated groups include, but are not limited to, butene, cyclohexene, and tetrahydropyridine. Fully unsaturated groups can be aromatic, anti-aromatic, or non-aromatic. Examples of fully unsaturated groups include, but are not limited to, phenyl, cyclooctatetraene, pyridyl, thienyl, and 1-methylpyridin-2(1H)-one.

[00139] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[00140] The terms "haloalkyl", "haloalkenyl", "haloaliphatic", and "haloalkoxy" mean

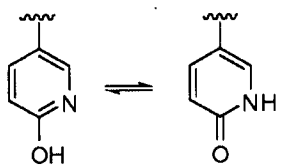
alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. This term includes perfluorinated alkyl groups, such as $-CF_3$ and $-CF_2CF_3$.

[00141] The terms "halogen", "halo", and "hal" mean F, Cl, Br, or I.

[00142] The term "aryl" used alone or as part of a larger moiety as in "arylalkyl", "arylalkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring".

[00143] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroarylalkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". Examples of heteroaryl rings include, but are not limited to, 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[00144] It shall be understood that the term "heteroaryl" includes certain types of heteroaryl rings that exist in equilibrium between two different forms. More specifically, for example, species such hydropyridine and pyridinone (and likewise hydroxypyrimidine and pyrimidinone) are meant to be encompassed within the definition of "heteroaryl."



[00145] The term "protecting group" and "protective group" as used herein, are interchangeable and refer to an agent used to temporarily block one or more desired functional groups in a compound with multiple reactive sites. In certain embodiments, a protecting group has one or more, or preferably all, of the following characteristics: a) is added selectively to a functional group in good yield to give a protected substrate that is b) stable to reactions occurring at one or more of the other reactive sites; and c) is selectively removable in good yield by reagents that do not attack the regenerated, deprotected functional group. As would be understood by one skilled in the art, in some cases, the reagents do not attack other reactive groups in the compound. In other cases, the reagents may also react with other reactive groups in the compound. Examples of protecting groups are detailed in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999 (and other editions of the book), the entire contents of which are hereby incorporated by reference. The term "nitrogen protecting group", as used herein, refers to an agent used to temporarily block one or more desired nitrogen reactive sites in a multifunctional compound. Preferred nitrogen protecting groups also possess the characteristics exemplified for a protecting group above, and certain exemplary nitrogen protecting groups are also detailed in Chapter 7 in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

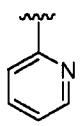
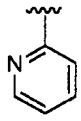
[00146] In some embodiments, a methylene unit of an alkyl or aliphatic chain is optionally replaced with another atom or group. Examples of such atoms or groups include, but are not limited to, nitrogen, oxygen, sulfur, -C(O)-, -C(=N-CN)-, -C(=NR)-, -C(=NOR)-, -SO-, and -SO_2-. These atoms or groups can be combined to form larger groups. Examples of such larger groups include, but are not limited to, -OC(O)-, -C(O)CO-, -CO_2-, -C(O)NR-, -C(=N-CN), -NRCO-, -NRC(O)O-, -SO_2NR-, -NRSO_2-, -NRC(O)NR-, -OC(O)NR-, and -NRSO_2NR-, wherein R is, for example, H or C_{1-6}aliphatic. It should be understood that these groups can be bonded to the methylene units of the aliphatic chain via single, double, or triple bonds. An example of an optional replacement (nitrogen atom in this case) that is bonded to the aliphatic chain via a double bond would be –CH_2CH=N-CH_3. In some cases, especially on the terminal end, an optional replacement can be bonded to the aliphatic group via a triple bond. One example of this would be $CH_2CH_2CH_2C{\equiv}N$. It should be understood that in this situation, the terminal nitrogen is not bonded to another atom.

[00147] It should also be understood that, the term "methylene unit" can also refer to

branched or substituted methylene units. For example, in an isopropyl moiety [-$CH(CH_3)_2$], a nitrogen atom (e.g. NR) replacing the first recited "methylene unit" would result in dimethylamine [-$N(CH_3)_2$]. In instances such as these, one of skill in the art would understand that the nitrogen atom will not have any additional atoms bonded to it, and the "R" from "NR" would be absent in this case.

[00148] Unless otherwise indicated, the optional replacements form a chemically stable compound. Optional replacements can occur both within the chain and/or at either end of the chain; i.e. both at the point of attachment and/or also at the terminal end. Two optional replacements can also be adjacent to each other within a chain so long as it results in a chemically stable compound. For example, a C_3 aliphatic can be optionally replaced by 2 nitrogen atoms to form –C–N≡N. The optional replacements can also completely replace all of the carbon atoms in a chain. For example, a C_3 aliphatic can be optionally replaced by -NR-, -C(O)-, and -NR- to form -NRC(O)NR- (a urea).

[00149] Unless otherwise indicated, if the replacement occurs at the terminal end, the replacement atom is bound to a hydrogen atom on the terminal end. For example, if a methylene unit of -$CH_2CH_2CH_3$ were optionally replaced with -O-, the resulting compound could be -OCH_2CH_3, -CH_2OCH_3, or -CH_2CH_2OH. In another example, if a methylene unit of -$CH_2CH_2CH_3$ was optionally replaced with -NH-, the resulting compound could be -$NHCH_2CH_3$, -CH_2NHCH_3, or -$CH_2CH_2NH_2$. It should be understood that if the terminal atom does not contain any free valence electrons, then a hydrogen atom is not required at the terminal end (e.g., -$CH_2CH_2CH{=}O$ or -$CH_2CH_2C{\equiv}N$).

[00150] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, geometric, conformational, and rotational) forms of the structure. For example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers are included in this invention. As would be understood to one skilled in the art, a substituent can freely rotate around any rotatable bonds. For example, a substituent drawn as  also represents  .

[00151] Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric,

geometric, conformational, and rotational mixtures of the present compounds are within the scope of the invention.

[00152] Unless otherwise indicated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[00153] Additionally, unless otherwise indicated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

Pharmaceutically Acceptable Salts, Solvates, Chlatrates, Prodrugs and Other Derivatives

[00154] The compounds described herein can exist in free form, or, where appropriate, as salts. Those salts that are pharmaceutically acceptable are of particular interest since they are useful in administering the compounds described below for medical purposes. Salts that are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of the invention or intermediates thereof.

[00155] As used herein, the term "pharmaceutically acceptable salt" refers to salts of a compound which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue side effects, such as, toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[00156] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. These salts can be prepared in situ during the final isolation and purification of the compounds.

[00157] Where the compound described herein contains a basic group, or a sufficiently basic bioisostere, acid addition salts can be prepared by 1) reacting the purified compound in its free-base form with a suitable organic or inorganic acid and 2) isolating the salt thus formed. In practice, acid addition salts might be a more convenient form for use and use of

the salt amounts to use of the free basic form.

[00158] Examples of pharmaceutically acceptable, non-toxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[00159] Where the compound described herein contains a carboxy group or a sufficiently acidic bioisostere, base addition salts can be prepared by 1) reacting the purified compound in its acid form with a suitable organic or inorganic base and 2) isolating the salt thus formed. In practice, use of the base addition salt might be more convenient and use of the salt form inherently amounts to use of the free acid form. Salts derived from appropriate bases include alkali metal (e.g., sodium, lithium, and potassium), alkaline earth metal (e.g., magnesium and calcium), ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00160] Basic addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum. The sodium and potassium salts are usually preferred. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Suitable inorganic base addition salts are prepared from metal bases, which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are

prepared from amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. Ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N, N'-dibenzylethylenediamine, chloroprocaine, dietanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, dicyclohexylamine and the like are examples of suitable base addition salts.

[00161] Other acids and bases, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid or base addition salts.

[00162] It should be understood that this invention includes mixtures/combinations of different pharmaceutically acceptable salts and also mixtures/combinations of compounds in free form and pharmaceutically acceptable salts.

[00163] The compounds described herein can also exist as pharmaceutically acceptable solvates (e.g., hydrates) and clathrates. As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds described herein. The term solvate includes hydrates (e.g., hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and the like).

[00164] As used herein, the term "hydrate" means a compound described herein or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00165] As used herein, the term "clathrate" means a compound described herein or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

[00166] In addition to the compounds described herein, pharmaceutically acceptable derivatives or prodrugs of these compounds may also be employed in compositions to treat or prevent the herein identified disorders.

[00167] A "pharmaceutically acceptable derivative or prodrug" includes any pharmaceutically acceptable ester, salt of an ester, or other derivative or salt thereof of a

compound described herein which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound described herein or an inhibitorily active metabolite or residue thereof. Particularly favoured derivatives or prodrugs are those that increase the bioavailability of the compounds when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

[00168] As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide a compound described herein. Prodrugs may become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds described herein that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed).

Abbreviations

[00169] The following abbreviations are used:

DMSO	dimethyl sulfoxide
DCM	dichloromethane
ATP	adenosine triphosphate
^{1}HNMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
LCMS	liquid chromatography-mass spectrometry
Rt	retention time
RT	room temperature
TEA	triethylamine
NMP	N-methyl-2-pyrrolidone

TFA	trifluoroacetic acid
Bp	boiling point
DMF	dimethylformamide
PTSA	*p*-Toluenesulfonic acid
DIPEA	N,N-diisopropylethylamine
mCPBA	meta-chloroperoxybenzoic acid
HOBt	hydroxybenzotriazole
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
T3P	Propylphosphonic anhydride
COMU	1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholino)]uroniumhexafluorophosphate
TCTU	[(6-chlorobenzotriazol-1-yl)oxy-(dimethylamino)methylene]-dimethyl-ammonium tetrafluoroborate
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
LDA	Lithium diisopropylamide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Compound Uses

[00170] One aspect of this invention provides compounds that are inhibitors of ATR kinase, and thus are useful for treating or lessening the severity of a disease, condition, or disorder in a subject or patient where ATR is implicated in the disease, condition, or disorder.

[00171] As used herein, the terms "subject" and "patient" are used interchangeably. The terms "subject" and "patient" refer to an animal, and more specifically a human. In one embodiment, the subject is a non-human animal such as a rat or dog. In a preferred embodiment, the subject is a human.

[00172] Another aspect of this invention provides compounds that are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abnormal cell proliferation. Such diseases include a proliferative or hyperproliferative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer and myeloproliferative disorders.

[00173] In some embodiments, said compounds are selected from the group consisting of a

compound of formula **I-A**. In another aspect, said compounds are selected from the group consisting of formula **I-B**. In another apect, said compounds are selected from the group consisting of formula **I** or **I-A-1**. The term "cancer" includes, but is not limited to the following cancers. Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: non-small cell, bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological/Female: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma,

intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma] hairy cell; lymphoid disorders; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma, undifferentiated thyroid cancer, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

[00174] In some embodiments, the cancer is selected from a cancer of the lung or the pancreas. In other embodiments, the cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer. In yet other embodiments, the cancer is selected from non-small cell lung cancer, small cell lung cancer, pancreatic cancer, biliary tract cancer, head and neck cancer, bladder cancer, colorectal cancer, glioblastoma, esophageal cancer, breast cancer, hepatocellular carcinoma, or ovarian cancer.

[00175] In some embodiments, the cancer is lung cancer. In other embodiments, the lung cancer is non-small cell lung cancer or small cell lung cancer. In another embodiment, the cancer is non-small cell lung cancer. In yet another embodiment, the non-small cell lung cancer is squamous non-small cell lung cancer.

[00176] Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions. In some embodiments, the cancer is selected from colorectal, thyroid, or breast cancer. In other embodiments, the cancer is triple negative breast cancer.

[00177] The term "myeloproliferative disorders", includes disorders such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, systemic mast cell disease, and hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia (APL), and acute lymphocytic leukemia (ALL).

Pharmaceutical Compositions

[00178] The present invention also provides compounds and compositions that are useful as inhibitors of ATR kinase.

[00179] One aspect of this invention provides pharmaceutically acceptable compositions that comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle.

[00180] The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[00181] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as

other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Combination Therapies

[00182] Another aspect of this invention is directed towards a method of treating cancer in a subject in need thereof, comprising administration of a compound of this invention or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent. In some embodiments, said method comprises the sequential or co-administration of the compound or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent.

[00183] As used herein, the term "in combination" or "co-administration" can be used interchangeably to refer to the use of more than one therapy (e.g., one or more therapeutic agents). The use of the term does not restrict the order in which therapies (e.g., therapeutic agents) are administered to a subject.

[00184] In some embodiments, said additional therapeutic agent is an anti-cancer agent. In other embodiments, said additional therapeutic agent is a DNA-damaging agent. In yet other embodiments, said additional therapeutic agent is selected from radiation therapy, chemotherapy, or other agents typically used in combination with radiation therapy or chemotherapy, such as radiosensitizers and chemosensitizers. In yet other embodiments, said additional therapeutic agent is ionizing radiation.

[00185] As would be known by one of skill in the art, radiosensitizers are agents that can be used in combination with radiation therapy. Radiosensitizers work in various different ways, including, but not limited to, making cancer cells more sensitive to radiation therapy, working in synergy with radiation therapy to provide an improved synergistic effect, acting additively with radiation therapy, or protecting surrounding healthy cells from damage caused by radiation therapy. Likewise chemosensitizers are agents that can be used in combination with chemotherapy. Similarly, chemosensitizers work in various different ways, including, but not limited to, making cancer cells more sensitive to chemotherapy, working in synergy with chemotherapy to provide an improved synergistic effect, acting additively to chemotherapy, or protecting surrounding healthy cells from damage caused by chemotherapy.

[00186] Examples of DNA-damaging agents that may be used in combination with

compounds of this invention include, but are not limited to Platinating agents, such as Carboplatin, Nedaplatin, Satraplatin and other derivatives; Topo I inhibitors, such as Topotecan, irinotecan/SN38, rubitecan and other derivatives; Antimetabolites, such as Folic family (Methotrexate, Pemetrexed and relatives); Purine antagonists and Pyrimidine antagonists (Thioguanine, Fludarabine, Cladribine, Cytarabine, Gemcitabine, 6-Mercaptopurine, 5-Fluorouracil (5FU) and relatives); Alkylating agents, such as Nitrogen mustards (Cyclophosphamide, Melphalan, Chlorambucil, mechlorethamine, Ifosfamide and relatives); nitrosoureas (eg Carmustine); Triazenes (Dacarbazine, temozolomide); Alkyl sulphonates (eg Busulfan); Procarbazine and Aziridines; Antibiotics, such as Hydroxyurea, Anthracyclines (doxorubicin, daunorubicin, epirubicin and other derivatives); Anthracenediones (Mitoxantrone and relatives); Streptomyces family (Bleomycin, Mitomycin C, actinomycin); and Ultraviolet light.

[00187] Other therapies or anticancer agents that may be used in combination with the inventive agents of the present invention include surgery, radiotherapy (in but a few examples, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, the DNA damaging agents listed herein, spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide.

[00188] A compound of the instant invention may also be useful for treating cancer in combination with any of the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®);

carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (dromostanolone®); dromostanolone propionate (masterone injection®); Elliott's B Solution (Elliott's B Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®);

pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); zoledronate (Zometa®) and vorinostat (Zolinza®).

[00189] For a comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

Compositions for Administration into a Subject

[00190] The ATR kinase inhibitors or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions, which comprise an amount of the ATR inhibitor effective to treat or prevent the diseases or conditions described herein and a pharmaceutically acceptable carrier, are another embodiment of the present invention.

[00191] The exact amount of compound required for treatment will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disorder, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of

factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00192] In some embodiments, these compositions optionally further comprise one or more additional therapeutic agents. For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known agents with which these compositions can be combined are listed above under the "Combination Therapies" section and also throughout the specification. Some embodiments provide a simultaneous, separate or sequential use of a combined preparation.

Modes of Administration and Dosage Forms

[00193] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the disorder being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. Alternatively, the dosing schedule of the compounds of the present invention may vary.

[00194] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan,

and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00195] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00196] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00197] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00198] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating

excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00199] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactosé, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00200] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00201] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice,

additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00202] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00203] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes, but is not limited to, subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[00204] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as

oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00205] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include, but are not limited to, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00206] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00207] The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00208] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00209] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but

are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00210] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[00211] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00212] The amount of protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions. Alternatively, a dosage of between 0.01 – 50 mg/kg body weight/dose of the inhibitor can be administered to a patient receiving these compounds.

[00213] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of inhibitor will also depend upon the particular compound in the composition.

Administering with another Agent

[00214] Depending upon the particular protein kinase-mediated conditions to be treated or

prevented, additional drugs, which are normally administered to treat or prevent that condition, may be administered together with the compounds of this invention.

[00215] Those additional agents may be administered separately, as part of a multiple dosage regimen, from the protein kinase inhibitor-containing compound or composition. Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor in a single composition.

[00216] Another aspect of this invention is directed towards a method of treating cancer in a subject in need thereof, comprising the sequential or co-administration of a compound of this invention or a pharmaceutically acceptable salt thereof, and an anti-cancer agent. In some embodiments, said anti-cancer agent is selected from Platinating agents, such as Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin and other derivatives; Topo I inhibitors, such as Camptothecin, Topotecan, irinotecan/SN38, rubitecan and other derivatives; Antimetabolites, such as Folic family (Methotrexate, Pemetrexed and relatives); Purine family (Thioguanine, Fludarabine, Cladribine, 6-Mercaptopurine and relatives); Pyrimidine family (Cytarabine, Gemcitabine, 5-Fluorouracil and relatives); Alkylating agents, such as Nitrogen mustards (Cyclophosphamide, Melphalan, Chlorambucil, mechlorethamine, Ifosfamide, and relatives); nitrosoureas (e.g. Carmustine); Triazenes (Dacarbazine, temozolomide); Alkyl sulphonates (e.g. Busulfan); Procarbazine and Aziridines; Antibiotics, such as Hydroxyurea; Anthracyclines (doxorubicin, daunorubicin, epirubicin and other derivatives); Anthracenediones (Mitoxantrone and relatives); Streptomyces family (Bleomycin, Mitomycin C, actinomycin) and Ultraviolet light.

[00217] Another embodiment provides administering a compound of this invention with an additional therapeutic agent that inhibits or modulates a base excision repair protein. In some embodiments, the base excision repair protein is selected from UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin. In other embodiments, the base excision repair protein is selected from PARP1, PARP2, or PolB. In yet other embodiments, the base excision repair protein is selected from PARP1 or PARP2. In some embodiments, the agent is selected from Olaparib (also known as AZD2281 or KU-0059436), Iniparib (also known as BSI-201 or SAR240550), Veliparib (also known as ABT-888), Rucaparib (also known as PF-01367338), CEP-9722, INO-1001, MK-4827, E7016,

BMN673, or AZD2461.

Biological Samples

[00218] As inhibitors of ATR kinase, the compounds and compositions of this invention are also useful in biological samples. One aspect of the invention relates to inhibiting ATR kinase activity in a biological sample, which method comprises contacting said biological sample with a compound described herein or a composition comprising said compound. The term "biological sample", as used herein, means an *in vitro* or an *ex vivo* sample, including, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. The term "compounds described herein" includes compounds of formula **I**, **I-A**, **I-A-1**, and **I-B**.

[00219] Inhibition of ATR kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, and biological specimen storage.

Study of Protein Kinases

[00220] Another aspect of this invention relates to the study of protein kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such protein kinases; and the comparative evaluation of new protein kinase inhibitors. Examples of such uses include, but are not limited to, biological assays such as enzyme assays and cell-based assays.

[00221] The activity of the compounds as protein kinase inhibitors may be assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of the activated kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/kinase complex and determining the amount of radiolabel bound, or by running a competition experiment where new inhibitors are incubated with the kinase bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of ATR is set forth in the Examples below.

[00222] Another aspect of the invention provides a method for modulating enzyme activity by contacting a compound described herein with ATR kinase.

Methods of Treatment

[00223] In one aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where ATR kinase is implicated in the disease state. In another aspect, the present invention provides a method for treating or lessening the severity of an ATR kinase disease, condition, or disorder where inhibition of enzymatic activity is implicated in the treatment of the disease. In another aspect, this invention provides a method for treating or lessening the severity of a disease, condition, or disorder with compounds that inhibit enzymatic activity by binding to the ATR kinase. Another aspect provides a method for treating or lessening the severity of a kinase disease, condition, or disorder by inhibiting enzymatic activity of ATR kinase with an ATR kinase inhibitor.

[00224] One aspect of the invention relates to a method of inhibiting ATR kinase activity in a patient, which method comprises administering to the patient a compound described herein, or a composition comprising said compound. In some embodiments, said method is used to treat or prevent a condition selected from proliferative and hyperproliferative diseases, such as cancer.

[00225] Another aspect of this invention provides a method for treating, preventing, or lessening the severity of proliferative or hyperproliferative diseases comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound, to a subject in need thereof. In some embodiments, said method is used to treat or prevent cancer. In some embodiments, said method is used to treat or prevent a type of cancer with solid tumors. In yet another embodiment, said cancer is selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: non-small cell, bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary

tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

[00226] In some embodiments, the cancer is selected from the cancers described herein. In some embodiments, said cancer is lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer. In other embodiments, the cancer is selected from a cancer of the lung or the pancreas.

[00227] In yet other embodiments, the cancer is selected from non-small cell lung cancer, small cell lung cancer, pancreatic cancer, biliary tract cancer, head and neck cancer, bladder

cancer, colorectal cancer, glioblastoma, esophageal cancer, breast cancer, hepatocellular carcinoma, or ovarian cancer.

[00228] In some embodiments, the lung cancer is small cell lung cancer and the additional therapeutic agents are cisplatin and etoposide. In other examples, the lung cancer is non-small cell lung cancer and the additional therapeutic agents are gemcitabine and cisplatin. In yet other embodiments, the non-small cell lung cancer is squamous non-small cell lung cancer. In another embodiment, the cancer is breast cancer and the additional therapeutic agent is cisplatin. In other embodiments, the cancer is triple negative breast cancer.

[00229] In certain embodiments, an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective in order to treat said disease. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of said disease.

[00230] One aspect provides a method for inhibiting ATR in a patient comprising administering a compound described herein as described herein. Another embodiment provides a method of treating cancer comprising administering to a patient a compound described herein, wherein the variables are as defined herein.

Some embodiments comprising administering to said patient an additional therapeutic agent selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said compound as a single dosage form or separately from said compound as part of a multiple dosage form.

[00231] In some embodiments, said DNA-damaging agent is selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonates, an antimetabolite, or an antibiotic. In other embodiments, said DNA-damaging agent is selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.

[00232] Examples of Platinating agents include Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Satraplatin and other derivatives. Other platinating agents include Lobaplatin, and Triplatin. Other platinating agents include Tetranitrate, Picoplatin, Satraplatin, ProLindac and Aroplatin.

[00233] Examples of Topo I inhibitor include Camptothecin, Topotecan, irinotecan/SN38,

rubitecan and other derivatives. Other Topo I inhibitors include Belotecan.

[00234] Examples of Topo II inhibitors include Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin and Teniposide.

[00235] Examples of Antimetabolites include members of the Folic family, Purine family (purine antagonists), or Pyrimidine family (pyrimidine antagonists). Examples of the Folic family include methotrexate, pemetrexed and relatives; examples of the Purine family include Thioguanine, Fludarabine, Cladribine, 6-Mercaptopurine, and relatives; examples of the Pyrimidine family include Cytarabine, gemcitabine, 5-Fluorouracil (5FU) and relatives.

[00236] Some other specific examples of antimetabolites include Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine and Hydroxyurea.

[00237] Examples of alkylating agents include Nitrogen mustards, Triazenes, alkyl sulphonates, Procarbazine and Aziridines. Examples of Nitrogen mustards include Cyclophosphamide, Melphalan, Chlorambucil and relatives; examples of nitrosoureas include Carmustine; examples of triazenes include Dacarbazine and temozolomide; examples of alkyl sulphonates include Busulfan.

[00238] Other specific examples of alkylating agents include Mechlorethamine, Cyclophosphamide, Ifosfamide, Trofosfamide, Chlorambucil, Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin and Plicamycin.

[00239] Examples of antibiotics include Mitomycin, Hydroxyurea; Anthracyclines, Anthracenediones, Streptomyces family. Examples of Anthracyclines include doxorubicin, daunorubicin, epirubicin and other derivatives; examples of Anthracenediones include Mitoxantrone and relatives; examples of Streptomyces family inclue Bleomycin, Mitomycin C, and actinomycin.

[00240] In certain embodiments, said platinating agent is Cisplatin or Oxaliplatin; said Topo I inhibitor is Camptothecin; said Topo II inhibitor is Etoposide; and said antibiotic is Mitomycin. In other embodiments, said platinating agent is selected from Cisplatin,

Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from a member of the Folic Family, the Purine Family, or the Pyrimidine Family; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, or Streptomyces family.

[00241] In some embodiments, the additional therapeutic agent is ionizing radiation. In other embodiments, the additional therapeutic agent is Cisplatin or Carboplatin. In yet other embodiments, the additional therapeutic agent is Etoposide. In yet other embodiments, the additional therapeutic agent is Temozolomide.

[00242] In certain embodiments, the additional therapeutic agent is selected from one or more of the following: Cisplatin, Carboplatin, gemcitabine, Etoposide, Temozolomide, or ionizing radiation.

[00243] Another embodiment provides methods for treating pancreatic cancer by administering a compound described herein in combination with another known pancreatic cancer treatment. One aspect of the invention includes administering a compound described herein in combination with gemcitabine. In some embodiments, the pancreatic cancer comprises one of the following cell lines: PSN-1, MiaPaCa-2 or Panc-1. According to another aspect, the cancer comprises one of the following primary tumor lines: Panc-M or MRC5.

[00244] Another aspect of the invention includes administering a compound described herein in combination with radiation therapy. Yet another aspect provides a method of abolishing radiation-induced G2/M checkpoint by administering a compound described herein in combination with radiation treatment.

[00245] Another aspect provides a method of treating pancreatic cancer by administering to pancreatic cancer cells a compound described herein in combination with one or more cancer therapies. In some embodiments, the compound is combined with chemoradiation, chemotherapy, and/or radiation therapy. As would be understood by one of skill in the art, chemoradiation refers to a treatment regime that includes both chemotherapy (such as gemcitabine) and radiation. In some embodiments, the chemotherapy is gemcitabine.

[00246] Yet another aspect provides a method of increasing the sensitivity of pancreatic cancer cells to a cancer therapy selected from gemcitabine or radiation therapy by

administering a compound described herein in combination with the cancer therapy.

[00247] In some embodiments, the cancer therapy is gemcitabine. In other embodiments, the cancer therapy is radiation therapy. In yet another embodiment the cancer therapy is chemoradiation.

[00248] Another aspect provides a method of inhibiting phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell comprising administering a compound described herein after treatment with gemcitabine (100 nM) and/or radiation (6 Gy) to a pancreatic cancer cell.

[00249] Another aspect provides method of radiosensitizing hypoxic PSN-1, MiaPaCa-2 or PancM tumor cells by administering a compound described herein to the tumor cell in combination with radiation therapy.

[00250] Yet another aspect provides a method of sensitizing hypoxic PSN-1, MiaPaCa-2 or PancM tumor cells by administering a compound described herein to the tumor cell in combination with gemcitabine.

[00251] Another aspect provides a method of sensitizing PSN-1 and MiaPaCa-2 tumor cells to chemoradiation by administering a compound described herein to the tumor cells in combination with chemoradiation.

[00252] Another aspect provides a method of disrupting damage-induced cell cycle checkpoints by administering a compound described herein in combination with radiation therapy to a pancreatic cancer cell.

[00253] Another aspect provides a method of inhibiting repair of DNA damage by homologous recombination in a pancreatic cancer cell by administering a compound described herein in combination with one or more of the following treatments: chemoradiation, chemotherapy, and radiation therapy.

[00254] In some embodiments, the chemotherapy is gemcitabine.

[00255] Another aspect provides a method of inhibiting repair of DNA damage by homologous recombination in a pancreatic cancer cell by administering a compound described herein in combination with gemcitabine and radiation therapy.

[00256] In some embodiments, the pancreatic cancer cells are derived from a pancreatic cell line selected from PSN-1, MiaPaCa-2 or Panc-1.

[00257] In other embodiments, the pancreatic cancer cells are in a cancer patient.

[00258] Another aspect of the invention provides a method of treating non-small cell lung cancer comprising administering to a patient a compound described herein in combination with one or more of the following additional therapeutic agents: Cisplatin or Carboplatin, Etoposide, and ionizing radiation. Some embodiments comprise administering to a patient a compound described herein in combination with Cisplatin or Carboplatin, Etoposide, and ionizing radiation. In some embodiments the combination is Cisplatin, Etoposide, and ionizing radiation. In other embodiments the combination is Carboplatin, Etoposide, and ionizing radiation.

[00259] Another embodiment provides a method of promoting cell death in cancer cells comprising administering to a patient a compound described herein, , or a composition comprising said compound.

[00260] Yet another embodiment provides a method of preventing cell repair of DNA damage in cancer cells comprising administering to a patient a compound described herein, or a composition comprising said compound. Yet another embodiment provides a method of preventing cell repair caused by of DNA damage in cancer cells comprising administering to a patient a compound of formula I, or composition comprising said compound.

[00261] Another embodiment provides a method of sensitizing cells to DNA damaging agents comprising administering to a patient a compound described herein, or a composition comprising said compound.

[00262] In some embodiments, the method is used on a cancer cell having defects in the ATM signaling cascade. In some embodiments, said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1. In other embodiments, said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX. According to another embodiment, the method is used on a cancer, cancer cell, or cell expressing DNA damaging oncogenes.

[00263] In another embodiment, the cell is a cancer cell expressing DNA damaging oncogenes. In some embodiments, said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.

[00264] According to another embodiment, the method is used on a cancer, cancer cell, or cell has a defect in a protein involved in base excision repair ("base excision repair protein").

There are many methods known in the art for determining whether a tumor has a defect in base excision repair. For example, sequencing of either the genomic DNA or mRNA products of each base excision repair gene (e.g., UNG, PARP1, or LIG1) can be performed on a sample of the tumor to establish whether mutations expected to modulate the function or expression of the gene product are present (Wang et al., Cancer Research 52:4824 (1992)). In addition to the mutational inactivation, tumor cells can modulate a DNA repair gene by hypermethylating its promoter region, leading to reduced gene expression. This is most commonly assessed using methylation-specific polymerase chain reaction (PCR) to quantify methylation levels on the promoters of base excision repair genes of interest. Analysis of base excision repair gene promoter methylation is available commercially (http://www.sabiosciences.com/dna_methylation_product/HTML/MEAH-421A.html).

[00265] Finally, the expression levels of base excision repair genes can be assessed by directly quantifying levels of the mRNA and protein products of each gene using standard techniques such as quantitative reverse transcriptase-coupled polymerase chain reaction (RT-PCR) and immunhohistochemistry (IHC), respectively (Shinmura et al., Carcinogenesis 25: 2311 (2004); Shinmura et al., Journal of Pathology 225:414 (2011)).

[00266] In some embodiments, the base excision repair protein is UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.

[00267] In sorme embodiments, the base excision repair protein is PARP1, PARP2, or PolB. In other embodiments, the base excision repair protein is PARP1 or PARP2.

[00268] The methods described above (gene sequence, promoter methylation and mRNA expression) may also be used to characterize the status (e.g., expression or mutation) of other genes or proteins of interesting, such DNA-damaging oncogenes expressed bv a tumor or defects in the ATM signaling cascade of a cell.

[00269] Yet another embodiment provides use of a compound described herein as a radio-sensitizer or a chemo-sensitizer.

[00270] Yet other embodiment provides use of a compound of formula I as a single agent (monotherapy) for treating cancer. In some embodiments, the compounds of formula I are used for treating patients having cancer with a DNA-damage response (DDR) defect. In

other embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, or H2AX.

Compounds and compositions for Use

[00271] One embodiment provides a compound or composition as described herein for use as a radio-sensitizer or a chemo-sensitizer. Another embodiment provides a compound or composition as described herein for use as a single agent (monotherapy) for treating cancer.

[00272] Another embodiment provides a compound or composition as described herein for treating patients having cancer with a DNA-damage response (DDR) defect. In some embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, or H2AX. In other embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1.

[00273] Another embodiment provides compounds or compositions described herein for treating cancer. In some embodiments, the compound or composition is further combined with an additional therapeutic agent described herein. In some embodiments, the compound or composition is further combined with a DNA damaging agent described herein.

[00274] In some embodiments, the cancer has a defect in a pathway described herein.

Manufacture of Medicaments

[00275] One embodiment provides the use of a compound or composition described herein for the manufacture of a medicament for use as a radio-sensitizer or a chemo-sensitizer. Another embodiment provides the use of a compound or composition described herein for the manufacture of a medicament for the manufacture of a medicament for use as a single agent (monotherapy) for treating cancer.

[00276] Yet another embodiment provides the use of a compound or composition described herein for the manufacture of a medicament for the manufacture of a medicament for treating patients having cancer with a DNA-damage response (DDR) defect.

[00277] In some embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, or H2AX. In other embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1.

[00278] Another embodiment provides the use of a compound or composition described herein for the manufacture of a medicament for treating cancer. In some embodiments, the compound or composition is combined with an additional therapeutic agent, such as a DNA damaging agent, described herein. In another embodiment, the cancer has a defect in a pathway described herein.

EXPERIMENTAL MATERIALS AND METHODS

[00279] All commercially available solvents and reagents were used as received. Microwave reactions were carried out using a CEM Discovery microwave. Flash Chromatography, e.g., was carried out on an ISCO© Combiflash^{R} Companion^{TM} system eluting with a 0 to 100% EtOAc/petroleum ether gradient. Other methods known in the art were also utilized to perform Flash Chromotography. Samples were applied pre-absorbed on silica. Where stated, supercritical fluid chromatography (SFC) was performed on a Berger Minigram SFC machine. All ^{1}H NMR spectra were recorded using a Bruker Avance III 500 instrument at 500 MHz. MS samples were analyzed on a Waters SQD mass spectrometer with electrospray ionization operating in positive and negative ion mode. Samples were introduced into the mass spectrometer using chromatography. All final products had a purity ≥95%, unless specified otherwise in the experimental details. HPLC purity was measured on a Waters Acquity UPLC system with a Waters SQD MS instrument equipped with a Waters UPLC BEH C8 1.7 μm, 2.1 x 50 mm column and a Vanguard BEH C8 1.7 μm, 2.1 x 5 mm guard column.

[00280] As used herein, the term "Rt(min)" refers to the HPLC retention time, in minutes, associated with the compound. Unless otherwise indicated, the HPLC methods utilized to obtain the reported retention times are as described below:

HPLC Method A

Instrument: Waters Acquity UPLC-MS;

Column: Waters UPLC BEH C8 1.7 μm, 2.1 x 50 mm with Vanguard BEH C8 1.7 μm, 2.1 x 5 mm guard column;

Column temperature: 45°C;

Mobile Phase A: 10mM ammonium formate in water:acetonitrile 95:5, pH 9;

Mobile Phase B: acetonitrile;

Detection: 210-400 nm

Gradient: initial: 2% B, 0-1.15 min: 2% B to 98% B, 1.15-1.35 min: hold at 98% B, 1.35-1.40 min: 98% B to 2% B, 1.40-1.50 min: hold at 2% B;

Flow rate: 1.0 mL/minute;

HPLC Method B

Instrument: Waters Acquity UPLC-MS;

Column: Waters UPLC BEH C8 1.7 μm, 2.1 x 50 mm with Vanguard BEH C8 1.7 μm, 2.1 x 5 mm guard column;

Column temperature: 45°C;

Mobile Phase A: 10mM ammonium formate in water:acetonitrile 95:5, pH 9;

Mobile Phase B: acetonitrile;

Detection: 210-400 nm;

Gradient: 0-0.40 min: 2% B, 0.40-4.85 min: 2% B to 98% B, 4.85-4.90 min: 98% B to 2% B, 4.90-5.00 min: hold at 2% B;

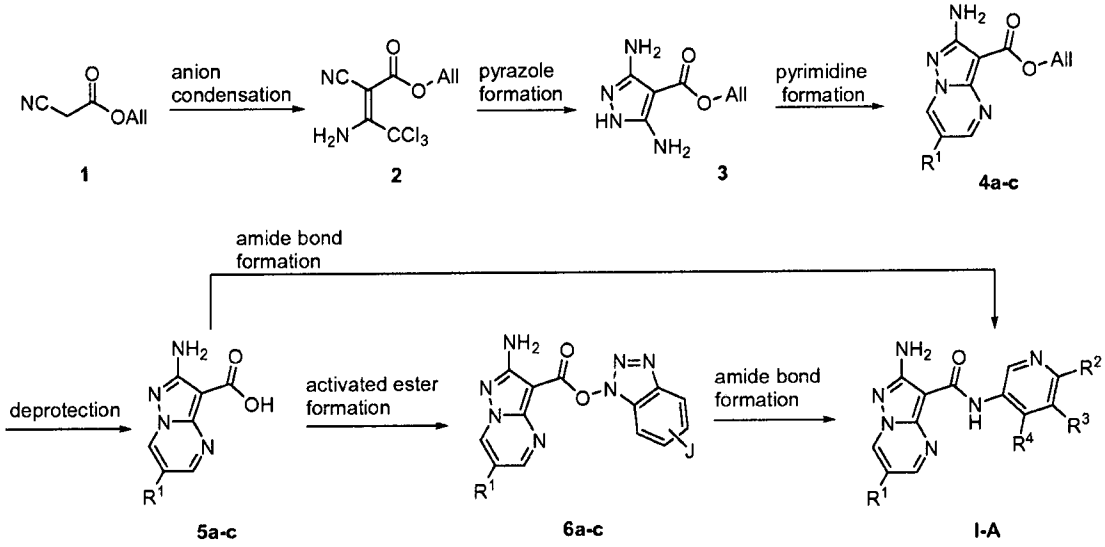
Flow rate: 0.6 mL/minute.

EXAMPLES AND SCHEMES

[00281] The compounds of the disclosure may be prepared in light of the specification using steps generally known to those of ordinary skill in the art. Those compounds may be analyzed by known methods, including but not limited to LCMS (liquid chromatography mass spectrometry) and NMR (nuclear magnetic resonance). The following generic schemes and examples illustrate how to prepare the compounds of the present disclosure. The examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

[00282] It will be understood that when an inconsistency exists between the chemical structure and the corresponding name provided herein, the chemical structure will control.

Scheme 1: General approach for the preparation of compounds I-A



[00283] Compounds of this invention can be synthesised according to methods similar to the one depicted in **Scheme 1**.

[00284] The anion of commercially available allyl cyanoacetate **1** can react with trichloroacetonitrile to provide intermediate **2**. In the anion condensation step, the anion of commercially available allyl cyanoacetate **1** can be generated with a base such as potassium acetate in an appropriate solvent such as an alcohol (e.g., isopropylalcohol). The anion then reacts with trichloroacetonitrile at room temperature (specific details are given in **Preparation 1**, *Step 1* below).

[00285] Intermediate **2** then reacts with hydrazine to form the diaminopyrazole **3**. In the pyrazole formation step, intermediate **2** is reacted with hydrazine (or its hydrate) in an aprotic solvent, such as DMF, to provide the diaminopyrazole **3**. The reaction occurs under basic conditions (e.g., in the presence of potassium acetate or AcONa) with heating (e.g., 110°C) to ensure complete cyclisation (specific details are given in **Preparation 1**, *Step 2* below).

[00286] Intermediate **3** can further be condensed with a dielectrophilic coupling partner to form the pyrimidine **4a-c**. In the pyrimidine formation step, intermediate **3** is reacted with a 1,3-dielectrophilic species (e.g., a 1,3-dialdehyde or a 3-(dialkylamino)-prop-2-enal) in various types of solvents (e.g., DMF or DMSO/water) to furnish the bicyclic cores **4a-c**. When one or two of the electrophilic centers is protected/masked (e.g., aldehyde masked as a ketal), introduction of a sulfonic acid (e.g., PTSA) is required to liberate the reactive functional group (specific details are given in **Preparation 4**, *Step 1* below).

[00287] Deprotection, e.g, via hydrolysis, of the allyl ester leads to the carboxylic acids **5a-c**. In the deprotection step, compound **4a-c** is subjected to hydrolytic conditions that are known to those skilled in the art. For example, treatment of **4a-c** with phenylsilane or 4-methylbenzenesulfinate in the presence of a catalytic amount of palladium (e.g., $Pd(PPh_3)_4$) leads to the formation of the corresponding carboxylic acid **5a-c**. Alternatively, compounds **4a-c** could be treated with aqueous alkali (e.g., NaOH, KOH) to produce acids **5a-c** (specific details are given in **Preparation 4**, *Step 2* below).

[00288] In the activated ester formation step, the carboxylic acids **5a-c** are reacted with amide coupling agents known to those skilled in the art. When the coupling agent is chosen appropriately, the reactions can proceed rapidly (~1h) at room temperature in the presence of an organic base (e.g., triethylamine, DIPEA) to provide the activated esters **6a-c**. For example, when the amide coupling agents TBTU [J=H] or TCTU [J=Cl] are used, compounds **6a-c** are obtained readily by filtration of the reaction mixture (specific details are given in **Preparation 4**, *Step 3* below).

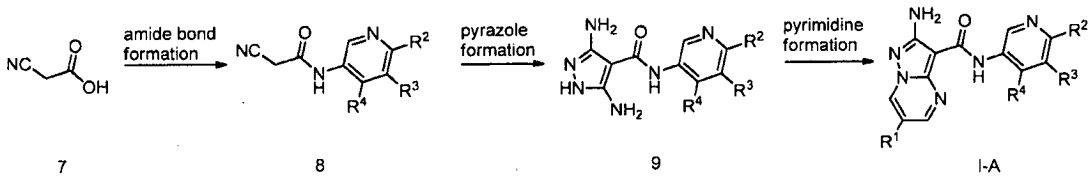
[00289] Formation of the activated esters **6a-c** prior to the amide bond formation to prepare **I-A** is generally preferred, although a direct conversion of **5a-c** into the compounds of formula **I-A** of this invention is also possible. Alternative activated esters can also be utilised (isolated or formed *in situ*) and will be known to those skilled in the art (e.g., using TBTU, TCTU, HATU, T3P, COMU coupling agents).

[00290] In the amide bond formation step, activated esters **6a-c** can react with a substituted 3-aminopyridine to provide compounds of formula **I-A** of this invention. The reaction conditions for the amide coupling are generally in an aprotic solvent (e.g., NMP, pyridine, DMF, etc ...) with heating (e.g., $\geq$ 90°C) (specific details are given in **Example 1** below). The 3-aminopyridine may be further functionalized following amide bond formation.

[00291] Alternatively, the two steps described above can be combined: carboxylic acids **5a-c** can be used as starting points for the amide bond formation, the activated esters being generated in situ, using the same amide couplings agents as those described above. Compounds **I-A** of this invention are isolated in a similar manner to the one described above (specific details are given in **Example 3a** below).

[00292] Compounds of formula **I**, **I-A-1**, and **I-B** can also be prepared using similar methods.

Scheme 2: Alternative approach for the preparation of compounds I-A



[00293] Alternatively, compounds of the present disclosure can be prepared according to methods similar to the one depicted in **Scheme 2**.

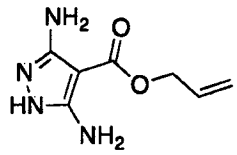
[00294] The amide **8** can readily be prepared from commercially available cyanoacetic acid **7**. In the amide bond formation step, cyanoacetic acid **7** can react with a substituted 3-aminopyridine to provide compounds **8** of this invention. The reaction conditions for the amide coupling are generally in an aprotic solvent (e.g., DCM, NMP, DMF, etc), in the presence of an organic base, such as an aliphatic amine, (e.g., triethylamine or DIPEA) and an amide coupling agent known to those skilled in the art: for example EDCI, TBTU, COMU, T3P, etc (specific details are given in **Example 3e**, *step 1* below).

[00295] In the pyrazole formation step, the anion of cyanoamide **8** can be generated with a base (such as potassium or sodium acetate) in an appropriate solvent such as an alcohol (e.g., ethanol). The anion then reacts with trichloroacetonitrile at room temperature (specific details are given in **Example 3e**, *step 2* below). The resulting solid, which can be collected by filtration, is then reacted with hydrazine (or its hydrate) in an aprotic solvent, such as DMF or NMP, to provide the diaminopyrazole **9**, the latter being further condensed with a dielectrophilic coupling partner to form the pyrimidine portion of the compounds of formula **I-A** of this invention.

[00296] In the pyrimidine formation step, intermediate **9** is reacted with a 1,3-dielectrophilic species (e.g., a 1,3-dialdehyde or a 3-(dialkylamino)-prop-2-enal) in various types of solvents (e.g., iPrOH/water, DMF, or DMSO/water) to furnish the desired products **I-A**. When one or two of the electrophilic centers is protected/masked (e.g., aldehyde masked as a ketal), introduction of a sulfonic acid (e.g., PTSA) is required to liberate the reactive functional group. (specific details are given in **Example 3e**, *step 3* below).

[00297] Compounds of formula **I**, **I-A-1**, and **I-B** can also be prepared using similar methods.

Preparation 1: Allyl 3,5-diamino-1*H*-pyrazole-4-carboxylate



3

Step 1: allyl 3-amino-4,4,4-trichloro-2-cyanobut-2-enoate **2**

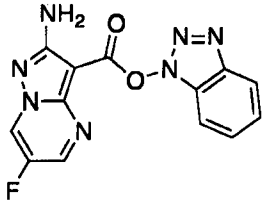
[00298] To a solution of KOAc (589.4 g, 6.006 mol) in isopropanol (3 L) was added allyl cyanoacetate (429.4 g, 403.2 mL, 3.432 mol) and the reaction mixture was cooled to 5°C. Trichloroacetonitrile (495.5 g, 3.432 mol) was added in 50 mL portions, maintaining temperature below 15°C. The reaction mixture was then allowed to warm to 20°C and stirred for 3 h. Water (~4 L) was added to dissolve the inorganic materials and precipitate out the desired product. The mixture was stirred for 20 minutes and the solid was isolated by filtration under vacuum. This solid was filtered, washed with water (2 x 0.5 L) and dried in a vacuum oven overnight at 40°C to afford allyl 3-amino-4,4,4-trichloro-2-cyanobut-2-enoate **2** as an off-white powder (787 g, 85%).

Step 2: Allyl 3,5-diamino-1H-pyrazole-4-carboxylate **3**

[00299] To a suspension of allyl 3-amino-4,4,4-trichloro-2-cyano-but-2-enoate **2** (619 g, 2.297 mol) and KOAc (676.3 g, 6.891 mol) in DMF (2.476 L) at 0°C was slowly added hydrazine hydrate (172.5 g, 167.6 mL, 3.446 mol) over 15 min. The reaction mixture was then stirred at ambient temperature for 2 h, at which stage ^{1}H NMR shows complete consumption of the starting material. Reaction mixture was then heated overnight at 110°C before being allowed to cool to ambient and stirred for another 48h. The mixture was filtered through a sintered glass funnel to remove the precipitated solid and the filtrate was evaporated under reduced pressure to give a thick liquid. DCM (approx 2 L) was added, and the mixture filtered again to remove additional solids that have precipitated. The filtrate was purified through a 1 kg silica gel plug (gradient of DCM/MeOH as an eluent), and the solvent was removed to afford an orange solid which was suspended in acetonitrile and heated at about 70°C until all the solid went into solution, at which point the solution was allowed to

cool to ambient temperature, then to 2°C. The precipitate that formed was isolated by filtration under vacuum, washed with chilled MeCN (~50 mL) and dried to constant mass in a vacuum oven to furnish the title compound as an off-white powder (171.2 g, 41%).

Preparation 2a: 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxylate



6a

Step 1: allyl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4a**

[00300] To a suspension of allyl 3,5-diamino-1H-pyrazole-4-carboxylate **3** (42.72 g, 234.5 mmol) in DMSO (270.8 mL) / Water (270.8 mL), was added p-TsOH hydrate (46.72 g, 245.6 mmol) and 3-(diisopropylamino)-2-fluoro-prop-2-enal (described in *Tetrahedron Letters*, 33(3), 357-60; 1992) (38.69 g, 223.3 mmol). The reaction mixture was heated to 100°C for 3h during which time a solid slowly precipitated out of solution. The orange suspension was allowed to cool down to RT overnight. The solid was filtered, washed with water and dried under vacuum to give allyl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4a** as a sand solid (45.05 g, 85% yield).

Step 2: 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a**

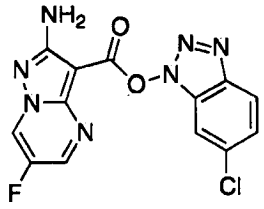
[00301] To a suspension of allyl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4a** (45 g, 190.5 mmol) in DCM (1.35 L) was added phenylsilane (41.23 g, 46.96 mL, 381.0 mmol), followed by $Pd(PPh_3)_4$ (8.805 g, 7.620 mmol). The reaction was stirred at room temperature for 2h 30min. The reaction mixture was filtered and the solid was washed with DCM to give a light yellow solid (43.2g). This solid was triturated further in DCM (225 mL) at RT for 45 min, then filtered and dried overnight under vacuum to provide 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a** as a light yellow solid (37.77g, 100% yield).

[00302] In an alternative method, 4-methylbenzenesulfinate (anhydrous, 1.2 eqv, 22.6g, 127mmol) was suspended in dry DMSO (20 vol, 500ml). The stirred mixture was warmed to 30°C under a nitrogen atmosphere. Upon complete dissolution $Pd(PPh_3)_4$ (2 mol%, 2.4g, 2.1 mmol) was added. The mixture was stirred for 10 min at 25-30°C after which time a turbid yellow solution was present. Allyl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate (25g, 105.8mmol) was added portionwise, maintaining the temperature at 25-30°C. Once addition was complete the cloudy solution was stirred until the reaction was complete by HPLC (2-3 hrs). A heavy precipitate formed after 15 minutes post addition of the substrate. The mixture became thicker as the reaction proceeded. The reaction mixture was diluted with water (125 ml) and 2M HCl (66 ml) was added slowly, maintaining the temperature at 25-30°C. The slurry was stirred for 30 minutes, then filtered. The filtration was slow (2hrs). The resulting solid was washed with water, then dried on the sinter. The solid was slurried in DCM (8 vol) for 1hr. The solid was filtered (rapid filtration) and washed with DCM. The solid was re-slurried in chloroform (8 vol) for 1 hr. The acid was filtered and dried on the sinter. It was further dried in a vacuum oven at 50°C for 24 hrs. The product was obtained as an off-white solid (18.6g, 85%); 1H NMR (500 MHz, DMSO-d6) δ 12.14 (1H, brs), 9.31 (1H, dd), 8.69 (1H, m), 6.47 (2H, brS); 19F NMR (500 MHz, DMSO-d6) δ -153.65; MS (ES+) 197.1.

Step 3: 1H-benzo[d][1,2,3]triazol-1-yl 2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxylate **6a**

[00303] To a suspension of 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a** (20 g, 102.0 mmol) in chloroform (300 mL) was added Et_3N (11.35 g, 15.63 mL, 112.2 mmol). The suspension was stirred for ~ 5mins and then (benzotriazol-1-yloxy-dimethylamino-methylene)-dimethyl-ammonium Boron Tetrafluoride was added (32.75 g, 102.0 mmol). The suspension was heated to 60°C for 1h before the thick suspension was allowed to cool down to RT. The resulting suspension was filtered, washed with chloroform (200 mL) and dried under vacuum overnight to afford the title compound **6a** as a light yellow powder (32.5g, 88%).

Preparation 2b: (6-chlorobenzotriazol-1-yl)-2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate 6a*

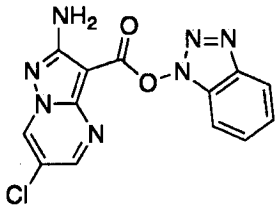


6a*

[00304] In a 2.5 L three-necked flask equipped with stirrer bar, condenser, nitrogen line and Hanna temperature probe was charged 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a** (60 g, 305.9 mmol), chloroform (900.0 mL) and triethylamine (32.44 g, 44.68 mL, 320.6 mmol). [(6-chlorobenzotriazol-1-yl)oxy-(dimethylamino)methylene]-dimethyl-ammonium (Boron Tetrafluoride Ion (1)) (87.00 g, 244.7 mmol) was added portionwise over 5 mins (internal dropped from 22.7 to 21.5°C on complete addition). Mixture heated at 60°C (internal temp) for 2h, still a cream suspension. Mixture cooled to room temperature then solid collected by filtration, washed well with chloroform (until filtrate runs essentially colourless) and dried by suction to leave product **6a*** as a cream solid (82.2g, 77% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (dd, 1H), 8.91 (d, 1H), 8.22 (dd, 1H), 8.09 (dd, 1H), 7.57 (dd, 1H) and 6.87 (s, 2H). MS (ES+) 348.1.

[00305] In an alternative method, 2-Amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid **5a** (30g, 153 mmol) was slurried in acetonitrile (540ml). Triethylamine (22.5ml, 153mmol) was added, followed by [(6-chlorobenzotriazol-1yl)oxy-(dimethylamino)methylene]-dimethylammonium tetrafluoroborate (TCTU, 54.4g, 153mmol). The mixture was stirred at room temperature for 2 hrs. The product was isolated by filtration-the filter cake was washed with acetonitrile (2x60ml) (49.3g, 93%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (dd, 1H), 8.91 (d, 1H), 8.22 (dd, 1H), 8.09 (dd, 1H), 7.57 (dd, 1H) and 6.87 (s, 2H); 19F NMR (500 MHz, DMSO-d6) δ -150.1; MS (ES+) 348.1.

Preparation 3: 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate



6b

Step 1: 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4b**

[00306] To a suspension of allyl 3,5-diamino-1H-pyrazole-4-carboxylate **3** (1 g, 5.489 mmol) in DMF (5 mL) was added (Z)-2-chloro-3-dimethylamino-prop-2-enylidene]-dimethyl-ammonium hexafluorophosphate (1.683 g, 5.489 mmol), followed by triethylamine (722.1 mg, 994.6 µL, 7.136 mmol). The reaction mixture was heated to 60°C for 4h during which time a solid slowly precipitated out of solution. The brown suspension was allowed to cool down to RT. The solid was filtered, washed with water and dried under vacuum to give allyl 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4b** as a brown solid (1.092 g, 72% yield).

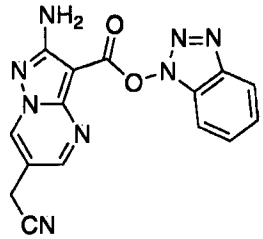
Step 2: 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5b**

[00307] To a suspension of allyl 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4b** (1 g, 3.96 mmol) in DCM (15 mL) was added phenylsilane (856.6 mg, 0.9756 mL, 7.916 mmol), followed by $Pd(PPh_3)_4$ (182.9 mg, 0.1583 mmol). The reaction was stirred at room temperature for 7h. The reaction mixture was filtered and the solid was washed with DCM to give a light yellow solid (43.2g). This solid was triturated further in DCM (225 mL) at RT for 45 min, then filtered and dried overnight under vacuum to provide 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5b** as a yellow solid (791m, 94% yield).

Step 3: 1H-benzo[d][1,2,3]triazol-1-yl 2-amino-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate **6b**

[00308] To a solution of 2-amino-6-chloro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5b** (1.51 g, 7.103 mmol) in chloroform (15.1 mL) was added TBTU boron tetrafluoride (2.737 g, 8.524 mmol) and TEA (862.5 mg, 1.188 mL, 8.524 mmol). The reaction mixture was stirred at 50°C for one hour. The resulting suspension was filtered, and the solid triturated in ethyl acetate to afford the title compound **6b** as a yellow solid (2.05 g, 88%).

Preparation 4: 1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-amino-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate



6c

Step 1: allyl 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4c**

[00309] To a suspension of allyl 3,5-diamino-1H-pyrazole-4-carboxylate **3** (63.49 g, 348.5 mmol) in a mixture of DMSO (340 mL) and water (340 mL), was added 3-(dimethoxymethyl)-4,4-dimethoxy-butanenitrile (**Scheme 3**, below) (85 g, 418.2 mmol), followed by para-toluene Sulfonic acid hydrate (1) (11.27 g, 59.24 mmol). The reaction mixture was heated to 85°C and stirred overnight. The reaction mixture was cooled with an ice bath. The mixture was diluted with EtOAc (680 mL) and a saturated aqueous solution of $NaHCO_3$ (1.36 L). The precipitate was filtered and rinsed with water, then with a mixture of water and EtOAc. The brown solid was dried under vacuum to give allyl 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4c** as a brown solid (55.94 g, 62% yield).

Step 2: 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5c**

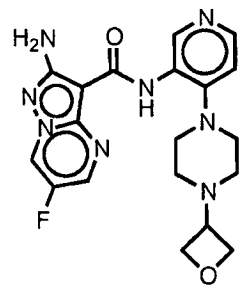
[00310] To a suspension of allyl 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylate **4c** (10.2 g, 39.65 mmol) in DCM (350 mL) was added phenylsilane (8.581g, 9.773 mL, 79.3 mmol), followed by $Pd(PPh_3)_4$ (1.5 g, 1.298 mmol). The reaction was stirred at room temperature for 2h. The reaction mixture was filtered and the solid was washed with DCM and dried under vacuum to provide 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5c** as a yellow solid (8.61g, 100% yield).

Step 3: 1H-benzo[d][1,2,3]triazol-1-yl 2-amino-6-(cyanomethyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate **6c**

[00311] To a solution of 2-amino-6-(cyanomethyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5c** (5.11 g, 23.53 mmol) in DCM (51 mL) was added TBTU boron tetrafluoride (9.067 g, 28.24 mmol) and TEA (2.858 g, 3.937 mL, 28.24 mmol). The reaction mixture was stirred

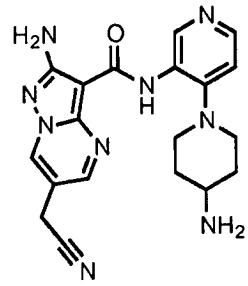
at room temperature for one hour. The resulting suspension was filtered, and the solid triturated in hot chloroform to afford the title compound **6c** as a beige solid (6.59 g, 84%).

Example 1: 2-amino-6-fluoro-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-1)



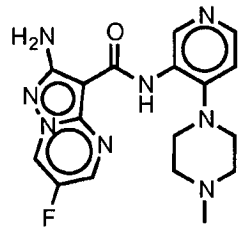
[00312] To a suspension of benzotriazol-1-yl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **6a** (prepared according to methods similar to the one depicted in **Preparation 2a**) (5 g, 15.62 mmol) in NMP (78.27 mL) was added 4-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-3-amine (prepared according to methods similar to the one depicted in **Preparation N-1**, described below) (3.660 g, 15.62 mmol) and the resulting mixture heated at 100°C for 18 hours. The reaction mixture was cooled to RT and then passed through a pre-wetted SCX cartridge (2 x 50 g cartridge) and the cartridge was washed with methanol. The product was eluted with 2M ammonia in methanol and the eluent was concentrated *in vacuo* to leave a dark solid that was purified by column chromatography on silica using the ISCO column companion, eluting with DCM and 90:10:1 DCM:MeOH:NH_3 (0-100% gradient, 40 g column). Product fractions were combined and concentrated *in vacuo* to leave the product as a yellow solid which was then recrystallised from methanol to leave pure product as a yellow solid. MS (ES+) 413.2.

Example 2: 2-amino-*N*-(4-(4-aminopiperidin-1-yl)pyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-2)



[00313] To a solution of tert-butyl N-[1-[3-[[2-amino-6-(cyanomethyl)pyrazolo[1,5-a]pyrimidine-3-carbonyl]amino]-4-pyridyl]-4-piperidyl]carbamate prepared according to a method similar to the one described in **Example 1** (70 mg, 0.1424 mmol) in DCM (4 mL) was added TFA (1 mL, 12.98 mmol) and the mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was evaporated to dryness and purified by HPLC: 10-90% ACN in Water (TFA modifier) and the fractions were freeze-dried. The solid residue was dissolved in methanol (1 mL) and loaded onto a pre-wetted (15 mL methanol) 2 g SCX-2 cartridge. The cartridge was washed with methanol (2x15 mL) then the product eluted as a free base using 2M ammonia in methanol solution (3x15 mL). The product-containing fractions were evaporated to dryness, re-dissolved in water/methanol and freeze-dried to afford the desired product as a yellow solid (17 mg, 31%). MS (ES+) 391.1.

Example 3a: 2-amino-6-fluoro-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-3)



[00314] A mixture of 4-(4-methylpiperazin-1-yl)pyridin-3-amine (prepared according to methods similar to the one depicted in **Preparation N-1**, described below) (588.1 mg, 3.059 mmol), 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a** (prepared according to methods similar to the ones depicted in the sequence **Step 1** - **Step 2** of **Preparation 2a**) (500 mg, 2.549 mmol), TBTU (1.146 g, 3.569 mmol) and Et_3N (515.9 mg, 710.6 µL, 5.098 mmol) in NMP (7 mL) was stirred at 110°C in a sealed tube, for 20h. The

reaction mixture was diluted with EtOAc, washed with a saturated bicarbonate aqueous solution and brine. The organic was dried over $MgSO_4$ and concentrated after filtration. The solid was triturated in DCM and then filtered off. It was further purified by Fractionlynx HPLC to yield the title compound as a colourless solid. MS (ES+) 371.3.

[00315] Alternatively, compound **I-N-3** can be prepared according to **Scheme 2** using the procedure described in **Example 3b**.

Example 3b: 2-amino-6-fluoro-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-3)

Step 1: 2-cyano-N-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)acetamide **8**

[00316] To an ice cold solution of 2-cyanoacetic acid **7** (1.15 g, 13.52 mmol) in DCM (40 mL) was added oxalyl chloride (1.3 mL, 14.90 mmol) dropwise, followed by a catalytic amount of DMF. The reaction mixture was stirred at room temperature for 3h and then concentrated *in vacuo* to remove solvent. The residue was added to a solution of 4-(4-methylpiperazin-1-yl)pyridin-3-amine (Prepared according to methods similar to the one depicted in **Preparation N-1**, described below) (1.3 g, 6.762 mmol) and Et_3N (1.026 g, 1.413 mL, 10.14 mmol) in THF (40 mL) and the reaction mixture was stirred at room temperature for 18h. The mixture was diluted with EtOAc, washed with a saturated bicarbonate aqueous solution and brine. The aqueous layer was further extracted with DCM (20mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give 2-cyano-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)acetamide **8** as a yellow oil. MS (ES+) 260.1.

Step 2: 3,5-diamino-N-[4-(4-methylpiperazin-1-yl)-3-pyridyl]-1H-pyrazole-4-carboxamide **9**

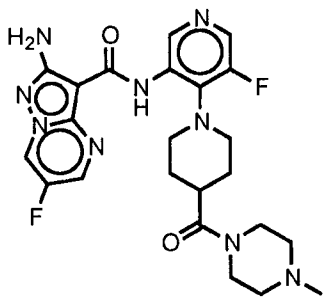
[00317] To a suspension of 2-cyano-N-[4-(4-methylpiperazin-1-yl)-3-pyridyl]acetamide **8** (1.6 g, 6.170 mmol) in ethanol (40 mL) was added sodium acetate (1.052 g, 12.83 mmol), followed by trichloroacetonitrile (1.042 g, 733.8 µL, 7.219 mmol) dropwise. The heterogeneous mixture was stirred at room temperature under an atmosphere of nitrogen for 18h. The reaction mixture was concentrated under vacuum, and the residue was dissolved in NMP (30 mL). Hydrazine hydrate (803 mg, 780.4 µL, 16.04 mmol) was added and the reaction mixture was stirred at room temperature for 3h. The solvents were removed under vacuum and the residue triturated in DCM to form a brown solid which was isolated by filtration to provide 3,5-diamino-N-[4-(4-methylpiperazin-1-yl)-3-pyridyl]-1H-pyrazole-4-

carboxamide **9** (1g, 51%). MS (ES+) 317.1.

Step 3: 2-amino-6-fluoro-N-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00318] A mixture of (Z)-3-(diisopropylamino)-2-fluoro-prop-2-enal (***Tetrahedron Letters*** (1992), 33(3), 357-60) (22.81 mg, 0.1317 mmol), 4-methylbenzenesulfonic acid (Water (1)) (30.05 mg, 0.1580 mmol), 3,5-diamino-N-[4-(4-methylpiperazin-1-yl)-3-pyridyl]-1H-pyrazole-4-carboxamide (50 mg, 0.1580 mmol) in DMSO (1 mL) / H2O (0.5 mL) was stirred at 140°C for 25 min. The crude mixture was purified by Fractionlynx HPLC. The aqueous fractions were combined and lyophilised to yield 2-amino-6-fluoro-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. (10mg, 21%).

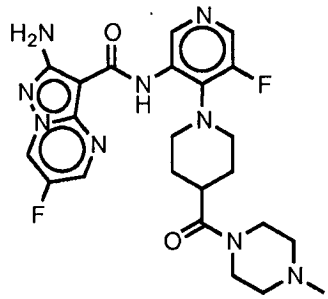
Example 3c: 2-amino-6-fluoro-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-G-4)



[00319] A suspension of benzotriazol-1-yl 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **6a** (6.271 g, 20.02 mmol), [1-(3-amino-5-fluoro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone hydrobromide **17a** (6.98 g, 16.68 mmol) and DIPEA (2.802 g, 3.776 mL, 21.68 mmol) in pyridine (63 mL) were placed in a sealed tube and heated at 100°C for 24 h. The mixture cooled to room temperature then concentrated *in vacuo*. The resulting solid was loaded onto silica and purified by chromatography (330g SiO_2, 0.5-7.5% MeOH (containing 10% ammonium hydroxide)/DCM). The residue was stirred in ethanol for 5 mins and the solid that formed was collected by filtration, washed with minimal ethanol, dried by suction for 2 h, affording desired product as a pale yellow solid (4.71 g, 56.5%). MS (ES+) 500.2; ^{1}H NMR (DMSO-d6) δ 10.63 (s, 1H), 9.67 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 9.25 (dd, J = 2.6, 0.7 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 6.79 (s, 2H), 3.60 (t, J = 5.0 Hz, 2H), 3.55 (t, J = 4.9 Hz, 2H), 3.19 (m, 2H), 3.03 (m, 2H), 2.95 (tt, J = 11.7, 3.6 Hz, 1H), 2.34

(t, J = 5.0 Hz, 2H), 2.29 (t, J = 5.1 Hz, 2H), 2.20 (s, 3H), 2.13 (qd, J = 12.4, 3.9 Hz, 2H), 1.75 - 1.72 (m, 2H).

Example 3d: 2-amino-6-fluoro-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-G-4)

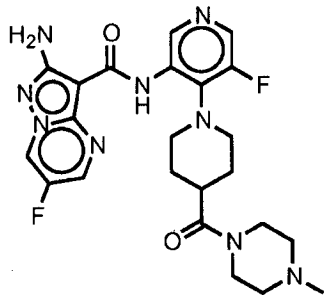


In an alternative method to the the one reported in **Example 3c**, *compound* **I-G-4** *can be prepared as follows:*

[00320] A 2 L flask equipped with an overhead stirrer, an air condenser, a thermometer and a nitrogen line was charged with 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid **5a** (14.19 g, 72.36 mmol), then pyridine (353 mL) followed by [(6-chlorobenzotriazol-1-yl)oxy-(dimethylamino)methylene]-dimethyl-ammonium trifluoroborate (22.14 g, 65.78 mmol), with stirring at ambient temperature. The suspension was heated at 50°C over 1 h period. DIPEA (17.85 g, 24.06 mL, 138.1 mmol) was then added, followed by [1-(3-amino-5-fluoro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone hydrochloride **17b** (prepared according to **Preparation N-14**) (23.54 g, 65.78 mmol). The internal temperature was raised to 90°C and the reaction mixture stirred at this temperature for 13 h. The mixture was then allowed to cool slowly and the solvent was evaporated *in vacuo*. The residue was slurried in DCM (250 ml) and the orange solid was partitioned between DCM (1 L) and 2M sodium carbonate (200 mL). The organic layer was separated, washed with 2M sodium carbonate (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave an orange solid. This solid residue was further slurried in EtOH (115 mL) for 10 mins then collected by filtration, washed with further ethanol (approx 100 mL) dried by suction to afford product as a pale yellow solid, 18.75g, 57%).

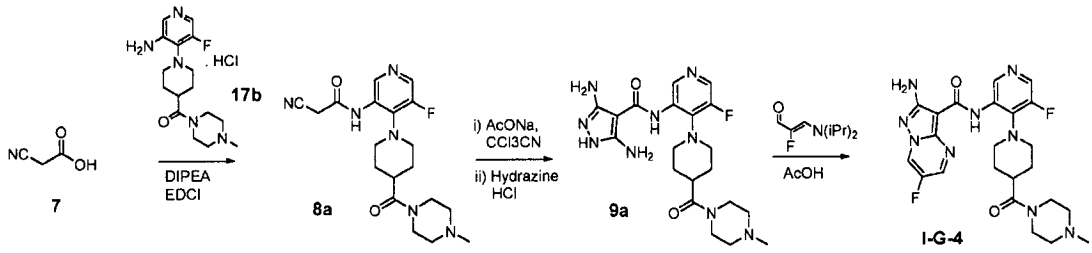
Example 3e: 2-amino-6-fluoro-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

(Compound I-G-4)



[00321] In an alternative method to the the ones reported in **Example 3c** and **3d**, compound **I-G-4** can be prepared as follows:

Scheme 2a:



Step 1: 2-cyano-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)acetamide **8a**

[00322] To a solution of [1-(3-amino-5-fluoro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone hydrochloride **17b** (300 mg, 0.8383 mmol) and DIPEA (541.8 mg, 730.2 µL, 4.192 mmol) in DCM (8 mL) was added cyanoacetic acid **7** (106.9 mg, 1.257 mmol) . The reaction mixture was cooled on an ice bath and EDCI (241.0 mg, 1.257 mmol) was then added. The mixture was stirred at room temperature overnight, then heated under reflux for 4h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL), washed with water (2 x 10 ml), then saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to afford the desired product **8a** as an orange foam (292mg, 90%). MS (ES+) 389.2.

Step 2: 3,5-diamino-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-1H-pyrazole-4-carboxamide **9a**

[00323] 2-Cyano-N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-

pyridyl]acetamide **8a** (290 mg, 0.7466 mmol) was slurried in ethanol (3.3 mL). Sodium acetate (127.4 mg, 1.553 mmol) was added, followed by trichloroacetonitrile (129.4 mg, 91.13 µL, 0.8959 mmol) and the reaction mixture was stirred at room temperature for 1 hr, after which time an off-white precipitate had formed. The solid was collected by filtration, washed with minimal ethanol then minimal water and dried by suction to give a white solid (155 mg). The filtrate was concentrated in vacuo to remove ethanol then residual aqueous solution was extracted with EtOAc (3x). The combined organic layers was dried ($MgSO_4$), filtered and concentrated to dryness in vacuo to leave a viscous oil which was triturated in EtOAc (5 mL) to form an off white precipitate that was collected by filtration, washed with minimal EtOAc and dried by suction to leave a second crop of solid (49 mg). A total of 204 mg (51%) of 3-amino-4,4,4-trichloro-2-cyano-N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-pyridyl]but-2-enamide was isolated; MS (ES+) 532.0.

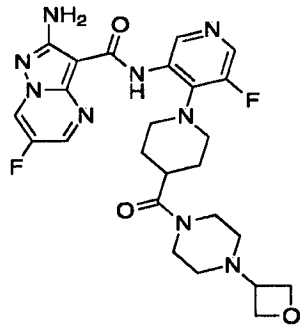
[00324] 3-Amino-4,4,4-trichloro-2-cyano-N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-pyridyl]but-2-enamide (4.1g, 7.695 mmol) was dissolved in N-methylpyrrolidinone (40 mL). Hydrazine hydrate (1.002g, 973.8 µL, 20.01 mmol) was added and the reaction mixture was stirred at room temperature for 10 mins, then heated at 80°C for 3.5h. The mixture was concentrated in vacuo and the residue was then partitioned between EtOAc/water. The organic organic layer was washed with water (2x), brine (1x), dried (MgSO4), filtered and concentraed in vacuo to provide the desired compound as a white solid. (64%). MS (ES+) 446.1, ^{1}H NMR (500 MHz, DMSO) 11.03 (s, 1H), 9.45 (s, 1H), 8.69 (s, 1H), 8.52 (d, J = 4.7 Hz, 1H), 7.36 (br s, 4H),4.47 - 4.43 (m, 1H), 4.23 - 4.21 (m, 1H), 3.50 - 3.47 (m, 2H), 3.41 - 3.39 (m,2H), 3.24 - 3.15 (m, 2H) 3.05 - 2.98 (m, 2H), 2.93 - 2.88 (m, 2H), 2.77 - 2.76 (m, 4H), 1.73 - 1.71 (m, 4H).

Step 3: 2-amino-6-fluoro-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide **I-G-4**

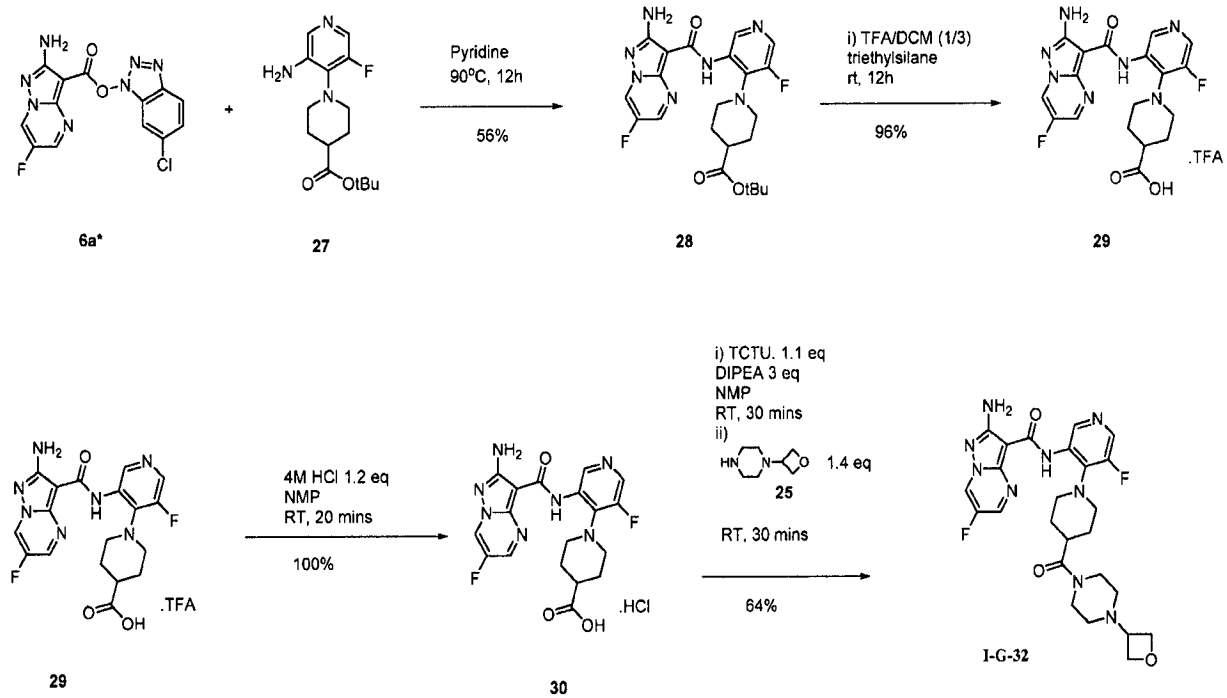
[00325] To a suspension of 3,5-diamino-N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-pyridyl]-1H-pyrazole-4-carboxamide **9a** (106 mg, 1.19 mmol) in IPA/water (1:1, 1 mL) and acetic acid (71.46 mg, 67.67 µL, 0.1078 mmol) was added 3-(diisopropylamino)-2-fluoro-prop-2-enal (41.21 mg, 0.2379 mmol). The reaction mixture was heated under reflux for 6h and was then allowed to cool to room temperature overnight. IPA was removed *in vacuo*, and the resulting aqueous solution was partitioned between DCM and 2M sodium carbonate solution. The organic layer was washed with 1:1 brine/water, dried

($MgSO_4$) filtered and concentrated in vacuo to leave a yellow solid which was stirred as a suspension in ethanol (0.5 mL) for 2h. The solid was collected by filtration to give the desired compound **I-G-4** (63mg, 53%).

Example 3f: 2-amino-6-fluoro-N-[5-fluoro-4-[4-[4-(oxetan-3-yl)piperazine-1-carbonyl]-1-piperidyl]-3-pyridyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-G-32)



Scheme 2b: Preparation of compound I-G-32



Step 1: tert-butyl 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylate **28**

[00326] A mixture of (6-chlorobenzotriazol-1-yl) 2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxylate **6a*** (44.02 g, 126.6 mmol) and tert-butyl 1-(3-amino-5-fluoro-4-

pyridyl)piperidine-4-carboxylate **27** (prepared according to **Preparation N-15**) (34 g, 115.1 mmol) in pyridine (510.0 mL) was heated at 95°C internally overnight (18h). Mixture was cooled to room temperature (product precipitated) then added ethanol (340.0 mL) and stirred at room temperature for 10 mins. Collected yellow solid by filtration, washed well with ethanol, dried by suction, then on high vac line for 1h to leave product **28** as a yellow solid, (32.5g 56% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.58 (s, 1H), 9.51 (dd, 1H), 8.72 (dd, 1H), 8.25 (d, 1H), 6.81 (s, 2H), 3.15 - 2.93 (m, 4H), 2.55 – 2.47 (masked signal, 1H), 2.02 – 1.91 (m, 4H), 1.47 (s, 9H). MS (ES+) 474.2.

Step 2: 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylic acid trifluorocetate **29**

[00327] To a suspension of tert-butyl 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylate **28** (69.7 g, 147.2 mmol) in DCM (348.5 mL) and triethylsilane (18.83 g, 25.87 mL, 161.9 mmol) was added TFA (151.1 g, 102.1 mL, 1.325 mol) (mixture sets solid on initial addition of TFA then goes into solution after complete addition). Resulting orange solution was stirred at room temperature overnight. Additional TFA (16.78 g, 11.34 mL, 147.2 mmol) was added and the mixture stirred at room temperature for 2h. Mixture then heated at 40°C for 20 mins to force reaction to completion. Mixture was concentrated in vacuo, chloroform (300 mL) was added and mixture again concentrated in vacuo to leave an orange solid suspension. Mixture triturated in DCM (approx. 200 mL), stirred for 20 mins then solid collected by filtration, washed with minimal DCM and dried by suction to leave a yellow solid. Filtrate was concentrated in vacuo, residue re-slurried in DCM (approx 50 mL), stirred for 20 mins then solid collected by filtration, washed with minimal DCM and dried by suction to leave a yellow solid which was combined with first crop of solid. Solid dried under vacuum overnight to leave desired product **29** as a yellow solid (82.8g, 96%). ^{1}H NMR (500 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.59 (s, 1H), 9.50 (dd, 1H), 8.84 (dd, 1H), 8.33 (d, 1H), 3.13 – 3.10 (m, 4H), 2.57 – 2.47 (masked signal, 1H) and 2.08 - 1.93 (m, 4H). MS (ES+) 418.1.

Step 3: 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylic acid hydrochloride **30**

[00328] To a solution of 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylic acid (Trifluoroacetic Acid) **29** (73 g, 124.7 mmol) in NMP (662.7 mL) was added hydrogen chloride (4M in 1,4-dioxane)

(37.40 mL of 4 M, 149.6 mmol). After a few seconds a yellow precipitate formed. Mixture stirred at room temperature for 20 mins, then solid collected by filtration, washed with minimal NMP then MTBE, and dried by suction to leave pure product **30** as a light yellow solid, (59.7g, quantitative yield). MS (ES+) 418.1.

Step 4: 2-amino-6-fluoro-N-[5-fluoro-4-[4-[4-(oxetan-3-yl)piperazine-1-carbonyl]-1-piperidyl]-3-pyridyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide **(Compound I-G-32)**

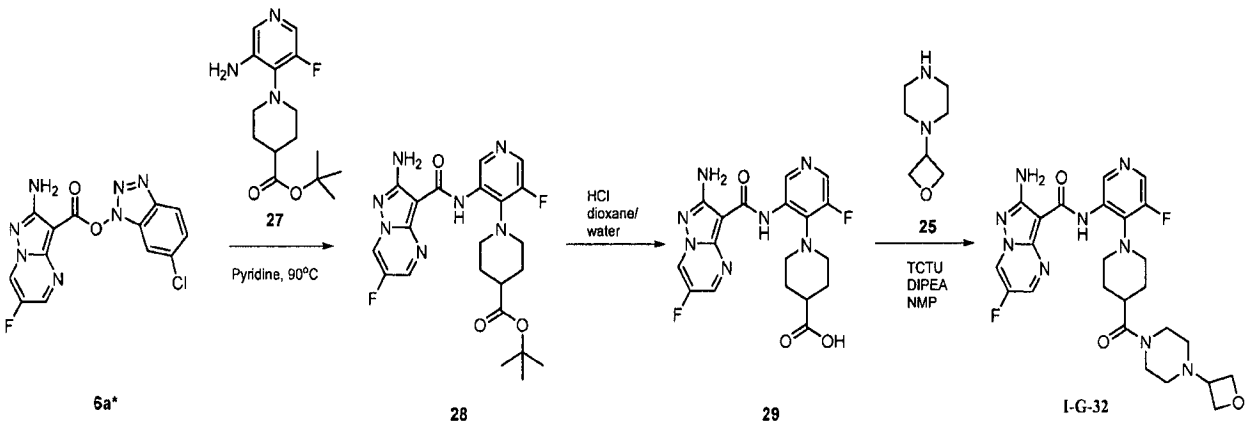
[00329] To a yellow suspension of 1-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-5-fluoro-4-pyridyl]piperidine-4-carboxylic acid (Hydrochloric Acid) **30** (59.7 g, 131.5 mmol) in NMP (477.6 mL) was added DIPEA (50.99 g, 68.72 mL, 394.5 mmol) then [(6-chlorobenzotriazol-1-yl)oxy-(dimethylamino)methylene]-dimethyl-ammonium (Boron Tetrafluoride Ion (1)) (51.44 g, 144.7 mmol). A yellow suspension forms after a few minutes. The mixture was sirred for 30 mins at room temperature then 1-(oxetan-3-yl)piperazine **25** (prepared according to **Preparation N-32**, below) (26.18 g, 184.1 mmol) was added. The cream/tan suspension turns to an orange solution (exotherms from 23.9 to 29.4°C). The flask was placed on ice/water bath until internal temperature was at 24°C, then ice bath was removed and internal temperature steady at 24°C thereafter.

[00330] The solution was stirred for 30 mins at room temperature then cooled on an ice/salt/water bath to 10°C before the slow addition of water (1.015 L) in 100 mL portions. Prior to adding the next 100mL of water, waited for exotherm to between 17°C and 20°C (internal) then allow to cool to between 10 and 15°C. Repeated until all water added. Once exotherm had ceased, ice/salt/water bath removed and mixture stirred at ambient temperature for 20 mins (thick yellow/cream suspension forms). Solid collected by filtration through a sinter funnel, washed well with water then dried by suction for 10 mins. Vacuum removed and solid slurried in water on sinter funnel, then vacuum reapplied and solid dried by suction overnight then dried in vacuum oven for 24 h at 40°C <10 mBar.

[00331] Solid (54.5g) suspended in ethanol (545 mL, 10 vol eq.) and heated under reflux for 2h then cooled to room temperature over 2h. Solid collected by filtration, washed with minimum ethanol and dried by suction for 1h to leave product as a pale yellow solid. Solid placed in vacuum oven at 23.5°C and <10mBar overnight to leave product **I-G-32** as a pale yellow solid, (51g, 64% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.67 (s, 1H), 9.48 (dd, 1H), 9.26 (dd, 1H), 8.26 (d, 1H), 6.79 (s, 2H), 4.55 (t, 2H), 4.47 (t, 2H), 4.34 (t, 0.7H), 3.61 (dt, 4H), 3.48 - 3.41 (m, 2.5H), 3.22 - 3.17 (m, 2H), 3.05 - 3.03 (m, 2H), 3.99 -

2.93 (m, 1H), 2.28 (dt, 4H), 2.17 - 2.10 (m, 2H), 1.74 (d, 2H), 1.07 (t, 2H). MS (ES+) 542.3.

Scheme 2c: Alternative approach to prepare compound I-G-32



Step 1: tert-butyl 1-(3-(2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylate **28**

[00332] 6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxylate **6a*** (45g, 129.4mmol) and *tert*-butyl 1-(3-amino-5-fluoropyridin-4-yl)piperidine-4-carboxylate **27** (40.1g, 135.9mmol) were slurried in pyridine (675ml). The mixture was heated at 95°C under nitrogen until the reaction was complete (determined by HPLC analysis). The mixture was cooled and ethanol (450ml) was added dropwise. The mixture was filtered and the filter cake washed with ethanol (2x70ml). The damp cake was dried to give the product **28** as a yellow crystalline solid (47.7g, 78%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.58 (s, 1H), 9.51 (dd, 1H), 8.72 (dd, 1H), 8.25 (d, 1H), 6.81 (s, 2H), 3.15 - 2.93 (m, 4H), 2.55 – 2.47 (masked signal, 1H), 2.02 – 1.91 (m, 4H), 1.47 (s, 9H); 19F NMR (500 MHz, DMSO-d6) δ – 153.5, -136.3; MS (ES+) 474.2.

Step 2: 1-(3-(2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylic acid **29**

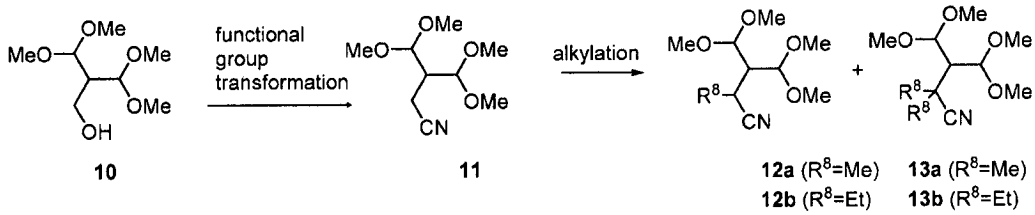
[00333] *Tert*-butyl 1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylate **28** (36g, 76mmol) was suspended in a solution of HCl in 1,4-dioxane (4M, 670ml). Water (36ml) was added dropwise to the rapidly stirred slurry. The mixture was stirred under nitrogen until the reaction was complete (determined by HPLC analysis). The mixture was diluted with 1,4-dioxane (180ml) and filtered. The filter cake was washed with TBME (2x72ml). The damp cake was dried to give a pale brown solid (hydrochloride salt, 32.7g, 95%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.53-9.49 (m, 2H), 8.82 (m, 1H), 8.50 (m, 1H), 3.13 – 3.22 (m, 4H), 2.57 – 2.47 (masked signal, 1H)

and 2.08 - 1.93 (m, 4H); 19F NMR (500 MHz, DMSO-d6) δ – 152.9, -133.8; MS (ES+) 418.1.

Step 3: 2-amino-6-fluoro-N-(5-fluoro-4-(4-(oxetan-3-yl)piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**compound I-G-32**)

[00334] To a solution of 1-(oxetan-3-yl)piperazine (525mg, 3.69mmol) in THF (12ml) was added DIPEA (1.72ml, 9.91mmol), followed by 1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylic acid (hydrochloride salt, 1.5g, 3.3mmol). [(6-chlorobenzotriazol-1-yl)oxy-(dimethylamino)methylene]-dimethyl-ammonium tetrafluoroborate (TCTU, 1.29g, 3.64mmol) was added and the mixture stirred under nitrogen until reaction completion (determined by HPLC analysis). The mixture was cooled and water (24ml) was added dropwise. The mixture was allowed to warm to ambient and stirred for 3 hrs, then filtered. The filter cake was washed with (3x3ml). The damp cake was dried under vacuum (with a nitrogen bleed) at 40°C. The product was obtained as a yellow solid (1.54g, 86%); ^{1}H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.67 (s, 1H), 9.48 (dd, 1H), 9.26 (dd, 1H), 8.26 (d, 1H), 6.79 (s, 2H), 4.55 (t, 2H), 4.47 (t, 2H), 4.34 (t, 0.7H), 3.61 (dt, 4H), 3.48 - 3.41 (m, 2.5H), 3.22 - 3.17 (m, 2H), 3.05 - 3.03 (m, 2H), 3.99 - 2.93 (m, 1H), 2.28 (dt, 4H), 2.17 - 2.10 (m, 2H), 1.74 (d, 2H), 1.07 (t, 2H); 19F NMR (500 MHz, DMSO-d6) δ – 152.8, -136.1; MS (ES+) 542.3.

Scheme 3—Preparation of butanenitrile intermediates



10 **11** **12a** (R^8=Me) **13a** (R^8=Me) **12b** (R^8=Et) **13b** (R^8=Et)

Step 1: 3-(dimethoxymethyl)-4,4-dimethoxybutanenitrile **11**

[00335] 2-(dimethoxymethyl)-3,3-dimethoxy-propan-1-ol **10** (*Journal of the American Chemical Society* (1973), 95(26), 8741) (92 g, 473.7 mmol) was dissolved in dry THF (920 mL) and the mixture was cooled down with an ice bath. Triethylamine (143.8g, 198.1 mL,

1.421 mol) was added at once, followed by dropwise addition of methane sulfonyl chloride (59.69g, 40.33mL, 521.1 mmol), over 1h and keeping the internal temperature below 5°C. The reaction mixture was stirred for 1 h and then allowed to warm to room temperature. The mixture was diluted with ethyl acetate (920mL) and water (920mL). The layers were separated and the organic layer was isolated, washed with a saturated solution of $NaHCO_3$, then brine. The organics were dried over $MgSO_4$, filtered and evaporated to give [2-(dimethoxymethyl)-3,3-dimethoxypropyl]methanesulfonate as an orange oil (125.31g, 97%) which was used directly without further purification.

[00336] Tetraethylammonium cyanide (142.3g, 910.8mmol) was added portionwise over 10 minutes to a solution of [2-(dimethoxymethyl)-3,3-dimethoxypropyl]methanesulfonate (124g, 455.4mmol) in MeCN (1.24L). The reaction mixture was stirred at room temperature for 72h, then portioned between ethyl acetate (1.24L) and water (1.24L). The layers were separated and the organic layer was isolated, washed with brine. The organics were dried over $MgSO_4$, filtered and evaporated to give 3-(dimethoxymethyl)-4,4-dimethoxybutanenitrile **11** as a dark brown oil (86.1g).

Step 2: 3-(dimethoxymethyl)-4,4-dimethoxy-2-methylbutanenitrile **12a** *and 3-(dimethoxymethyl)-4,4-dimethoxy-2,2-dimethylbutanenitrile* **13a**

[00337] To a solution of 3-(dimethoxymethyl)-4,4-dimethoxy-butanenitrile **11** (250 mg, 1.205 mmol) in THF (3 mL) at -75°C was added a solution of iodomethane (513.1 mg, 225.0 µL, 3.615 mmol) in THF (1 ml). A THF solution of (bis(trimethylsilyl)amino)sodium (1.808 mL of 2M, 3.615 mmol) was then added, keeping the temperature below -60°C. After addition, the reaction mixture was stirred at -75°C for 2hrs and then slowly quenched with aqueous saturated NH_4Cl solution (5ml). The mixture diluted with water and ether and layers separated. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil which was purified by chromatography on silica gel, eluting with a petroleum ether:EtOAc gradient of 100:0 to 80:20. Solvents were concentrated *in vacuo* to afford a clear oil (194mg). NMR proved this oil to be a mixture of 80% mono methyl compound **12a** with and 20% bis methyl compound **13a**. This mixture was used directly in subsequent steps.

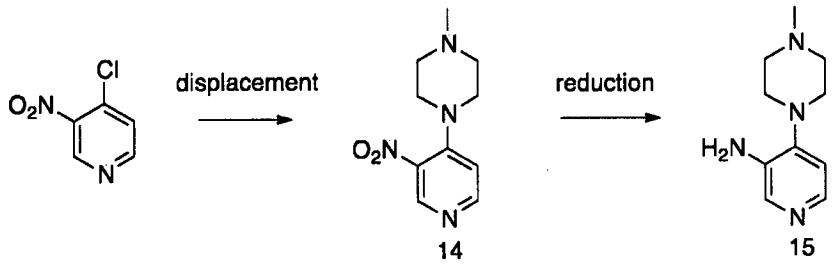
Step 3: 3-(dimethoxymethyl)-2-ethyl-4,4-dimethoxybutanenitrile **12b** *and 3-(dimethoxymethyl)-2-diethyl-4,4-dimethoxybutanenitrile* **13b**

[00338] When ethyl iodide was used instead of methyl iodide in a similar procedure to

Scheme 3, *step 2*, above, a mixture of monosubsituted compound **12b** and disubstituted compound **13b** was isolated and used directly in subsequent steps.

Preparation N-1: 4-(4-methylpiperazin-1-yl)pyridin-3-amine 15

Scheme 4



Step 1: 1-methyl-4-(3-nitro-4-pyridyl)piperazine **14**

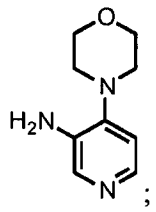
[00339] 4-chloro-3-nitro-pyridine (2g, 12.61 mmol) in dioxane (15 mL) was treated with 1-methylpiperazine (1.515 g, 1.678 mL, 15.13 mmol) and DIPEA (2.445 g, 3.295 mL, 18.92 mmol). The mixture was stirred at 80°C for 1 hour, cooled to RT. The mixture was partioned between EtOAc and an aqueous saturated solution of $NaHCO_3$ (40ml). Combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to give an orange oil which was purified by chromatography on silica eluting with 5-10%MeOH/EtOAc/0.5-1%NH_4OH to give 1-methyl-4-(3-nitro-4-pyridyl)piperazine **14** as a deep yellow oil which crystallised on standing. (2.56 g, 11.52 mmol, 91.36%). MS (ES+) 223.4.

Step 2: 4-(4-methylpiperazin-1-yl)pyridin-3-amine **15**

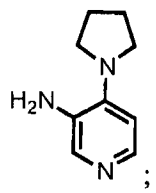
[00340] 1-methyl-4-(3-nitro-4-pyridyl)piperazine **14** (2.56g, 11.52 mmol) in methanol (200 mL) was treated with palladium on carbon (10% wt% Degussa) (300 mg) and hydrogenated under balloon pressure at RT for 3 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 4-(4-methylpiperazin-1-yl)pyridin-3-amine **15** as a colourless solid (2.124 g, 11.05 mmol, 95.89%). MS (ES+) 193.1.

[00341] The following 3-aminopyridine intermediates were prepared using **Preparation N-1**:

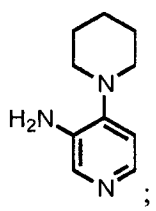
4-morpholinopyridin-3-amine;



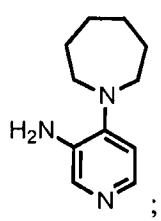
4-(pyrrolidin-1-yl)pyridin-3-amine:



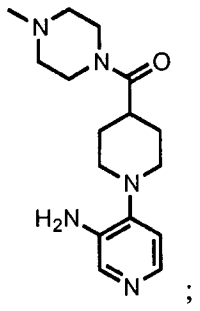
4-(piperidin-1-yl)pyridin-3-amine:



4-(azepan-1-yl)pyridin-3-amine:

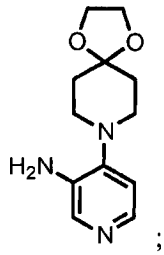


(1-(3-aminopyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone:



;

4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-amine:



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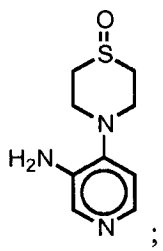
4-(3-aminopyridin-4-yl)thiomorpholine 1-oxide:



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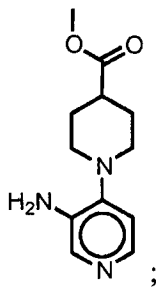
methyl 1-(3-aminopyridin-4-yl)piperidine-4-carboxylate:



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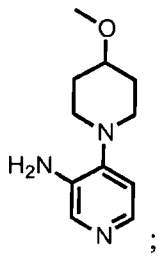
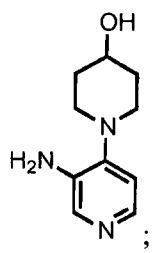
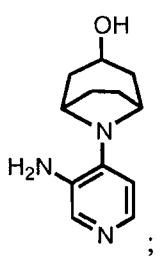
4-(4-methoxypiperidin-1-yl)pyridin-3-amine:



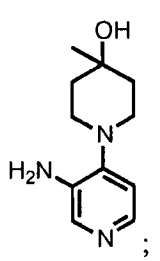
1-(3-aminopyridin-4-yl)piperidin-4-ol:



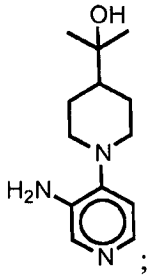
8-(3-aminopyridin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol:



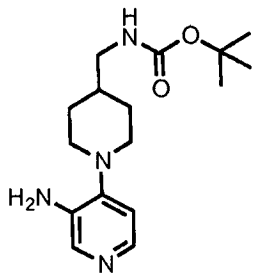
1-(3-aminopyridin-4-yl)-4-methylpiperidin-4-ol:



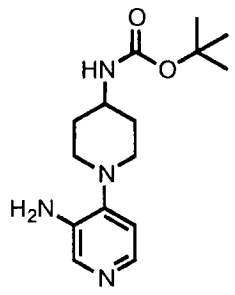
2-(1-(3-aminopyridin-4-yl)piperidin-4-yl)propan-2-ol:



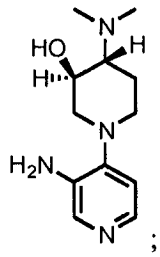
tert-butyl ((1-(3-aminopyridin-4-yl)piperidin-4-yl)methyl)carbamate:



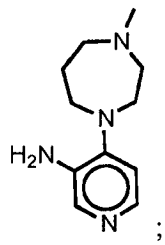
tert-butyl (1-(3-aminopyridin-4-yl)piperidin-4-yl)carbamate:



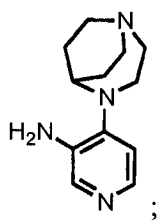
(3R,4R)-1-(3-aminopyridin-4-yl)-4-(dimethylamino)piperidin-3-ol:



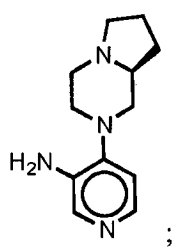
4-(4-methyl-1,4-diazepan-1-yl)pyridin-3-amine:



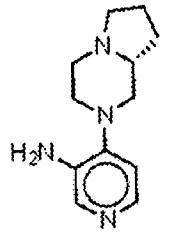
4-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-3-amine:



(S)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-amine:



(R)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-amine:



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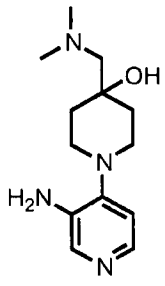
1-(3-aminopyridin-4-yl)-4-((dimethylamino)methyl)piperidin-4-ol:



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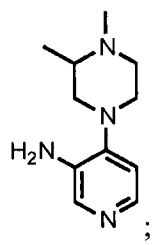
4-(3,4-dimethylpiperazin-1-yl)pyridin-3-amine:



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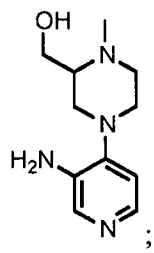
(4-(3-aminopyridin-4-yl)-1-methylpiperazin-2-yl)methanol:



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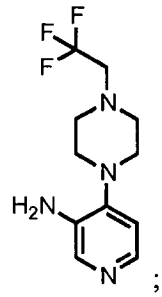
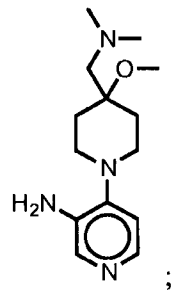
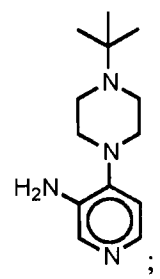
4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-3-amine:



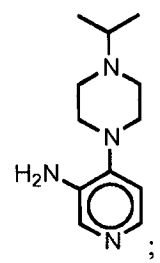
4-(4-((dimethylamino)methyl)-4-methoxypiperidin-1-yl)pyridin-3-amine:



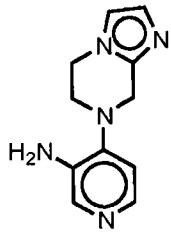
4-(4-(tert-butyl)piperazin-1-yl)pyridin-3-amine:



4-(4-isopropylpiperazin-1-yl)pyridin-3-amine:



4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)pyridin-3-amine:



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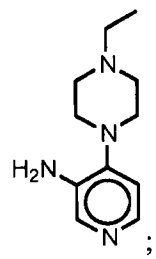
4-(4-ethylpiperazin-1-yl)pyridin-3-amine:



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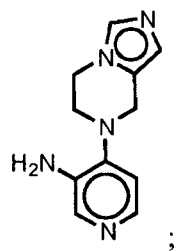
4-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)pyridin-3-amine:



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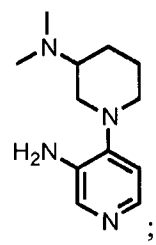
4-(3-(dimethylamino)piperidin-1-yl)pyridin-3-amine:



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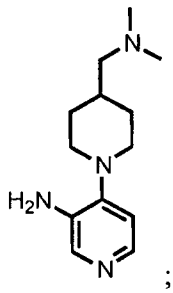
4-(4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-amine:



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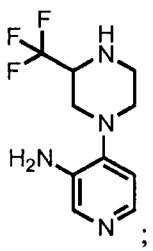
4-(3-(trifluoromethyl)piperazin-1-yl)pyridin-3-amine:



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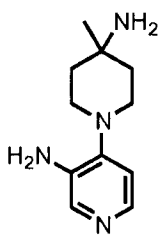
4-(4-amino-4-methylpiperidin-1-yl)pyridin-3-amine:



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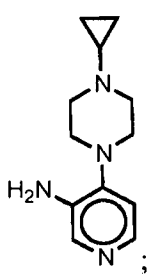
4-(4-cyclopropylpiperazin-1-yl)pyridin-3-amine:



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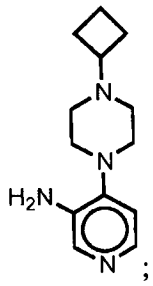
4-(4-cyclobutylpiperazin-1-yl)pyridin-3-amine:



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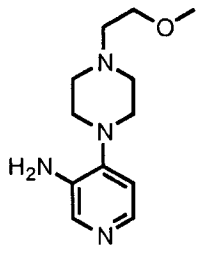
4-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-amine:



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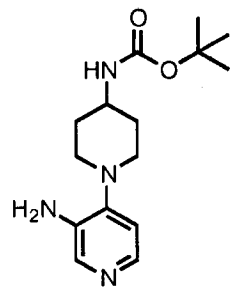
tert-butyl (1-(3-aminopyridin-4-yl)piperidin-4-yl)carbamate:



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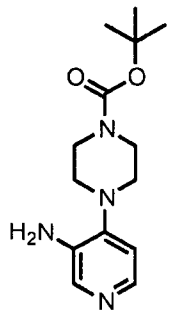
tert-butyl 4-(3-aminopyridin-4-yl)piperazine-1-carboxylate:



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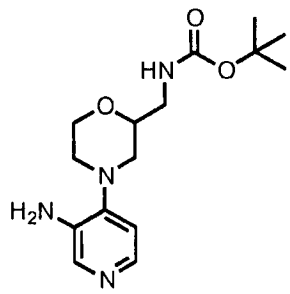
tert-butyl ((4-(3-aminopyridin-4-yl)morpholin-2-yl)methyl)carbamate:



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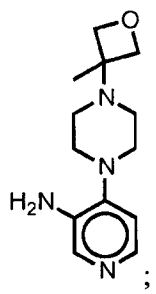
4-(4-(3-methyloxetan-3-yl)piperazin-1-yl)pyridin-3-amine:



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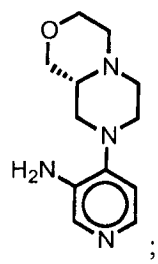
(*R*)-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-amine:



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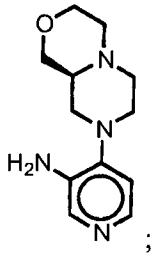
(*S*)-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-amine:



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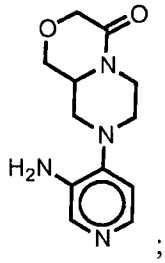
8-(3-aminopyridin-4-yl)hexahydropyrazino[2,1-*c*][1,4]oxazin-4(3*H*)-one:



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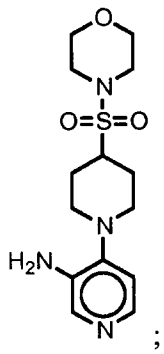
4-(4-(morpholinosulfonyl)piperidin-1-yl)pyridin-3-amine:



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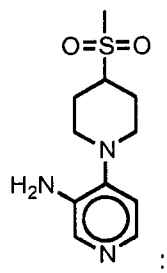
4-(4-(methylsulfonyl)piperidin-1-yl)pyridin-3-amine:



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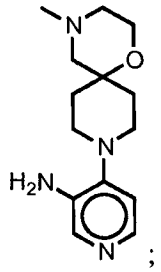
4-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)pyridin-3-amine:



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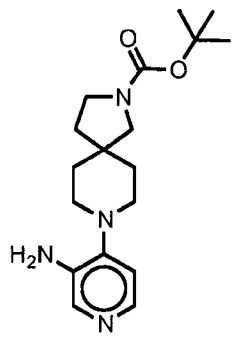
tert-butyl 8-(3-aminopyridin-4-yl)-2,8-diazaspiro[4.5]decane-2-carboxylate:



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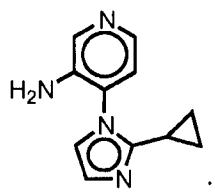
4-(2-cyclopropyl-1*H*-imidazol-1-yl)pyridin-3-amine:



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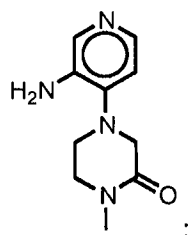
4-(3-aminopyridin-4-yl)-1-methylpiperazin-2-one:



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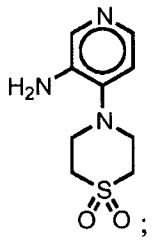
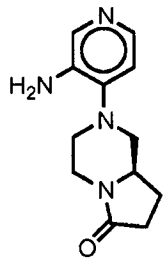
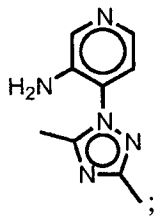
4-(3-aminopyridin-4-yl)thiomorpholine 1,1-dioxide:



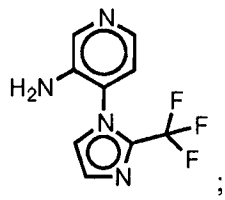
(*R*)-2-(3-aminopyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one:



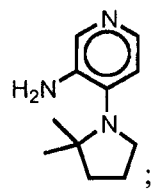
4-(3,5-dimethyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine:



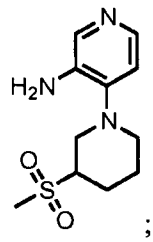
4-(2-(trifluoromethyl)-1*H*-imidazol-1-yl)pyridin-3-amine:



4-(2,2-dimethylpyrrolidin-1-yl)pyridin-3-amine:



4-(3-(methylsulfonyl)piperidin-1-yl)pyridin-3-amine:



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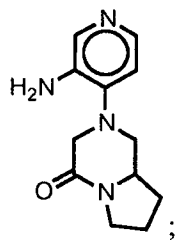
2-(3-aminopyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one:



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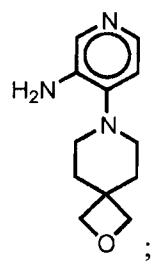
4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridin-3-amine:



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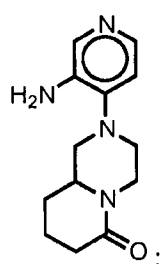
2-(3-aminopyridin-4-yl)hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-6(2*H*)-one:



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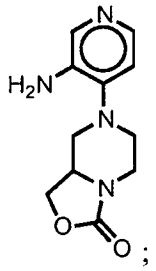
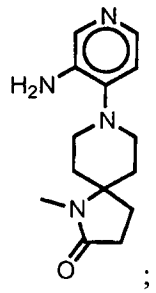
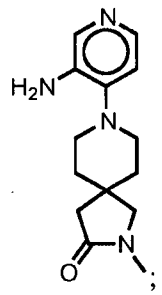
7-(3-aminopyridin-4-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one:



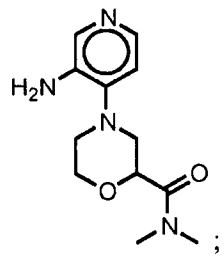
8-(3-aminopyridin-4-yl)-1-methyl-1,8-diazaspiro[4.5]decan-2-one:



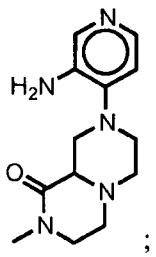
8-(3-aminopyridin-4-yl)-2-methyl-2,8-diazaspiro[4.5]decan-3-one:



4-(3-aminopyridin-4-yl)-*N*,*N*-dimethylmorpholine-2-carboxamide:



8-(3-aminopyridin-4-yl)-2-methyloctahydro-1*H*-pyrazino[1,2-*a*]pyrazin-1-one:



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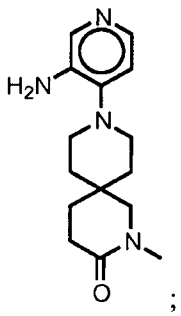
9-(3-aminopyridin-4-yl)-2-methyl-2,9-diazaspiro[5.5]undecan-3-one:



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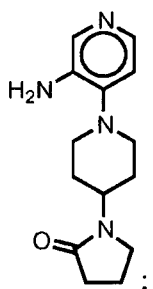
1-(1-(3-aminopyridin-4-yl)piperidin-4-yl)pyrrolidin-2-one:



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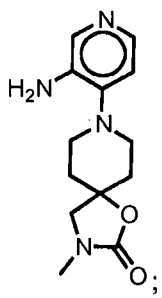
8-(3-aminopyridin-4-yl)-3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one:



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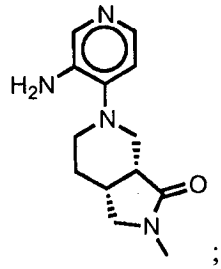
(3a*S*,7a*S*)-5-(3-aminopyridin-4-yl)-2-methylhexahydro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one:



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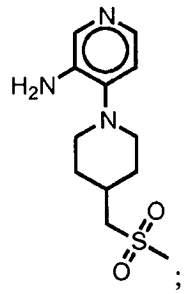
4-(4-((methylsulfonyl)methyl)piperidin-1-yl)pyridin-3-amine:



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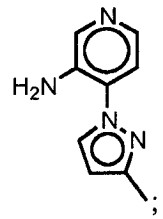
4-(3-methyl-1*H*-pyrazol-1-yl)pyridin-3-amine:



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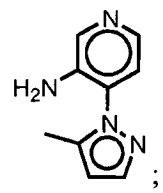
4-(5-methyl-1*H*-pyrazol-1-yl)pyridin-3-amine:



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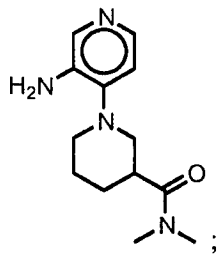
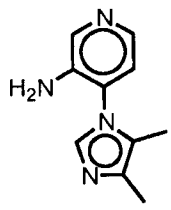
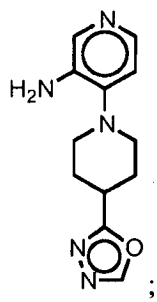
1-(3-aminopyridin-4-yl)-*N*,*N*-dimethylpiperidine-3-carboxamide:



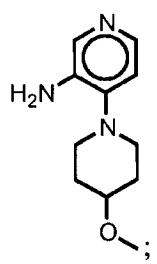
4-(4,5-dimethyl-1*H*-imidazol-1-yl)pyridin-3-amine:



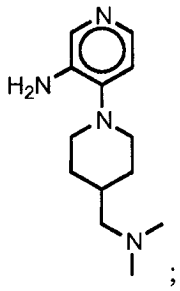
4-(4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl)pyridin-3-amine:



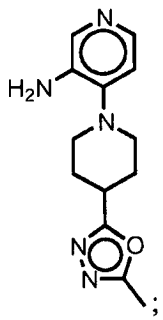
4-(4-methoxypiperidin-1-yl)pyridin-3-amine:



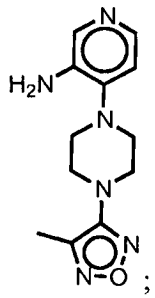
4-(4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-amine:



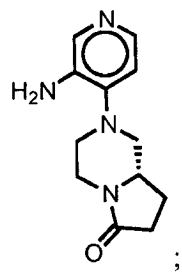
4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)pyridin-3-amine:



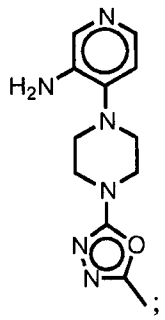
4-(4-(4-methyl-1,2,5-oxadiazol-3-yl)piperazin-1-yl)pyridin-3-amine:



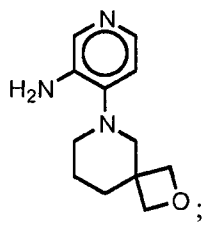
(*S*)-2-(3-aminopyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one:



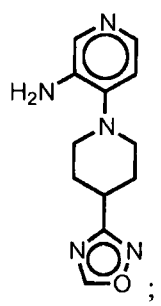
4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyridin-3-amine:



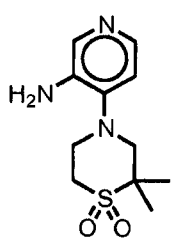
4-(2-oxa-6-azaspiro[3.5]nonan-6-yl)pyridin-3-amine:



4-(4-(1,2,4-oxadiazol-3-yl)piperidin-1-yl)pyridin-3-amine:

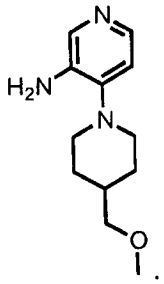


4-(3-aminopyridin-4-yl)-2,2-dimethylthiomorpholine 1,1-dioxide:



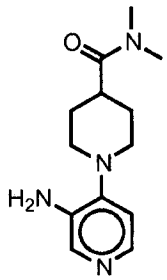
; and

4-(4-(methoxymethyl)piperidin-1-yl)pyridin-3-amine:



Miscellanous preparations of aminopyridines

Preparation N-2: 1-(3-aminopyridin-4-yl)-*N*,*N*-dimethylpiperidine-4-carboxamide



Step 1: 1-(3-amino-4-pyridyl)piperidine-4-carboxylic acid

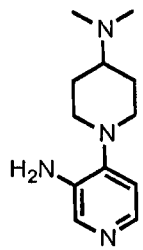
[00342] A microwave vial was charged with methyl 1-(3-amino-4-pyridyl)piperidine-4-carboxylate (prepared according to methods similar to the one depicted in **Preparation N-1**) (176 mg, 0.7106 mmol), MeOH (3 mL) and H_2O (0.1 mL). LiOH (51.06 mg, 2.132 mmol) was added and the mixture was stirred overnight at 50 °C. The reaction was quenched by addition of an aqueous solution of HCl until pH= 3-4 is reached. The reaction mixture was then concentrated under reduced pressure to yield 1-(3-amino-4-pyridyl)piperidine-4-carboxylic acid that was used without further purification. MS (ES+) 222.1.

Step 2: 1-(3-aminopyridin-4-yl)-N,N-dimethylpiperidine-4-carboxamide

[00343] A microwave vial was charged with 1-(3-amino-4-pyridyl)piperidine-4-carboxylic acid (125 mg, 0.197mmol), TBTU (200 mg, 0.62mmol) and N-methylmethanamine (3.5mL, 2M in MeOH). The tube was sealed and the mixture stirred for 3h at 120°C. The crude was redissolved in MeOH and loaded into a MeOH pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure to yield 1-(3-aminopyridin-4-yl)-*N*,*N*-

dimethylpiperidine-4-carboxamide. MS (ES+) 249.2.

Preparation N-3: 4-(4-(dimethylamino)piperidin-1-yl)pyridin-3-amine



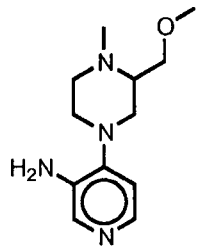
Step 1: tert-butyl (1-(3-aminopyridin-4-yl)piperidin-4-yl)(methyl)carbamate

[00344] To a solution of tert-butyl N-[1-(3-nitro-4-pyridyl)-4-piperidyl]carbamate (2100 mg, 6.514 mmol) (prepared according to methods similar to the one depicted in **Step 1** of **Preparation N-1**) and iodomethane (4.623 g, 2.028 mL, 32.57 mmol) in DMF at 0°C was added portionwise sodium hydride (312.7 mg, 7.817 mmol). The reaction was stirred at 0°C for 1 h, and at room temperature for 1 h. The reaction was quenched by pouring the reaction mixture onto a saturated aqueous solution of ammonium chloride, then extracted with ethyl acetate (2 x 50 mL). The combined organics was washed with brine (2 x 50 mL), dried and evaporated to leave an orange solid. To the crude solid dissolved in MeOH (50 mL) was added Pd/C (10%) (346mg) and the mixture was stirred under a hydrogen atmosphere for 4 h. The reaction was filtered through celite and evaporated to leave *tert*-butyl (1-(3-aminopyridin-4-yl)piperidin-4-yl)(methyl)carbamate as a yellow oil. (600mg, 20%) MS (ES+ -tBu) 251.1.

Step 2: 4-(4-(dimethylamino)piperidin-1-yl)pyridin-3-amine

[00345] A solution of $LiAlH_4$ (49.57 mg, 1.306 mmol) was added dropwise to a solution of tert-butyl *N*-[1-(3-amino-4-pyridyl)-4-piperidyl]-N-methyl-carbamate (100 mg, 0.3264 mmol) in THF at room temp. The reaction was stirred at 50°C for 3h, then at room temperature, the reaction mixture was quenched by the dropwise addition of wet THF. The reaction mixture was partitioned between 1N NaOH (50 mL) and diethyl ether (50 mL). The combined organics was dried ($MgSO_4$) and evaporated to leave 4-(4-(dimethylamino)piperidin-1-yl)pyridin-3-amine as a yellow oil. MS (ES+) 221.1.

Preparation N-4: 4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)pyridin-3-amine



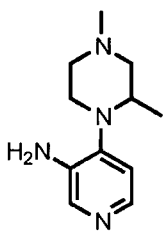
Step 1: 2-(methoxymethyl)-1-methyl-4-(3-nitropyridin-4-yl)piperazine

[00346] To (1-methyl-4-(3-nitropyridin-4-yl)piperazin-2-yl)methanol (prepared according to methods similar to the one depicted in **Step 1** of **Preparation N-1**) (250 mg, 0.9910 mmol) in DMF (2 mL) at 0°C was added NaH (59.43 mg, 1.486 mmol). The reaction mixture was stirred for 10 min before MeI (281.3 mg, 123.4 μL, 1.982 mmol) was added dropwise. The reaction mixture was allowed to warm to RT and was stirred for 2 hours. The reaction mixture was loaded on a pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure. The residue was purified by column chromatography on silica, eluting with 1-15% MeOH:DCM yielding 2-(methoxymethyl)-1-methyl-4-(3-nitropyridin-4-yl)piperazine (84 mg, 32%). MS (ES+) 237.1.

Step 2: 4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)pyridin-3-amine

[00347] To a solution of 2-(methoxymethyl)-1-methyl-4-(3-nitropyridin-4-yl)piperazine (84mg, 0.31mmol) in methanol was added Pd on C (10%, wet, Degussa) (10 mg) and the reaction mixture was stirred overnight at room temperature under a balloon of hydrogen. The catalyst was filtered off and and the filtrate was concentrated under reduced pressure to yield 4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)pyridin-3-amine as a film. (72 mg, 96%). MS (ES+) 267.1.

Preparation N-5: 4-(2,4-dimethylpiperazin-1-yl)pyridin-3-amine



Step 1: 2-methyl-1-(3-nitro-4-pyridyl)piperazine

[00348] To a solution of *tert*-butyl 3-methyl-4-(3-nitropyridin-4-yl)piperazine-1-carboxylate (prepared according to methods similar to the one depicted in **Step 1** of **Preparation N-1**) in DCM (5 mL) was added TFA (1.445 g, 976.4 μL, 12.67 mmol). The reaction mixture was stirred for 48h at RT, then the solvent was removed under reduced pressure. The crude was redissolved in MeOH and loaded into a MeOH pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure to yield 2-methyl-1-(3-nitro-4-pyridyl)piperazine (334mg, 71%). MS (ES+) 223.1.

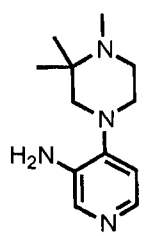
Step 2: 2,4-dimethyl-1-(3-nitropyridin-4-yl)piperazine

[00349] To 2-methyl-1-(3-nitro-4-pyridyl)piperazine in DMF (1.5 mL of 0.3 M, 0.4500 mmol) at 0°C was added NaH (18.00mg, 0.4500 mmol). The reaction was stirred for 10 mins then MeI (60.68 mg, 26.61 μL, 0.4275 mmol) was added. The reaction mixture was stirred for 4 hours at RT and quenched by the addition of water. The crude was loaded onto a MeOH pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure. The residue was purified by column chromatography eluting with 1-15% MeOH:DCM to yield 2,4-dimethyl-1-(3-nitropyridin-4-yl)piperazine. MS (ES+) 237.2.

Step 3: 4-(2,4-dimethylpiperazin-1-yl)pyridin-3-amine

[00350] A solution of 2,4-dimethyl-1-(3-nitro-4-pyridyl)piperazine (89 mg, 0.3767 mmol) in methanol (4 mL) and Pd on C (10%, wet, Degussa) (20 mg) was hydrogenated overnight at RT under an atmosphere of hydrogen (balloon). The catalyst was filtered off through a Celite cartridge, washed with methanol. The filtrate was concentrated under reduced pressure yielding 4-(2,4-dimethylpiperazin-1-yl)pyridin-3-amine (71 mg, 91%). MS (ES+) 207.2.

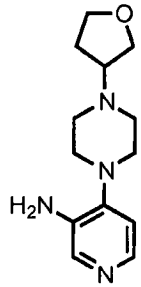
Preparation N-6: 4-(3,3,4-trimethylpiperazin-1-yl)pyridin-3-amine



[00351] To 4-(3,3-dimethylpiperazin-1-yl)pyridin-3-amine (prepared according to methods similar to the one depicted in **Preparation N-1**) (120 mg, 0.5817 mmol) in DMF (2 mL) at 0

°C was added NaH (20.94 mg, 0.5235 mmol). The reaction mixture was stirred for 10 mins at 0°C then MeI (276.3uL, 0.5526mmol, 2M in TBDME) was added. The reaction mixture was allowed to warm to RT and was stirred for 2hours at RT. The crude was loaded onto a MeOH pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure to yield 4-(3,3,4-trimethylpiperazin-1-yl)pyridin-3-amine (128mg, 73%). MS (ES+) 221.1.

Preparation N-7: 4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-amine



Step 1: 1-(3-nitropyridin-4-yl)-4-(tetrahydrofuran-3-yl)piperazine

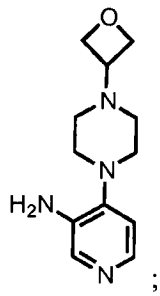
[00352] A round-bottomed flask was charged with 1-(3-nitro-4-pyridyl)piperazine (prepared according to methods similar to the one depicted in **Step 1** of **Preparation N-1**), dihydrofuran-3(2*H*)-one (98mg, 1.13 mmol) and acetic acid (129uL, 2.27 mmol) in MeCN (4mL). $Na(OAc)_3BH$ (482.4mg, 2.27 mmol) was added and the reaction mixture was stirred at RT for 1h. The reaction mixture was partitioned between EtOAC and an aqueous saturated solution of Na_2CO_3. The organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure to give 1-(3-nitropyridin-4-yl)-4-(tetrahydrofuran-3-yl)piperazine as a yellow solid. MS (ES+) 279.1.

Step 2: 4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-amine

[00353] A solution of 1-(3-nitropyridin-4-yl)-4-(tetrahydrofuran-3-yl)piperazine (316mg, 1.13mmol) in MeOH (15 mL), Pd on C (10%, wet, Degussa) (120mg) was stirred overnight at RT under an hydrogen atmosphere (balloon). The mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude was redissolved in MeOH and loaded into a MeOH pre-washed SCX column, rinsed with MeOH and the product was released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure to give 4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-amine as a solid which was used in next step without further purification. (300mg, purity 77%, yield 82%). MS (ES+) 249.2.

[00354] The following aminopyridine were prepared according to methods similar to the one depicted in **Preparation N-7**:

4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-amine:



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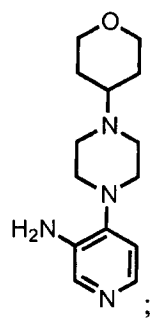
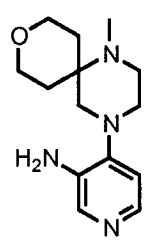
4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)pyridin-3-amine:



; and

4-(1-methyl-9-oxa-1,4-diazaspiro[5.5]undecan-4-yl)pyridin-3-amine:



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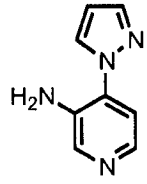
Preparation N-8: 4-(1H-pyrazol-1-yl)pyridin-3-amine



Step 1: 3-nitro-4-(1H-pyrazol-1-yl)pyridine

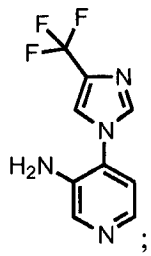
[00355] A suspension of pyrazole (150mg, 2.2mmol) and Cs_2CO_3(526mg, 1.6mmol) in anhydrous MeCN (3.5 mL) was stirred for 20 min under an inert atmosphere. 4-chloro-3-nitro-pyridine (233mg, 1.47mmol) was then added and stirred overnight at 75°C. The insoluble was filtered off and the filtrate was concentrated under reduced pressure yielding 3-nitro-4-(1*H*-pyrazol-1-yl)pyridine that was used without further purification. (410mg, 98%). MS (ES+) 191.1.

Step 2: 4-(1H-pyrazol-1-yl)pyridin-3-amine

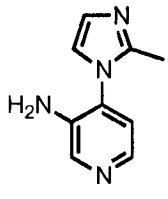
[00356] To a solution of 3-nitro-4-(1*H*-pyrazol-1-yl)pyridine (410mg, 2.15mmol) in MeOH (15mL) was added Pd on C (10%, wet, Degussa) (129mg) and the reaction mixture was vigorously stirred overnight at RT under an atmosphere of hydrogen (balloon). The catalyst was filtered off and the filtrate was concentrated under reduced pressure yielding 4-(1*H*-pyrazol-1-yl)pyridin-3-amine. (285mg, 82%). MS (ES+) 161.1.

[00357] The following aminopyridine were prepared according to methods similar to the one depicted in **Preparation N-8**:

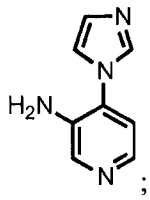
4-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-3-amine:



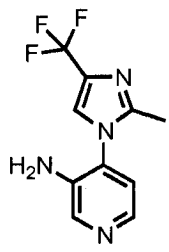
4-(2-methyl-1H-imidazol-1-yl)pyridin-3-amine:


;

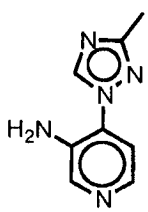
4-(1H-imidazol-1-yl)pyridin-3-amine:


;

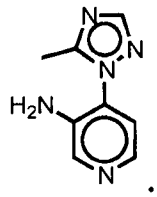
4-(2-methyl-4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-3-amine:


;

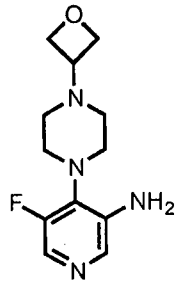
4-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine:


; and

4-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine:



Preparation N-9: 5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-amine



Step 1: 1-(3-chloro-5-fluoropyridin-4-yl)piperazine

[00358] In a 100 mL sealed reaction vessel/bomb, 3-chloro-5-fluoro-4-iodo-pyridine (5600 mg, 21.75 mmol) was taken up in NMP (12 mL). To the resulting clear brown solution was added DIPEA (3.373 g, 4.546 mL, 26.10 mmol) followed by piperazine (2.810 g, 32.62 mmol). The vessel was sealed and heated thermally at 120°C for 18hrs. The mixture was allowed to cool to RT and was concentrated *in vacuo* to afford a brown gum which was purified by chromatography on silica, eluting with a gradient of DCM-DCM:MeOH:NH_3(90:10:1) 100-0 to 0:100. Fractions containing clean product were collected and concentrated *in vacuo* to afford 1-(3-chloro-5-fluoropyridin-4-yl)piperazine as a cream solid. (3.52g, 75%). MS (ES+) 216.0.

Step 2: 1-(3-chloro-5-fluoro-4-pyridyl)-4-(oxetan-3-yl)piperazine

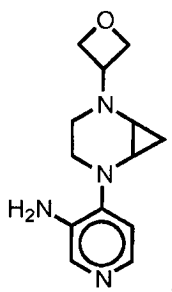
[00359] To a suspension of 1-(3-chloro-5-fluoropyridin-4-yl)piperazine (900 mg, 4.173 mmol) in THF (9.000 mL) was added 3-oxetanone (601.4 mg, 8.346 mmol). To this mixture, under N_2, was added sodium triacetoxyborohydride (2.034 g, 9.598 mmol) portionwise over 5 min and the reaction mixture was stirred at RT overnight. MeOH (2ml) was added to the flask before the mixture was concentrated *in vacuo*. The residue was partitioned between water (50ml) and EtAOc (50ml). The aqueous phase was basified to pH 7-8 with NH_4OH. Combined organics washed with brine (30ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 1-(3-chloro-5-fluoro-4-pyridyl)-4-(oxetan-3-yl)piperazine as a cream solid that was used in next step without further purification. MS (ES+) 272.1.

Step 3: 5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-amine

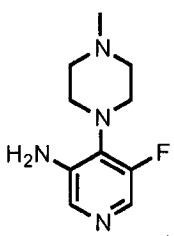
[00360] In a pressure tube containing 1-(3-chloro-5-fluoro-4-pyridyl)-4-(oxetan-3-yl)piperazine (800 mg, 2.944 mmol) was added dioxane (6 mL). To this solution was added tert-butyl carbamate (517.3 mg, 4.416 mmol), Cs_2CO_3 (1.918 g, 5.888 mmol), xantphos (85.17 mg, 0.1472 mmol) followed by $Pd_2(dba)_3$ (134.8 mg, 0.1472 mmol). The tube was sealed and heated thermally for 60h at 115°C. The reaction mixture was cooled to RT and filtered on a pad of celite. The cake was washed with EtOAc and the combined filtrate was concentrated *in vacuo* to a black oil. The residue was taken up in DCM (2ml) and TFA (3ml) was added. The resulting dark brown clear solution was stirred at RT for 2h and then concentrated *in vacuo*. The residue was loaded onto a SCX-2 (10g) cartridge. Flushed with MeOH (x3, CV) before eluting the desired product with 2M NH_3 in MeOH (x3 CV). The basic eluent was concentrated *in vacuo* to afford a dark brown oil that was purified by chromatography on silica eluting with DCM-DCM:MeOH:NH_3(90:10:1) a gradient of 100-0 to 30:70. Fractions containing product were collected and concentrated *in vacuo* to afford 5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-amine as a light brown solid. 295mg: MS (ES+) 253.2.

[00361] The following aminopyridines were prepared according to methods similar to the one depicted in **Preparation N-9**:

4-(5-(oxetan-3-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-3-amine:



Preparation N-10: 5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-amine



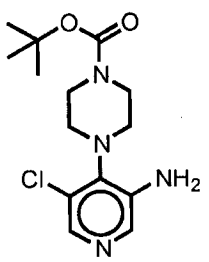
Step 1: 1-(3-chloro-5-fluoropyridin-4-yl)-4-methylpiperazine

[00362] A solution of 3-chloro-5-fluoro-4-iodo-pyridine (2.18 g, 8.468 mmol), 1-methylpiperazine (1.272 g, 1.409 mL, 12.70 mmol) and DIPEA (2.189 g, 2.950 mL, 16.94 mmol) in MeCN (13.08 mL) was heated at 130°C in the microwave for 300 min. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica eluting with 0-10% MeOH/ DCM. Product fractions were combined and concentrated *in vacuo* to leave 1-(3-chloro-5-fluoropyridin-4-yl)-4-methylpiperazine as a yellow/brown oil. (1.16g, 59%). MS (ES+) 230.0.

Step 2: 5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00363] A mixture of tert-butyl carbamate (709.9 mg, 6.060 mmol), Cs_2CO_3 (3.291 g, 10.10 mmol), xantphos (146.1 mg, 0.2525 mmol), $Pd_2(dba)_3$ (231.2 mg, 0.2525 mmol) and 1-(3-chloro-5-fluoro-4-pyridyl)-4-methyl-piperazine (1.16 g, 5.050 mmol) in dioxane (11.60 mL) was heated at 110°C for 1h. At room temperature, tert-butyl carbamate (709.9 mg, 6.060 mmol), xantphos (146.1 mg, 0.2525 mmol) and $Pd_2(dba)_3$ (231.2 mg, 0.2525 mmol) was added and the mixture was further heated at 120°C in the microwave for 1h. The reaction mixture was then filtered through a celite pad and washed with methanol and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica, using the ISCO column companion system eluting with 0-10% MeOH/DCM. Product fractions were combined and concentrated *in vacuo* to yield 5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-amine as a light brown viscous oil. (642mg, 60%). MS (ES+) 211.1.

Preparation N-11: *tert*-butyl 4-(3-amino-5-chloropyridin-4-yl)piperazine-1-carboxylate



Step 1: tert-butyl 4-(3-chloro-5-nitropyridin-4-yl)piperazine-1-carboxylate

[00364] A mixture of 4-bromo-3-chloro-5-nitro-pyridine (700 mg, 2.948 mmol), tert-butyl piperazine-1-carboxylate (823.6 mg, 4.422 mmol) and DIPEA (762.0 mg, 1.027 mL, 5.896 mmol) in NMP (2.5 mL) was stirred overnight at RT. The reaction mixture was partitioned

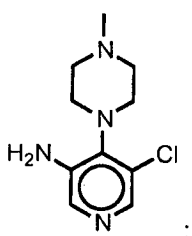
between EtOAc and water. Combined organic extract was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure to yield *tert*-butyl 4-(3-chloro-5-nitropyridin-4-yl)piperazine-1-carboxylate which was used in next step without further purification (1g, 99%). MS (ES+) 343.1.

Step 2: tert-butyl 4-(3-amino-5-chloropyridin-4-yl)piperazine-1-carboxylate

[00365] To a solution of *tert*-butyl 4-(3-chloro-5-nitropyridin-4-yl)piperazine-1-carboxylate (900 mg, 2.626 mmol) and $ZnBr_2$ (118.3 mg, 28.16 μL, 0.5252 mmol) in methanol (27.00 mL) was added Pd on C (10%, wet, Degussa) (300 mg). The reaction mixture was stirred at RT for 4h under an atmosphere of hydrogen (balloon). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to yield *tert*-butyl 4-(3-amino-5-chloropyridin-4-yl)piperazine-1-carboxylate which was used without further purification (820mg, 99%). MS (ES+) 313.2.

[00366] The following aminopyridines were prepared according to methods similar to the one depicted in **Preparation N-11**:

5-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-amine:



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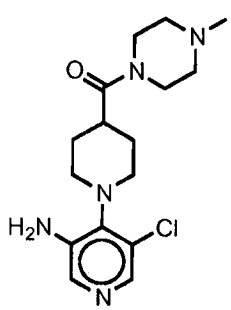
(1-(3-amino-5-chloropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone:



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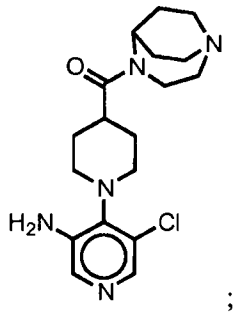
(1-(3-amino-5-chloropyridin-4-yl)piperidin-4-yl)(1,4-diazabicyclo[3.2.2]nonan-4-yl)methanone:



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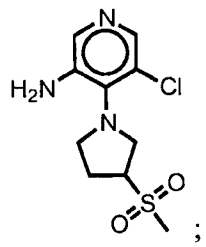
5-chloro-4-(3-(methylsulfonyl)pyrrolidin-1-yl)pyridin-3-amine:



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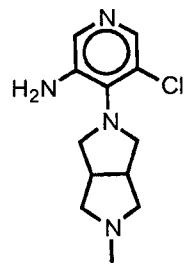
5-chloro-4-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyridin-3-amine:



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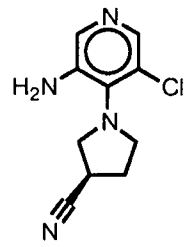
(*R*)-1-(3-amino-5-chloropyridin-4-yl)pyrrolidine-3-carbonitrile:



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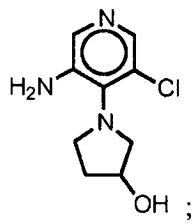
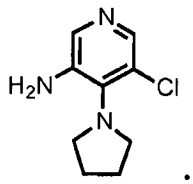
1-(3-amino-5-chloropyridin-4-yl)pyrrolidin-3-ol:



; and

5-chloro-4-(pyrrolidin-1-yl)pyridin-3-amine:



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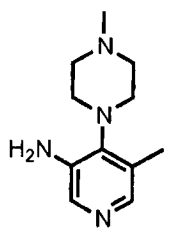
Preparation N-12: 1-methyl-4-(3-methyl-5-nitropyridin-4-yl)piperazine



Step 1: 1-methyl-4-(3-methyl-5-nitro-4-pyridyl)piperazine

[00367] To an oven dried flask under nitrogen was added 1-(3-bromo-5-nitro-4-pyridyl)-4-methyl-piperazine (synthesized from 3-bromo-4-chloro-5-nitropyridine according to methods similar to the one depicted in **Step 1** of **Preparation N-1**) (750 mg, 2.491 mmol), Pd_2dba_3 (34.21 mg, 0.03736 mmol) and X-Phos (35.62 mg, 0.07473 mmol). Anhydrous THF (37.50 mL) was added followed by 1,4-diazabicyclo[2.2.2]octane trimethylalumane (638.6 mg, 2.491 mmol). The reaction was heated at reflux for 2 hours then cooled to ambient temperature. The reaction mixture was partitioned between water and EtOAc. The combine organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by column chromatography on silica using the ISCO column companion system (24 g column, Ethyl acetate/ petroleum ether(0-100% EtOAc)) to yield 1-methyl-4-(3-methyl-5-nitro-4-pyridyl)piperazine as a yellow oil. (290mg, 49%). MS (ES+) 237.1.

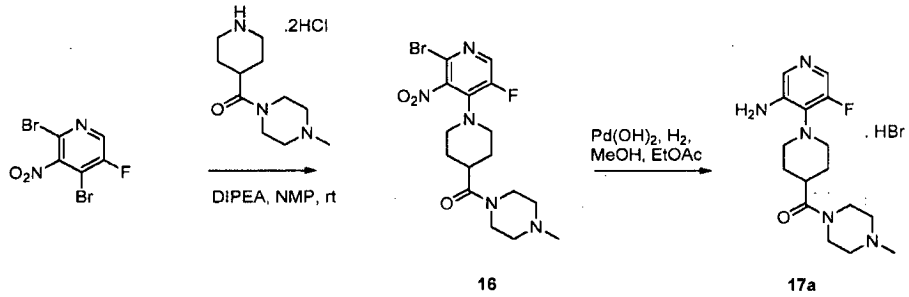
Step 2: 5-methyl-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00368] A suspension of Pd on C, (10%, wet, Degussa) (130.6 mg, 0.1227 mmol) with 1-

methyl-4-(3-methyl-5-nitro-4-pyridyl)piperazine (290 mg, 1.227 mmol) in methanol (5.800 mL) was stirred at rt overnight under an atmosphere of hydrogen (balloon). The reaction mixture was filtered through a celite pad and washed with methanol and ethyl acetate and the filtrate concentrated *in vacuo* to leave 5-methyl-4-(4-methylpiperazin-1-yl)pyridin-3-amine as a yellow oil (243mg, 96%). MS (ES+) 207.1.

Preparation N-13: (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone (hydrobromide) 17a

Scheme 5



Step 1: (1-(2-bromo-5-fluoro-3-nitropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone **16**

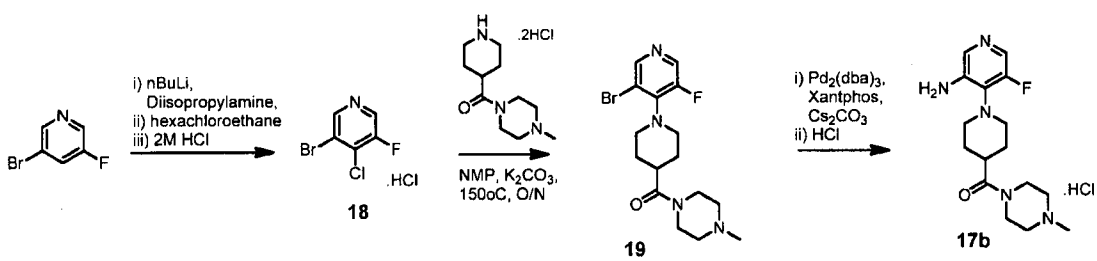
[00369] A round-bottomed flask was charged with (4-methylpiperazin-1-yl)-(4-piperidyl)methanone dihydrochloride (16.45 g, 57.89 mmol) and DIPEA (23.20 g, 31.27 mL, 179.5 mmol) in NMP (160 mL). 2, 4-Dibromo-5-fluoro-3-nitro-pyridine (17.36 g, 57.89 mmol) was added and the reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. Additional (4-methylpiperazin-1-yl)-(4-piperidyl)methanone dihydrochloride (1.65g, 0.1eq) and DIPEA (1mL, 0.1eq) was added and stirred at room temperature for a further 3 h. The mixture diluted with EtOAc, washed with water (3x). The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were combined, washed with brine, dried (sodium sulfate), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (330g SiO_2, 0 to 5% MeOH (containing 10% ammonium hydroxide)/DCM) to afford product as a yellow solid (20.24 g, 81%). MS (ES+) 432.0.

Step 2: (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone hydrobromide **17a**

[00370] [1-(2-Bromo-5-fluoro-3-nitro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone **16** (20.24 g, 47.04 mmol) was dissolved/suspended in MeOH (389 mL)/EtOAc (78 mL) and $Pd(OH)_2$ (1.651 g, 2.352 mmol) was added. The resulting mixture was degassed by vacuum/nitrogen cycles (x5) and the atmosphere was exchanged by vacuum/hydrogen cycles (x5). The reaction mixture was stirred vigorously under a hydrogen atmosphere (balloon) for 6 hrs. Additional $Pd(OH)_2$ (4.95g) was added and the reaction mixture was stirred overnight under hydrogen. The mixture was filtered through celite, washing through with methanol. The filtrate was concentrated *in vacuo* to leave an orange gum. Approx. 150 mL of ethanol was added and the mixture rotated on buchii for 10 mins, a yellow precipitate had formed during this time. The suspension was sonicated for 5 mins and the solid was then collected by filtration, washed with minimal ethanol and dried by suction for 1 h to afford product as a pale yellow solid. A second crop of product was obtained by concentrating the filtrate *in vacuo.* The residue was then slurried in minimal ethanol and sonicated for 5 mins then solid collected by filtration, dried by suction to leave second crop of product as a yellow solid. Both crops of product were combined to afford product as a yellow solid (15.8 g, 79%). MS (ES+) 322.2.

Preparation N-14: (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone (hydrochloride) 17b

Scheme 6



Step 1: 3-bromo-4-chloro-5-fluoropyridine hydrochloride **18**

[00371] To a solution of diisopropylamine (6.899 g, 9.555 mL, 68.18 mmol) in THF (75 mL) cooled to -78°C, was added butyllithium (25 mL of 2.5 M in hexanes, 62.5 mmol). The reaction mixture was allowed to warm to -20°C then cooled back down to -78°C. A solution of 3-bromo-5-fluoro-pyridine (10 g, 56.82 mmol) in THF (25 mL) was added dropwise keeping temperature below -70°C (approx 30 mins). The reaction mixture was stirred at -78°C for 30 min and a solution of 1,1,1,2,2,2-hexachloroethane (14.8 g, 62.5 mmol) in THF

(20 mL) was then added dropwise, keeping temperature below -70°C (over approx 30 mins). The mixture was stirred at -78°C for 20 minutes, allowed to warm to room temperature, cooled back to 0°C and quenched with water (100 mL). EtOAc (400 mL) was then added, and organic layer separated, washed with water (2x), brine (1x), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a brown solid. The solid was triturated in pentane (100mL) for 10 minutes, then filtered. The filtrate was concentrated *in vacuo* to afford product as a brown oil that turned to a crystalline solid on standing, 11.85 g, 89%). ^{1}H NMR (DMSO-d6) δ 8.78 (s, 1H), 8.76 (s, 1H).

[00372] To a solution of 3-bromo-4-chloro-5-fluoro-pyridine (7.56 g, 32.18 mmol) in pentane (100 mL) was added hydrogen chloride (2M in ether) (17.7 mL of 2 M, 35.4 mmol). An off-white precipitate formed instantly. The mixture was stirred for 5 minutes then the solid was collected by filtration, washed with pentane and dried by suction to afford the desired product as an off-white solid (4.79 g, 60%). ^{1}H NMR (DMSO-d6) δ 8.77 (s, 1H), 8.75 (s, 1H).

Step 2: (1-(3-bromo-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone **19**

[00373] A mixture of (4-methylpiperazin-1-yl)-(4-piperidyl)methanone dihydrochloride (50.65 g, 178.2 mmol), 3-bromo-4-chloro-5-fluoro-pyridine hydrochloride **18** (40 g, 162 mmol) and dipotassium carbonate (94.04 g, 680.4 mmol) in NMP (400 mL) was heated at 150°C overnight. The mixture was cooled to room temperature then filtered to remove inorganic salts and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (800 mL), washed with brine (100 mL x 4), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown viscous oil. This residue was purified by silica gel column (approx 800 g of silica), product loaded onto silica in DCM, then eluting with 3% methanol (containing 10% ammonium hydroxide)/DCM to afford the desired product as a brown oil which crystallised on standing (27.44 g, 44%). MS (ES+) 387.1.

Step 3: (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone hydrochloride **17b**

[00374] $Pd_2(dba_3)$ (3.818 g, 4.169 mmol) and Xantphos (4.824 g, 8.337 mmol) were added to a degassed (3 x vacuum/N_2 cycles) mixture of diphenylmethanimine (16.62 g, 15.39 mL, 91.71 mmol), [1-(3-bromo-5-fluoro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone **19** (32.12 g, 83.37 mmol), tert-butyl carbamate (3.649 g, 31.15 mmol), and

Cs_2CO_3 (81.49 g, 250.1 mmol) in dioxane (550 mL) in a round bottom flask under N_2. The reaction mixture was flushed with nitrogen via 2 x vacuum/N_2 cycles then stirred at 100°C overnight under N_2. The mixture cooled to room temperature then partitioned between EtOAc (1 L) and water (100 mL). The organic layer was separated, washed with water (2x 100 mL), brine (1x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a dark orange viscous oil (56.15 g). This crude residue was then dissolved in THF (482 mL) and hydrogen chloride (300 mL of 2 M, 600 mmol) and the mixture was heated at 60°C for 30 minutes. THF was removed *in vacuo* and the remaining aqueous solution was washed with EtOAc (2x) then basified to pH = 8 with 2M NaOH solution (approx. 310 mL), and extracted with EtOAc (3x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange solid (25.44 g).The orange solid was dissolved in dioxane (300 mL) then 4M HCl in dioxane (19.8 mL, 79.16 mmol) was added slowly over 10 mins. The mixture was stirred for 20 minutes and the precipitate that formed was collected by filtration, washed with dioxane (approx 100 mL), diethyl ether (100 mL), dried by suction to afford desired product as a white solid (25.13 g, 84%). MS (ES+) 322.2.

Step 3a: (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone ***17***

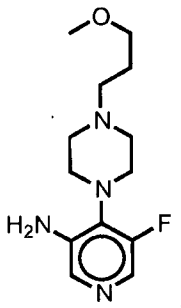
[00375] In an alternative method to *Step 3*, above, Tris(dibenzylideneacetone)dipalladium (1.189 g, 1.298 mmol) and xantphos (1.502 g, 2.596 mmol) were added to a degassed (3 x vacuum/N_2 cycles) mixture of [1-(3-bromo-5-fluoro-4-pyridyl)-4-piperidyl]-(4-methylpiperazin-1-yl)methanone **19** (10 g, 25.96 mmol) and Cs_2CO_3 (16.92 g, 51.92 mmol) in dioxane (150 mL) under N_2 . The mixture was stirred at 100°C overnight. The reaction was cooled to ambient temperature and the precipitate was filtered off and washed with EtOAc (50mL). The filtrate was partitioned between EtOAc and water. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to leave tert-butyl N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-pyridyl]carbamate as a red solid that was used in next step without further purification. MS (ES+) 422.2.

[00376] To a suspension of tert-butyl N-[5-fluoro-4-[4-(4-methylpiperazine-1-carbonyl)-1-piperidyl]-3-pyridyl]carbamate (3.34 g, 7.924 mmol) in dioxane (25 mL) was added HCl (4M in dioxane) (8 mL of 4 M) and the mixture was heated at 40°C overnight. The mixture was cooled to RT and the solid was collected by filtration, washed with dioxane (15 mL) then with EtOAc (2 x 20 ml) and dried *in vacuo* to leave a white solid which was partitioned

between EtOAc (70 ml) and 1M sodium carbonate (50 ml). Combined organic extract was dried and concentrated *in vacuo* to yield 2.26 g of an off-white solid that was slurried in MeCN (5 mL). The solid was collected by filtration, washed with minimal MeCN (3 to 5 mL), and dried by suction to leave (1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)(4-methylpiperazin-1-yl)methanone as a white solid. MS (ES+) 322.1.

[00377] The following aminopyridine intermediates were prepared using a procedure similar to either **Preparation N-13** or **Preparation N-14**:

5-fluoro-4-(4-(3-methoxypropyl)piperazin-1-yl)pyridin-3-amine:



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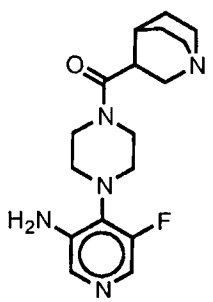
(4-(3-amino-5-fluoropyridin-4-yl)piperazin-1-yl)(quinuclidin-3-yl)methanone:



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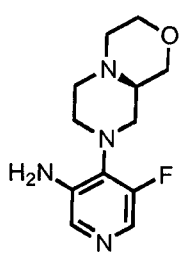
(*R*)-5-fluoro-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-amine:



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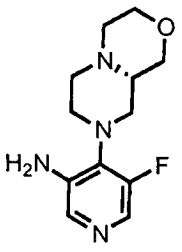
(*S*)-5-fluoro-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-amine:



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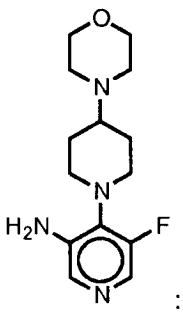
5-fluoro-4-(4-morpholinopiperidin-1-yl)pyridin-3-amine:



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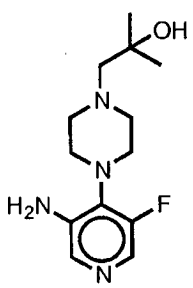
1-(4-(3-amino-5-fluoropyridin-4-yl)piperazin-1-yl)-2-methylpropan-2-ol:



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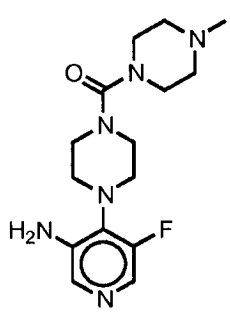
(4-(3-amino-5-fluoropyridin-4-yl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone:



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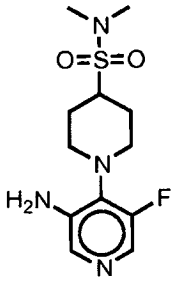
1-(3-amino-5-fluoropyridin-4-yl)-*N*,*N*-dimethylpiperidine-4-sulfonamide:



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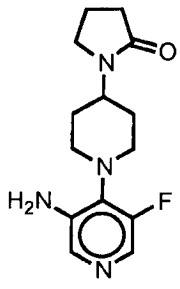
1-(1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)pyrrolidin-2-one:



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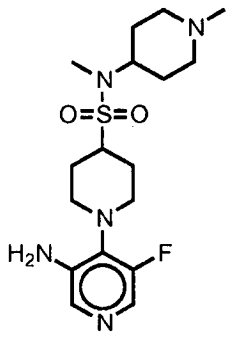
1-(3-amino-5-fluoropyridin-4-yl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)piperidine-4-sulfonamide:



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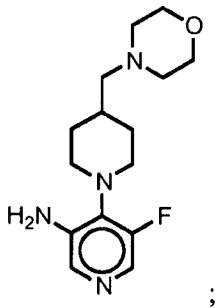
5-fluoro-4-(4-(morpholinomethyl)piperidin-1-yl)pyridin-3-amine:



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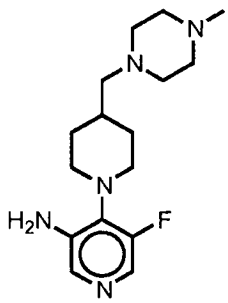
5-fluoro-4-(4-((4-methylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-amine:



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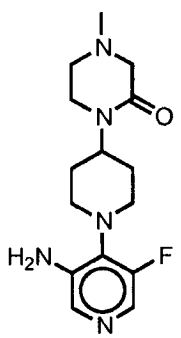
1-(1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)-4-methylpiperazin-2-one:



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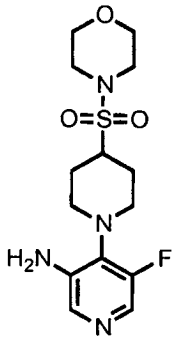
5-fluoro-4-(4-(morpholinosulfonyl)piperidin-1-yl)pyridin-3-amine:



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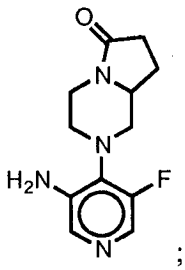
2-(3-amino-5-fluoropyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one:



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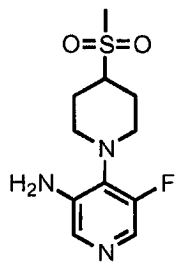
5-fluoro-4-(4-(methylsulfonyl)piperidin-1-yl)pyridin-3-amine:



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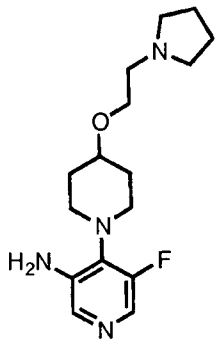
5-fluoro-4-(4-(2-(pyrrolidin-1-yl)ethoxy)piperidin-1-yl)pyridin-3-amine:



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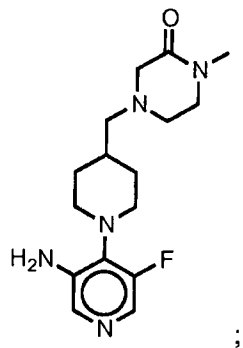
4-((1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)methyl)-1-methylpiperazin-2-one:



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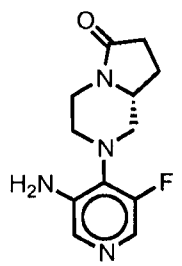
(*R*)-2-(3-amino-5-fluoropyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one:



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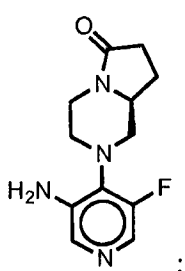
(*S*)-2-(3-amino-5-fluoropyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one:



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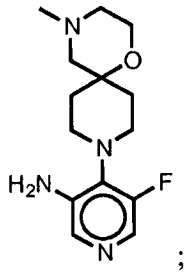

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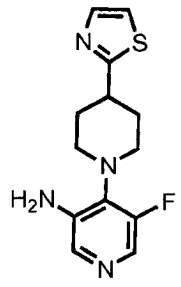

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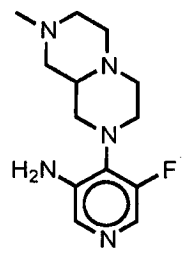
5-fluoro-4-(8-methylhexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-amine:



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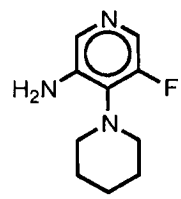
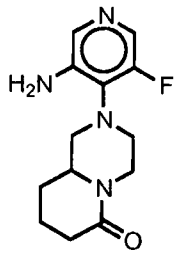
5-fluoro-4-(piperidin-1-yl)pyridin-3-amine:



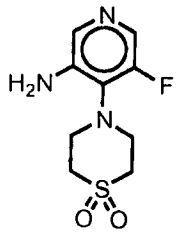
;

2-(3-amino-5-fluoropyridin-4-yl)hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-6(2*H*)-one:



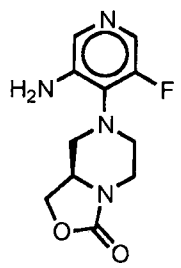
;

4-(3-amino-5-fluoropyridin-4-yl)thiomorpholine 1,1-dioxide:



;

(*R*)-7-(3-amino-5-fluoropyridin-4-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one:



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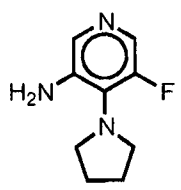
5-fluoro-4-(pyrrolidin-1-yl)pyridin-3-amine:



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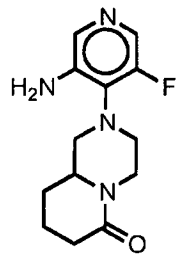
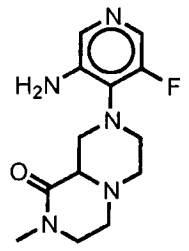
2-(3-amino-5-fluoropyridin-4-yl)hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-6(2*H*)-one:



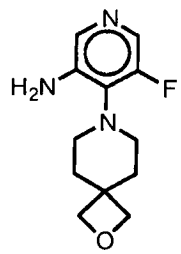
;

8-(3-amino-5-fluoropyridin-4-yl)-2-methyloctahydro-1*H*-pyrazino[1,2-*a*]pyrazin-1-one:



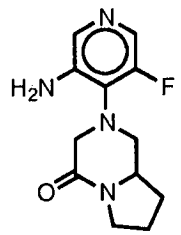
;

5-fluoro-4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridin-3-amine:



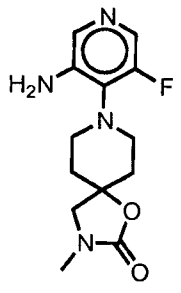
;

2-(3-amino-5-fluoropyridin-4-yl)hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one:

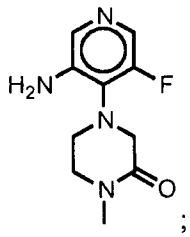


;

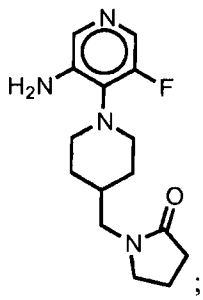
8-(3-amino-5-fluoropyridin-4-yl)-3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one:



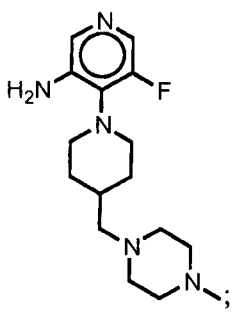
4-(3-amino-5-fluoropyridin-4-yl)-1-methylpiperazin-2-one:



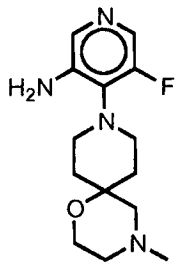
1-((1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)methyl)pyrrolidin-2-one:



5-fluoro-4-(4-((4-methylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-amine:

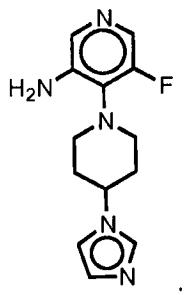


5-fluoro-4-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)pyridin-3-amine:



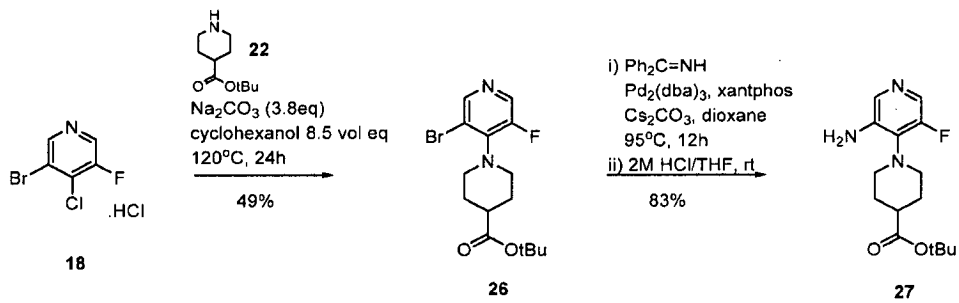
; and

4-(4-(1*H*-imidazol-1-yl)piperidin-1-yl)-5-fluoropyridin-3-amine:



Preparation N-15: tert-butyl 1-(3-amino-5-fluoro-4-pyridyl)piperidine-4-carboxylate

Scheme 7a:



Step 1: tert-butyl 1-(3-bromo-5-fluoro-4-pyridyl)piperidine-4-carboxylate **26**

[00378] A 3L flange flask equipped with a thermometer, condensor, nitrogen line and overhead stirrer was heated at 40°C (external) then charged with cyclohexanol (750 mL), disodium carbonate (129.8 g, 1.225 mol), 3-bromo-4-chloro-5-fluoro-pyridine (Hydrochloric Acid **18**) (137.5 g, 556.8 mmol) and tert-butyl piperidine-4-carboxylate (123.8 g, 668.2 mmol) rinsed in with cyclohexanol (350 mL). Mixture was heated to 120°C internal temperature overnight (18h). Reaction mixture was removed from hotplate and allowed to cool to room temperature. Water (687.5 mL) and EtOAc (687.5 mL) were added, stirred for 10 mins then transferred to separating funnel. Additional EtOAc (1.238 L) was added, mixed

and aqueous phase was removed. Organic phase was further washed with water (687 mL), aqueous phase removed, organic layer collected. Aqueous phases were combined and back extracted with EtOAc (687.5 mL), aqueous layer removed and organic phase combined with other organics. Organics concentrated in vacuo (water bath temp = 60°C, vaccum down to 2 mBar) leaving a viscous brown oil.

[00379] Oil was dissolved in 25% EtOAc/petrol then passed through a short silica pad, eluting with 25% EtOAc/petrol until no more product came off. Filtrate was concentrated in vacuo to leave a brown oil, 127.1g. Product re-purified by ISCO companion (1.5Kg Silica, loaded in DCM, eluting 0 to 20% EtOAc/petrol), product fractions combined and concentrated in vacuo to leave desired product **26** as a pale yellow to cream solid, (98g, 49% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 8.47 (s, 1H), 8.41 (d, 1H), 3.39 – 3.36 (m, 2H), 3.12 (tt, 2H), 2.49 – 2.43 (m, 1H), 1.91 – 1.87 (m, 2H), 1.71 – 1.64 (m, 2H) and 1.43 (s, 9H). MS (ES+) 361.0.

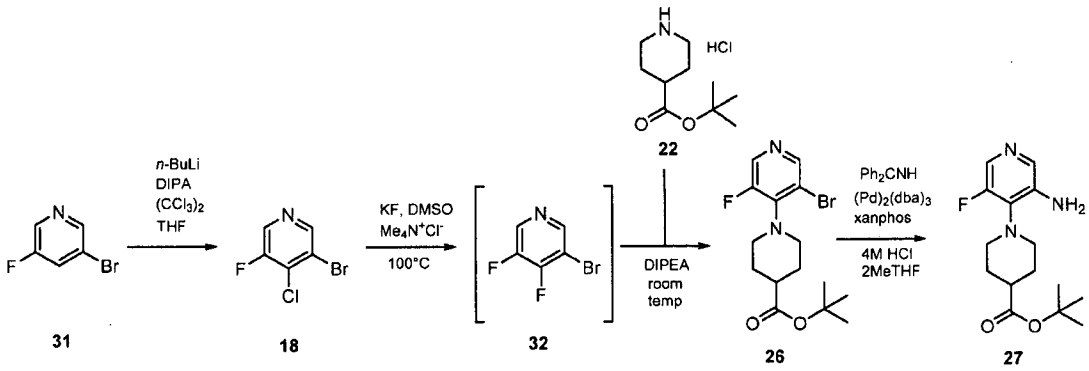
Step 2: tert-butyl 1-(3-amino-5-fluoro-4-pyridyl)piperidine-4-carboxylate **27**

[00380] To a solution of tert-butyl 1-(3-bromo-5-fluoro-4-pyridyl)piperidine-4-carboxylate **26** (98 g, 272.8 mmol), diphenylmethanimine (59.34 g, 54.94 mL, 327.4 mmol) and Cs2CO3 (177.8 g, 545.6 mmol) in Dioxane (1.274 L) was added xantphos (15.78 g, 27.28 mmol) and Pd2(dba)$_3$ (12.49 g, 13.64 mmol). The mixture was stirred under nitrogen at 95°C overnight. The mixture was cooled to room temperature then partitioned between EtOAc (1000 mL, 10 vol eq.) and water (490 mL, 5 vol eq.), mixed and organic layer separated. Organics washed further with water (1 x 250 mL), brine (250 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to leave crude product as a dark red viscous oil, 185.3g.

[00381] The obtained product oil (185.3g) was dissolved in THF (882.0 mL) and HCl (545.5 mL of 2 M, 1.091 mol) was added. The resulting mixture was stirred at room temperature for 20 mins. THF was removed in vacuo then additional (HCl (2M) (588.0 mL) was added. The aqueous was washed twice with EtOAc (294.0 mL). A large amount of a yellow precipitate formed during extraction in both organic and aqueous phase, the solid from both the organic and aqueous phase was collected by filtration and dried by suction. The mixed organic and aqueous filtrate was added to separating funnel, extracted with 2M HCl (2 x 200 mL). All aqueous phases plus solid collected on sinter (product) were combined to give a suspension. The pH was adjusted to 6 using 2M NaOH and extracted with DCM (3 x 600 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to

leave a pale orange waxy solid, 112.2g. This solid was slurried in MeCN (200 mL), stirred for 10 mins then solid collected by filtration, washed with minimal MeCN and dried by suction to leave product **27** as a white solid (66.8 g, 83% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.82 (d, 1H), 7.63 (d, 1H), 5.22 (s, 2H), 3.11 - 3.00 (m, 2H), 2.91 (tt, 2H), 2.36 (tt, 1H), 1.88 – 1.83 (m, 2H), 1.79 - 1.71 (m, 2H), 1.43 (s, 9H). MS (ES+) 297.1.

Scheme 7b: Alternative synthesis of tert-butyl 1-(3-amino-5-fluoro-4-pyridyl)piperidine-4-carboxylate



Step 1: 3-bromo-4-chloro-5-fluoropyridine hydrochloride **18**

[00382] A solution of diisopropylamine (101.2 g, 140.2 mL, 1.000 mol) in tetrahydrofuran (1.148 L) was cooled to between -25°C and -20°C. Butyllithium (2.5M in hexanes) (400 mL of 2.5 M, 1.000 mol) was added at such a rate as to maintain the reaction temperature below -20°C (addition 20 minutes). The mixture was then allowed to warm to 4°C over 1 hour, then re-cooled to -78°C. 3-bromo-5-fluoro-pyridine (153.0 g, 869.6 mmol) in tetrahydrofuran (382.5 mL) was added over 40 minutes. The mixture was stirred for 90 minutes, then a solution of 1,1,1,2,2,2-hexachloroethane (205.9 g, 869.6 mmol) in tetrahydrofuran (350.0 mL) was added dropwise over 40 minutes. Once the addition was complete the mixture was allowed to warm to ambient overnight. The mixture was cooled to 0°C then transferred into cold water (2 L), stirred for 20 mins then MTBE (2.5 L) added and stirred vigorously for 30 mins then transferred to separating funnel and organic layer separated. Aqueous was transferred back to reaction vessel and further extracted with MTBE (2.5 L), stirred for 10 mins vigorously then transferred to separating funnel and organic layer separated. Organics were combined, dried ($MgSO_4$), filtered and concentrated to a brown oil. The oil was dissolved in pentane (500 ml) and ether (300ml). HCl (2M in ether) (434.8 mL of 2 M, 869.6 mmol) was added slowly with stirring. On complete addition the mixture was stirred for 20 mins then solid collected by filtration, washed with ether and dried under vacuum for 1h to

leave product **18** as a beige solid (148.9g, 69%); ^{1}H NMR (500 MHz, DMSO-d6) δ 8.77 (2H, s); 19F NMR (500 MHz, DMSO-d6) δ -124.8; MS 210.8.

Step 2: tert-butyl 1-(3-bromo-5-fluoropyridin-4-yl)piperidine-4-carboxylate **26**

[00383] 3-bromo-4-chloro-5-fluoro-pyridine hydrochloride **18** (62 g, 251.1 mmol) was suspended in DCM (600 mL) and stirred. The mixture was cooled in an ice bath and sodium hydroxide (276.2 mL of 1 M, 276.2 mmol) was added slowly. The resulting mixture was stirred for 1 hour. The mixture was phase-separated. More DCM/water was added to aid phase separation. Some tarry particulates remained in the aqueous phase. The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was triturated with heptane. The heptane solution was filtered through a florsil pad, eluting with heptane. The filtrate was concentrated to an oil which solidified. This gave 41g of free base.

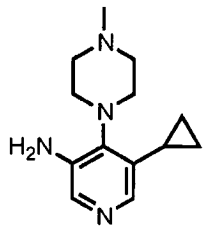
[00384] A thoroughly stirred mixture of 3-bromo-4-chloro-5-fluoropyridine free base (55 g, 0.26 mol), potassium fluoride (31 g, 0.53 mol) and Me_4NCl (5.8 g, 53 mmol) in DMSO (400 mL) was heated to 130°C for 2 hours. The reaction mixture was cooled to room temperature and *tert*-butyl piperidine-4-carboxylate hydrochloride **22** (66 g, 0.30 mol) and DIPEA (65 g, 0.50 mol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo*. The residue was portioned between DCM/water. The organic layer was washed with water (3x), dried over Na_2SO_4, and filtered over silica gel using DCM as eluent. The filtrated was evaporated to give *tert*-butyl 1-(3-bromo-5-fluoropyridin-4-yl)piperidine-4-carboxylate **26** (61g, 65%) as a light yellow solid; 1H NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.41 (d, 1H), 3.39 – 3.36 (m, 2H), 3.12 (tt, 2H), 2.49 – 2.43 (m, 1H), 1.91 – 1.87 (m, 2H), 1.71 – 1.64 (m, 2H) and 1.43 (s, 9H); 19F NMR (500 MHz, DMSO-d6) δ -135.2; MS (ES+) 361.0.

Step 3: tert-butyl 1-(3-amino-5-fluoropyridin-4-yl)piperidine-4-carboxylate **27**

[00385] *Tert*-butyl 1-(3-bromo-5-fluoropyridin-4-yl)piperidine-4-carboxylate **26** (800g, 2.23mol) was dissolved in 1,4-dioxane (7.5L). Diphenylmethanimine (484g, 2.67mol) was added in one portion followed by cesium carbonate (1.45Kg, 4.45mol), xantphos (129g, 223mmol) and $Pd_2(dba)_3$ (102g, 111mmol). Additional 1,4-dioxane (2.9L) was added and the mixture heated to 95°C under nitrogen until the reaction was complete.(determined by HPLC analysis). The mixture was cooled to 20°C and ethyl acetate (8L) and water (4L) were added. The organic phase was isolated and washed with water (4L) and brine (3.5L) and dried over magnesium sulphate and filtered. The filtrate was concentrated to a brown oil (1.3Kg). The

oil was dissolved in 2-methyltetrahydrofuran (7.2L) and 2M HCl was added at 20°C and the mixture stirred for 30 minutes. The aqueous layer was isolated and the organic layer extracted with 2M HCl (1.2L). The combined aqueous was neutralised with 2M NaOH (5.4L, pH 8-9). The product was extracted into 2-methyltetrahydrofuran (14L then 2x5L). The combined extracts were washed with water (1.6L) and the organic solution concentrated. The residue was slurried in acetonitrile (2L), filtered and dried. This gave the product **27** as a white solid (568.7g, 86.5%); 1H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, 1H), 7.63 (d, 1H), 5.22 (s, 2H), 3.11 - 3.00 (m, 2H), 2.91 (tt, 2H), 2.36 (tt, 1H), 1.88 – 1.83 (m, 2H), 1.79 - 1.71 (m, 2H), 1.43 (s, 9H); 19F NMR (500 MHz, DMSO-d6) δ – 140.0; MS (ES+) 297.1.

Preparation N-16: 5-cyclopropyl-4-(4-methylpiperazin-1-yl)pyridin-3-amine



Step 1: 1-(3-cyclopropyl-5-nitropyridin-4-yl)-4-methylpiperazine

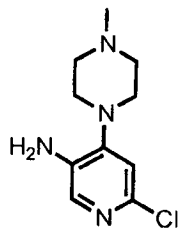
[00386] A mixture of 1-(3-bromo-5-nitro-4-pyridyl)-4-methyl-piperazine (synthesized from 1-methylpiperazine and 3-bromo-4-chloro-5-nitropyridine using procedure **Step 1** of **Preparation N-1**) (467.4 mg, 1.552 mmol), ferrous; dichloro-bis[cyclopenta-1,4-dien-1-yl(diphenyl)phosphaniumyl]palladium(2-); dichloromethane (63.37 mg, 0.07760 mmol), potassium carbonate (429.0 mg, 3.104 mmol) and cyclopropylboronic acid (200.0 mg, 2.328 mmol) in dioxane (5 mL) was degassed and flushed with nitrogen (x2). The reaction was heated at 100°C in a sealed tube for 18 h. At room temperature the reaction mixture was filtered through Celite and evaporated to dryness, yielding 1-(3-cyclopropyl-5-nitropyridin-4-yl)-4-methylpiperazine as a dark orange solid that was used directly in the next reaction without further purification (288mg, 66%). MS (ES+) 263.2

Step 2: 5-cyclopropyl-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00387] To a solution of 1-(3-cyclopropyl-5-nitro-4-pyridyl)-4-methyl-piperazine (220.4 mg, 0.8403 mmol) in methanol (25 mL) was added Pd on carbon (10%, Degussa, 6.387 mg, 0.006002 mmol). The reaction mixture was stirred at room temperature under a balloon of hydrogen, for 7 h. The reaction was filtered through a plug of Celite, washed with MeOH

and the filtrate was concentrated *in vacuo* yielding 5-cyclopropyl-4-(4-methylpiperazin-1-yl)pyridin-3-amine as an orange residue. (194mg, 99%).

Preparation N-17: 6-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-amine



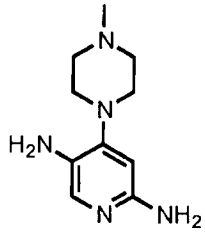
Step 1: 1-(2-chloro-5-nitropyridin-4-yl)-4-methylpiperazine

[00388] 1-methylpiperazine (298.5 mg, 330.6 µL, 2.980 mmol) in THF (5 mL) was added to a stirred solution of 2,4-dichloro-5-nitro-pyridine (500 mg, 2.591 mmol) and DIPEA (401.8 mg, 541.5 µL, 3.109 mmol) in THF (10 mL) at 0°C under an atmosphere of nitrogen. The reaction was allowed to stir at ambient temperature for 1 hour then the solvent removed *in vacuo*. The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% MeOH/DCM solutions) to give 1-(2-chloro-5-nitropyridin-4-yl)-4-methylpiperazine as a yellow solid (638 mg, 96% Yield). MS (ES+) 257.1.

Step 2: 6-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00389] 1-(2-chloro-5-nitro-4-pyridyl)-4-methyl-piperazine (580 mg, 2.260 mmol) was dissolved in AcOH (20 mL) / Water (2 mL) and Fe (2.524 g, 45.20 mmol) was added. The resulting mixture was stirred at 50°C for 30 minutes. The reaction was cooled to ambient temperature then loaded onto 50 g SCX-2 cartridge (pre-washed with MeOH). The cartridge was washed with DCM/MeOH mixtures, before the product was eluted with 2M NH_3 in MeOH/DCM mixtures. The solvent was removed *in vacuo* to give 6-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-amine as a purple solid (510 mg, 99% Yield). MS (ES+) 227.1.

Preparation N-18: 4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine



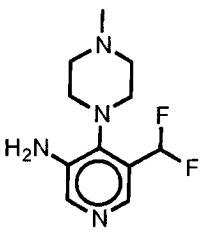
Step 1: 4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine

[00390] 1-methylpiperazine (265.5 mg, 294.0 µL, 2.651 mmol) in THF (5 mL) was added to a stirred suspension of 4-chloro-5-nitro-pyridin-2-amine (400 mg, 2.305 mmol) and DIPEA (357.5 mg, 481.8 µL, 2.766 mmol) in THF (10 mL) at 0°C under an atmosphere of nitrogen. The reaction was allowed to stir at ambient temperature for 90 hours before the solvent removed *in vacuo*. The residue was tritruated from DCM/MeOH and the resultant precipitate was washed with DCM/MeOH solutions. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% 2M NH_3 in MeOH/DCM) to give 4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine as a yellow solid (355 mg, 65% Yield). MS (ES+) 238.1.

Step 2: 4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine

[00391] Pd on C, (10%, wet, Degussa) (140 mg, 0.1316 mmol) was added to a stirred solution of 4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine (355 mg, 1.496 mmol) in a mixture of EtOAc (5 mL) and EtOH (50 mL). The reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 16 hours. The catalyst was removed by filtration through a pad of celite and the filtrate concentrated *in vacuo* to give 4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine as a brown solid (291 mg, 94% Yield). MS (ES+) 208.1.

Preparation N-19: 5-(difluoromethyl)-4-(4-methylpiperazin-1-yl)pyridin-3-amine



Step1: 5-bromo-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00392] 1-methylpiperazine (2.109 g, 21.06 mmol) in DCM (62.50 mL) was added to a stirred solution of 3-bromo-4-chloro-5-nitro-pyridine (5000 mg, 21.06 mmol) and DIPEA (3.266 g, 4.402 mL, 25.27 mmol) in DCM (62.50 mL) at RT. The reaction was allowed to stir at ambient temperature for 2h, then was concentrated *in vacuo* . The residue was partitioned between a saturated aqueous solution of $NaHCO_3$ and DCM. Combined organic extract was dried and concentrated *in vacuo*. The orange solid was suspended in Acetic acid (60.00 mL) before iron (7.059 g, 126.4 mmol) was added. The mixture was warmed at 50°C and stirred for 15min. The mixture was allowed to cool to RT and DCM:EtOAc (4:1) (400mL) was added to the reaction. The resulting brown suspension was filtered using a prewetted Celite cartridge (25g), washing with more DCM:MeOH (4:1) (200mL). Combined filtrate was concentrated *in vacuo* to afford a red/brown gum which was purified by chromatography on silica (Rf companion, 80g cartridge), eluting with DCM-DCM:MeOH:NE3(90:10:1) a gradient of 100-0 to 20:80. Fractions containing clean product were collected and concentrated *in vacuo* to afford 5-bromo-4-(4-methylpiperazin-1-yl)pyridin-3-amine as a viscous, clear light yellow oil that solidifies on standing. MS (ES+) 273.1.

Step 2: 1-(3-bromo-5-(2,5-dimethyl-1H-pyrrol-1-yl)pyridin-4-yl)-4-methylpiperazine

[00393] 5-bromo-4-(4-methylpiperazin-1-yl)pyridin-3-amine (3000 mg, 11.06 mmol), hexane-2,5-dione (6.312 g, 6.487 mL, 55.30 mmol) in acetic acid (20 mL) was heated at 70° C overnight. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and an aqueous saturated solution of $NaHCO_3$. Combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* yielding an oil that was purified by filtration on silica to yield 1-(3-bromo-5-(2,5-dimethyl-1H-pyrrol-1-yl)pyridin-4-yl)-4-methylpiperazine as an off-white solid. MS (ES+) 351.1.

Step 3: 5-(2,5-dimethyl-1H-pyrrol-1-yl)-4-(4-methylpiperazin-1-yl)nicotinaldehyde

[00394] A solution of 1-[3-bromo-5-(2,5-dimethylpyrrol-1-yl)-4-pyridyl]-4-methyl-piperazine (1250 mg, 3.579 mmol) in THF (35.79 mL) was cooled to -78°C and t-BuLi (2.105 mL of 1.7 M, 3.579 mmol) was added dropwise. The mixture was stirred for 30 mins at -78°C before DMF (261.6 mg, 277.1 µL, 3.579 mmol) was added dropwise. The mixture was stirred for 2 h at -78°C. The reaction was quenched with MeOH (5 mL) and allowed to warm to room temperature. The reaction was washed with an aqueous saturated solution of ammonium chloride (50 mL) and extracted with EtOAc (100 mL and 50 mL). The combined organics were dried ($MgSO_4$) and evaporated to leave an orange oil. Purification by column

chromatography (EtOAc to EtOAc:MeOH 20%) yielded 5-(2,5-dimethyl-1H-pyrrol-1-yl)-4-(4-methylpiperazin-1-yl)nicotinaldehyde as a pale yellow crystalline solid. MS (ES+) 299.2.

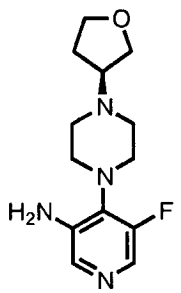
Step 4: 1-(3-(difluoromethyl)-5-(2,5-dimethyl-1H-pyrrol-1-yl)pyridin-4-yl)-4-methylpiperazine

[00395] To a solution of 5-(2,5-dimethylpyrrol-1-yl)-4-(4-methylpiperazin-1-yl)pyridine-3-carbaldehyde (100 mg, 0.3351 mmol) in methylene chloride (335.1 µL) at RT was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-{4}-sulfanyl)ethanamine (370.8 mg, 1.676 mmol) and the mixture was heated at reflux for 18 h. At room temperature, the reaction was quenched with water (2 mL) and extracted with methylene chloride (2 x 5mL) to yield 1-(3-(difluoromethyl)-5-(2,5-dimethyl-1H-pyrrol-1-yl)pyridin-4-yl)-4-methylpiperazine as a yellow oil. MS (ES+) 321.2.

Step 5: 5-(difluoromethyl)-4-(4-methylpiperazin-1-yl)pyridin-3-amine

[00396] A solution of 1-[3-(difluoromethyl)-5-(2,5-dimethylpyrrol-1-yl)-4-pyridyl]-4-methyl-piperazine (80 mg, 0.2497 mmol) and NH_2OH (165.0 mg, 4.994 mmol) in a mixture of triethylamine (101.1 mg, 139.3 µL, 0.9988 mmol), ethanol (1 mL) and H_2O (0.25 mL) was heated at reflux for 20 h. After cooling to RT the reaction was quenched by loading directly onto an SCX-2 cartridge and eluted with MeOH followed by NH_3/MeOH. The basic fraction was concentrated *in vacuo* yielding 5-(difluoromethyl)-4-(4-methylpiperazin-1-yl)pyridin-3-amine that was used in next step without further purification. MS (ES+) 243.1.

Preparation N-20: (*S*)-5-fluoro-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-amine



Step 1: (S)-1-(3-chloro-5-fluoropyridin-4-yl)-4-(tetrahydrofuran-3-yl)piperazine

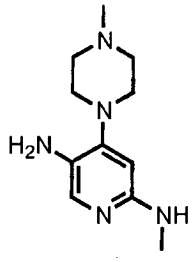
[00397] MsCl (393.3 mg, 265.7 µL, 3.433 mmol) was added to a solution of (3R)-tetrahydrofuran-3-ol (275 mg, 3.121 mmol) and Et_3N (379.0 mg, 522.0 µL, 3.745 mmol) in DCM (5 mL) at 0°C and the resulting solution stirred at RT overnight. The reaction mixture

was diluted with water (5 mL) and DCM (5 mL) and the layers separated. The aqueous layer was extracted further with DCM (2 x 5 mL) and the combined organic extracts washed with saturated aqueous sodium hydrogen carbonate solution (1 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in n-BuOH (5 mL) and 1-(3-chloro-5-fluoro-4-pyridyl)piperazine (1.010 g, 4.682 mmol) was added and the reaction mixture heated at 118°C overnight. The reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was purified by column chromatography on silica (24 g column, 0-100% EtOAc/ petroleum ether). Product fractions were combined and concentrated *in vacuo* to leave (S)-1-(3-chloro-5-fluoropyridin-4-yl)-4-(tetrahydrofuran-3-yl)piperazine as an off white solid. MS (ES+) 288.1.

Step 2: (S)-5-fluoro-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-amine

[00398] BrettPhos pre-catalyst (4.183 mg, 0.005250 mmol) and BrettPhos (2.818 mg, 0.005250 mmol) were added to a solution of tert-butyl carbamate (153.7 mg, 1.312 mmol), sodium tert-butoxide (128.7 mg, 1.339 mmol) and 1-(3-chloro-5-fluoro-4-pyridyl)-4-[(3S)-tetrahydrofuran-3-yl]piperazine (75 mg, 0.2625 mmol) in toluene (1.500 mL) and the resulting mixture sealed (reaction in a microwave tube) and placed into a preheated drysyn block at 100°C and heated for 6 h. Additional BrettPhos pre-catalyst (4.183 mg, 0.005250 mmol) and BrettPhos (2.818 mg, 0.005250 mmol) were added and the reaction mixture was resealed and heated at 100°C overnight. The reaction mixture was cooled to RT and quenched by addition of saturated aqueous NH_4Cl and then filtered through a celite pad washing with ethyl acetate. The filtrate was extracted with ethyl acetate (2 x 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil (102 mg). The residue was taken up in DCM (2 mL) and TFA (299.3 mg, 202.2 µL, 2.625 mmol) was added and the resulting solution stirred at rt for 2 h. The mixture was concentrated *in vacuo* and passed through an SCX catridge eluting the product with 2M ammonia in methanol. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica eluting with 0-20% MeOH/ DCM, 4 g column. Product fractions were combined and concentrated *in vacuo* to leave the product as a colourless oil. MS (ES+) 267.2.

Preparation N-21: N2-methyl-4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine



Step 1: 1-(2-chloro-5-nitropyridin-4-yl)-4-methylpiperazine

[00399] 1-methylpiperazine (119.3 mg, 132.6 μL, 1.191 mmol) in THF (1.5 mL) was added to a stirred solution of 2,4-dichloro-5-nitro-pyridine (200 mg, 1.036 mmol) and DIPEA (160.6 mg, 216.4 μL, 1.243 mmol) in THF (3.000 mL) at 0°C under an atmosphere of nitrogen . The reaction was allowed to stir at ambient temperature overnight. The reaction mixture was partitioned between ethyl acetate and $NaHCO_3$ (sat. aq. soln). The combined organics was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield 1-(2-chloro-5-nitro-4-pyridyl)-4-methyl-piperazine. (100%) MS (ES+) 257.1.

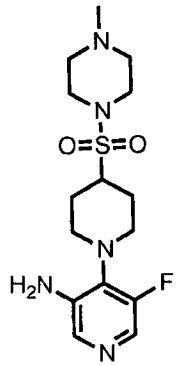
Step 2: N-methyl-4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine

[00400] 1-(2-chloro-5-nitro-4-pyridyl)-4-methyl-piperazine (265.9 mg, 1.036 mmol) and methylamine 2M in THF (2.590 mL of 2 M, 5.180 mmol) were heated overnight in a sealed tube at 60°C. The mixture was purified by chromatography on silica (Companion 12g) eluting with 0.5-15% MeOH:DCM, yielding N-methyl-4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine (243 mg, 93%). MS (ES+) 252.1.

Step: 3: N2-methyl-4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine

[00401] N-methyl-4-(4-methylpiperazin-1-yl)-5-nitro-pyridin-2-amine (243 mg, 0.9670 mmol) was dissolved in methanol (10 mL) and Pd on C, wet, Degussa (50 mg, 0.4698 mmol) was added. The reaction was evacuated and filled with hydrogen three times and left to stir at RT overnight. The catalyst was filtered off and the solvent was removed under reduced pressure to yield N2-methyl-4-(4-methylpiperazin-1-yl)pyridine-2,5-diamine (173 mg, 81%). MS (ES+) 222.1.

Preparation N-22: 5-fluoro-4-(4-((4-methylpiperazin-1-yl)sulfonyl)piperidin-1-yl)pyridin-3-amine



Step 1: 1-(3-chloro-5-fluoropyridin-4-yl)piperidin-4-ol

[00402] To a solution of 3-chloro-5-fluoro-4-iodo-pyridine (1 g, 3.885 mmol) in NMP (1 mL) was added DIPEA (753.1 mg, 1.015 mL, 5.828 mmol) and piperidin-4-ol (589.4 mg, 5.828 mmol) and the mixture heated to 120°C for 4 hours. The mixture was diluted with ethyl acetate (30ml), washed twice with water (20ml) and with brine.The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to a yellow solid that was purified by column chromatography using DCM and then 2% MeOH/DCM as eluent, yielding 1-(3-chloro-5-fluoro-4-pyridyl)piperidin-4-ol. MS (ES+) 231.0.

Step 2: S-(1-(3-chloro-5-fluoropyridin-4-yl)piperidin-4-yl) ethanethioate

[00403] isopropyl (NE)-N-isopropoxycarbonyliminocarbamate (723.1 mg, 3.576 mmol) was added dropwise to a solution of 1-(3-chloro-5-fluoro-4-pyridyl)piperidin-4-ol (750 mg, 3.251 mmol) and Triphenylphosphine (937.9 mg, 828.5 µL, 3.576 mmol) in THF at -20°C. After stirring for 15 mins, ethanethioic S-acid (272.2 mg, 255.6 µL, 3.576 mmol) was added, the mixture was allowed to warm to room temperature and was stirred for a further 30 minutes. The mixture was then diluted with ethylacetate (30ml), washed twice with water (20ml) and with brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to a yellow solid that was purified by column chromatography eluting with 5/95 ether/pet ether to elute side products and then 10/90 ether/pet ether. The relevant fractions were combined and concentrated *in vacuo* to afford S-(1-(3-chloro-5-fluoropyridin-4-yl)piperidin-4-yl) ethanethioate as a green solid. MS (ES+) 289.0.

Step 3: 1-(3-chloro-5-fluoropyridin-4-yl)piperidine-4-sulfonyl chloride

[00404] To a mixture of HCl (1.038 mL of 2 M, 2.077 mmol) and MeCN (8 mL) was added NCS (693.4 mg, 5.193 mmol) and the mixture cooled to 10°C and stirred until most of the NCS (693.4 mg, 5.193 mmol) was dissolved. A solution of S-[1-(3-chloro-5-fluoro-4-

pyridyl)-4-piperidyl] ethanethioate (500 mg, 1.731 mmol) in MeCN (8 mL) was added dropwise. The solution was stirred for 30 minutes at 10°C, diluted with ether and washed with dilute brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to yield 1-(3-chloro-5-fluoropyridin-4-yl)piperidine-4-sulfonyl chloride as a yellow solid. MS (ES+) 313.0.

Step 4: 1-((1-(3-chloro-5-fluoropyridin-4-yl)piperidin-4-yl)sulfonyl)-4-methylpiperazine

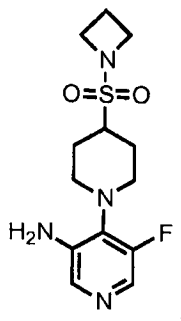
[00405] To a solution of 1-(3-chloro-5-fluoro-4-pyridyl)piperidine-4-sulfonyl chloride (400 mg, 1.277 mmol) in DCM (5 mL) was added TEA (129.2 mg, 178.0 µL, 1.277 mmol) followed by 1-methylpiperazine (255.8 mg, 2.554 mmol). The mixture was stirred at room temperature for 1h. The mixture was diluted with ethylacetate (30ml), washed twice with water (20ml) and with brine.The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to a yellow solid. The product was purified by column chromatography eluting with 5/95 methanol/DCM. The relevant fractions were combined and concentrated *in vacuo* to afford the 1-((1-(3-chloro-5-fluoropyridin-4-yl)piperidin-4-yl)sulfonyl)-4-methylpiperazineas a green solid. MS (ES+) 377.1.

Step 5: 5-fluoro-4-(4-((4-methylpiperazin-1-yl)sulfonyl)piperidin-1-yl)pyridin-3-amine

[00406] Tert-butyl carbamate (211.3 mg, 1.804 mmol), sodium tert-butoxide (173.4 mg, 1.804 mmol) , BrettPhos Pre-catalyst (143.7 mg, 0.1804 mmol) and BrettPhos (96.83 mg, 0.1804 mmol) were degassed by vacuum/nitrogen cycles (x5). A solution of 1-[[1-(3-chloro-5-fluoro-4-pyridyl)-4-piperidyl]sulfonyl]-4-methyl-piperazine (340 mg, 0.9022 mmol) in dry toluene (9.884 mL) was added and the resulting mixture was heated to 80°C. After 5 minutes at 80°C the reaction was cooled to RT and partitioned between ethyl acetate and water. The combined organics was dried with $MgSO_4$ and concentrated *in vacuo* to a yellow solid. The yellow solid was purified by column chromatography using 1% MeOH/DCM to elute side products and then 5-10% MeOH/DCM to elute product. Relevant fractions combined and concentrated *in vacuo* to yield a light yellow solid. It was dissolved in DCM (10 mL) followed by the addition of TFA (1.029 g, 695.3 µL, 9.022 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* to yield 5-fluoro-4-(4-((4-methylpiperazin-1-yl)sulfonyl)piperidin-1-yl)pyridin-3-amine as a light orange solid. MS (ES+) 358.1.

[00407] The following amines were prepared according to methods similar to the one depicted in **Procedure N-22**

4-(4-(azetidin-1-ylsulfonyl)piperidin-1-yl)-5-fluoropyridin-3-amine:



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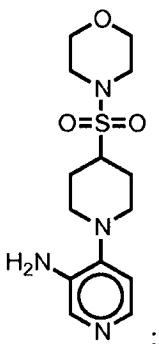
4-(4-(morpholinosulfonyl)piperidin-1-yl)pyridin-3-amine:



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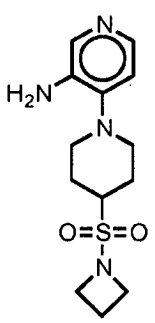
4-(4-(azetidin-1-ylsulfonyl)piperidin-1-yl)pyridin-3-amine:



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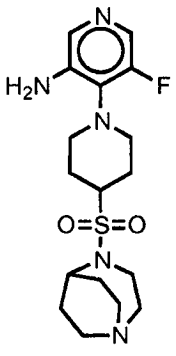
4-(4-(1,4-diazabicyclo[3.2.2]nonan-4-ylsulfonyl)piperidin-1-yl)-5-fluoropyridin-3-amine:



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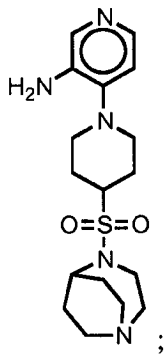
4-(4-(1,4-diazabicyclo[3.2.2]nonan-4-ylsulfonyl)piperidin-1-yl)pyridin-3-amine:



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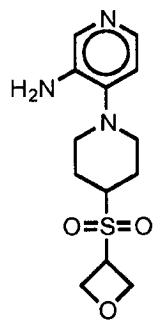
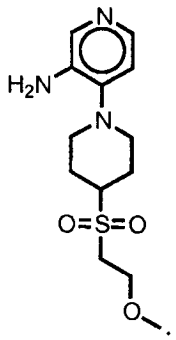
4-(4-(oxetan-3-ylsulfonyl)piperidin-1-yl)pyridin-3-amine:

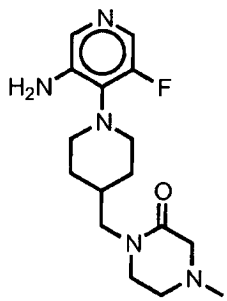


; and

4-(4-((2-methoxyethyl)sulfonyl)piperidin-1-yl)pyridin-3-amine:



Preparation N-23: 1-((1-(3-amino-5-fluoropyridin-4-yl)piperidin-4-yl)methyl)-4-methylpiperazin-2-one



Step 1: tert-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate

[00408] Methanesulfonyl chloride (186.3 mg, 125.9 μL, 1.626 mmol) was added dropwise to a stirred solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (350 mg, 1.626 mmol) and DIPEA (222.8 mg, 300.3 μL, 1.724 mmol) in DCM (5 mL) at 0°C. The reaction mixture was allowed to warm to ambient temperature over 16 hours then treated with water. The phases were separated and the aqueous phase extracted with DCM (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the sub-title compound as a white solid (505 mg, > 100% Yield) that was used directly assuming 100% yield and purity. MS (ES+ - *t*-Bu) 238.0.

Step 2: tert-butyl 4-((4-methyl-2-oxopiperazin-1-yl)methyl)piperidine-1-carboxylate

[00409] A 60% dispersion of sodium hydride (84.55 mg, 2.114 mmol) was added to a stirred solution of 4-methylpiperazin-2-one (241.3 mg, 2.114 mmol) in DMF (10 mL) and the reaction stirred at ambient temperature for 30 minutes. Tert-butyl 4-(methylsulfonyloxymethyl)piperidine-1-carboxylate (477 mg, 1.626 mmol) in DMF (5 mL) was added dropwise and the reaction stirred at ambient temperature for a further 92 hours

then at 50°C for a further 20 hours. The reaction was cooled to ambient temperature, quenched by the addition of water and the mixture extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 3), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% MeOH/DCM, loaded in DCM) to give tert-butyl 4-((4-methyl-2-oxopiperazin-1-yl)methyl)piperidine-1-carboxylate product as a colourless oil (99 mg, 20% Yield). MS (ES+) 312.2.

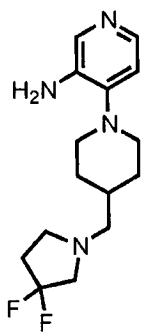
Step 3: 4-methyl-1-(piperidin-4-ylmethyl)piperazin-2-one

[00410] TFA (1 mL, 12.98 mmol) was added to a stirred solution of tert-butyl 4-[(4-methyl-2-oxo-piperazin-1-yl)methyl]piperidine-1-carboxylate (98 mg, 0.3147 mmol) in DCM (2 mL) and the reaction stirred at ambient temperature for 16 hours. The solvent was removed in vacuo and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 5g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures. The solvent was removed in vacuo to give 4-methyl-1-(piperidin-4-ylmethyl)piperazin-2-one as a colourless oil (65 mg, 98% Yield). MS (ES+) 212.0.

Step 4: tert-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate

[00411] **Preparation N-13** was followed. MS (ES+) 322.1.

Preparation N-24: 4-(4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidin-1-yl)pyridin-3-amine



Step 1: tert-butyl 4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidine-1-carboxylate

[00412] A mixture of 3,3-difluoropyrrolidine (Hydrochloric Acid (1)) (965 mg, 6.722 mmol), tert-butyl 4-formylpiperidine-1-carboxylate (1.720 g, 8.066 mmol), DIPEA (955.6

mg, 1.288 mL, 7.394 mmol) and crushed 4A MS (965 mg,) in DCE (30 mL) were stirred at ambient temperature for 3 hours. $NaBH(OAc)_3$ (Sodium Ion (1)) (2.848 g, 13.44 mmol) was added and the reaction stirred at ambient temperature for a further 16 hours. The mixture was filter through Celite (washing with DCM) and the filtrate concentrated in vacuo. The residue was purified by column chromatography (ISCO Companion, 80 g column, eluting with 0 to 10% MeOH/DCM, loaded in DCM) to give tert-butyl 4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidine-1-carboxylate as a colourless oil that was deprotected directly assuming 100% yield and purity. MS (ES+) 305.1.

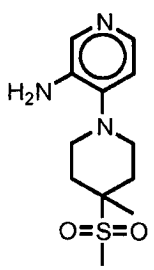
Step 2: 4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidine

[00413] TFA (766.5 mg, 517.9 μL, 6.722 mmol) was added to a stirred solution of tert-butyl 4-[(3,3-difluoropyrrolidin-1-yl)methyl]piperidine-1-carboxylate (2.046 g, 6.722 mmol) in DCM (15 mL) and the reaction stirred at ambient temperature for 66 hours. The solvent was removed in vacuo and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 50 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures. The solvent was removed in vacuo to give 4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidine as a pale yellow solid (1.15 g, 84% Yield over 2 steps). MS (ES+) 205.1.

Step 3: 4-(4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidin-1-yl)pyridin-3-amine

[00414] **Preparation N-1** was followed. MS (ES+) 297.2.

Preparation N-25: 4-(4-methyl-4-(methylsulfonyl)piperidin-1-yl)pyridin-3-amine



Step 1: tert-butyl 1-thia-6-azaspiro[2.5]octane-6-carboxylate

[00415] To a mixture of tert-butyl 1-oxa-8-azaspiro[2.5]octane-8-carboxylate (1 g, 4.689 mmol) and thiourea (356.9 mg, 4.689 mmol) was added water and the mixture stirred at room temperature for 72 h. the reaction mixture was partitioned between DCM and water, the organic extract was washed with brine, dried ($MgSO_4$) and concentrated to give 1-thia-6-

azaspiro[2.5]octane-6-carboxylate as a pale yellow oil which solidified upon standing. (910 mg, 84%). MS (ES+ - *t*-Bu) 173.9.

Step 2: tert-butyl 4-mercapto-4-methylpiperidine-1-carboxylate

[00416] To a solution of tert-butyl 1-thia-6-azaspiro[2.5]octane-6-carboxylate (430 mg, 1.875 mmol) in THF (5 mL) was added $LiAlH_4$ (Lithium Ion (1)) (0.9375 mL of 2 M, 1.875 mmol) and the solution was stirred at room temperature for 1 h. The reaction was quenched by careful dropwise addition of water (2 ml), stirred for 10 mins before the reaction mixture was partitioned between water and EtOAc. The organic extract was washed with brine, dried ($MgSO_4$) and concentrated to give tert-butyl 4-methyl-4-sulfanyl-piperidine-1-carboxylate as a colorless oil. (380 mg, 87%). MS (ES-) 231.0.

Step 3: tert-butyl 4-methyl-4-(methylthio)piperidine-1-carboxylate

[00417] To a solution of tert-butyl 4-methyl-4-sulfanyl-piperidine-1-carboxylate (380 mg, 1.642 mmol) in THF (5 mL) cooled to -78°C was added LiHMDS (1.724 mL of 1 M, 1.724 mmol) and the solution stirred for 10 mins before MeI (256.3 mg, 0.1124 mL, 1.806 mmol) was added and the solution allowed to warm to 0°C over approximately 1 h. The reaction was then quenched carefully by the addition of saturated ammonium chloride and extracted into EtOAc. The aqueous was further extracted with EtOAc and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated to give a yellow oil (390 mg, 96%).

Step 4: tert-butyl 4-methyl-4-(methylsulfonyl)piperidine-1-carboxylate

[00418] A solution of tert-butyl 4-methyl-4-methylsulfanyl-piperidine-1-carboxylate (380 mg, 1.549 mmol) in DCM (15 mL) was cooled to 0°C and 3-Chloroperoxybenzoic acid (867.8 mg, 3.872 mmol) was added portionwise over approx 10 mins. The solution was stirred for 30 mins and then allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with saturated sodium hydrogen carbonate (4 ml) and saturated sodium thiosulphate (4 ml) and stirred vigorously for 5 mins. The DCM layer was removed and the aqueous further extracted with DCM. The combined organic layers were washed with saturated sodium carbonate and brine, dried ($MgSO_4$) and concentrated to give tert-butyl 4-methyl-4-(methylsulfonyl)piperidine-1-carboxylate as a sticky oil which solidified upon standing (450 mg, 100%).

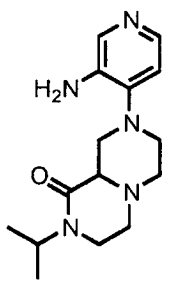
Step 5: 4-methyl-4-(methylsulfonyl)piperidine

[00419] To a solution of tert-butyl 4-methyl-4-methylsulfonyl-piperidine-1-carboxylate (430 mg, 1.550 mmol) in DCM (10 mL) was added TFA (3 mL, 38.94 mmol) and the solution stirred at room temperature for 1h. The reaction was concentrated and azeotroped twice with DCM to give 4-methyl-4-(methylsulfonyl)piperidine as a sticky oil that was used in next step without further purification. MS (ES+) 178.0.

Step 6: 4-(4-methyl-4-(methylsulfonyl)piperidin-1-yl)pyridin-3-amine

[00420] **Preparation N-1** was followed. MS (ES+) 270.1.

Preparation N-26: 8-(3-aminopyridin-4-yl)-2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazin-1-one



Step 1: 2-isopropyl-8-(3-nitropyridin-4-yl)octahydro-1H-pyrazino[1,2-a]pyrazin-1-one

[00421] NaH (15.87 mg, 0.3967 mmol) then 2-iodopropane (73.56 mg, 43.19 μL, 0.4327 mmol) were added to a solution of 2-(3-nitro-4-pyridyl)-3,4,6,7,8,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-9-one (100 mg, 0.3606 mmol) (prepared according to a procedure similar to *Step 1* of **Preparation N-1**) in THF (5 mL) under N_2. The reaction mixture was stirred at reflux for 24h then it was partitioned between EtOAc and a saturated bicarbonate aqueous solution. Combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to produce an oil that was used in next step without further purification. MS (ES+) 320.1.

Step 2: 8-(3-aminopyridin-4-yl)-2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazin-1-one

[00422] *Step 2* of **Preparation N-1** was followed. MS (ES+) 290.2

Preparation N-27: (S)-5-(3-aminopyridin-4-yl)hexahydro-2H-isothiazolo[2,3-a]pyrazine

1,1-dioxide

Step 1: (S)-tert-butyl 4-(methylsulfonyl)-3-(((methylsulfonyl)oxy)methyl)piperazine-1-carboxylate

[00423] To a solution of tert-butyl (3S)-3-(hydroxymethyl)piperazine-1-carboxylate (2.5 g, 11.56 mmol) in DCM (16.25 mL) at 0°C under a nitrogen atmosphere was added TEA (1.872 g, 2.579 mL, 18.50 mmol) and then dropwise MsCl (2.913 g, 1.968 mL, 25.43 mmol). The reaction was allowed to warm to ambient temperature and stirred thereat for 18 hours. The suspension was partitioned between DCM (2x50 mL) and water (50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to afford a pale honey-coloured oil (4.9 g). The residue was purified by column chromatography on ISCO Companion (ELSD) eluting with DCM (A): Methanol (B) (0-10% (B), 80 g, 16.0 CV, 60 mL/min) to afford a mixture of products (2.3 g). This oily residue was purified again by column chromatography on ISCO Companion (ELSD) eluting with DCM (A): Ethyl Acetate (B) (0-50% (B), 40 g, 25.0 CV, 40 mL/min) to afford (S)-tert-butyl 4-(methylsulfonyl)-3-(((methylsulfonyl)oxy)methyl)piperazine-1-carboxylate as a colourless oil (1.58 g, 37%). MS (ES+) 317.0.

Step 2: (S)-tert-butyl tetrahydro-2H-isothiazolo[2,3-a]pyrazine-5(3H)-carboxylate 1,1-dioxide

[00424] To a solution of tert-butyl (3S)-4-methylsulfonyl-3-(methylsulfonyloxymethyl)piperazine-1-carboxylate (500 mg, 1.342 mmol) in anhydrous THF (10 mL) at -78°C was added dropwise LiHMDS (1 M in THF) (1.476 mL of 1.0 M, 1.476 mmol). The reaction mixture was stirred and allowed to slowly reach ambient temperature over 90 mins and stirred thereat for 18 hours. The reaction was cooled again to -78°C and thereto was added dropwise LiHMDS (1 M in THF) (1.476 mL of 1.0 M, 1.476 mmol). The reaction mixture was stirred and allowed to slowly reach ambient temperature over 90 mins and stirred thereat for a further 2 hours. The reaction was quenched with water (5 mL) and partitioned between the aqueous and ethyl acetate (3x50 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford an orange oil (490 mg). The residue was purified by column chromatography on ISCO Companion (ELSD) eluting with petroleum ether (A): ethyl acetate (B) (0-40% (B), 12 g, 21.0 min, 30 mL/min) to afford

(S)-tert-butyl tetrahydro-2H-isothiazolo[2,3-a]pyrazine-5(3H)-carboxylate 1,1-dioxide as a pale cream solid (361 mg, 97%). MS (ES+ -*t*-Bu) 221.0

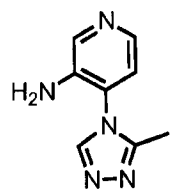
Step 3: (S)-hexahydro-2H-isothiazolo[2,3-a]pyrazine 1,1-dioxide

[00425] To a solution of tert-butyl (3aS)-1,1-dioxo-2,3,3a,4,6,7-hexahydroisothiazolo[2,3-a]pyrazine-5-carboxylate (360 mg, 1.303 mmol) in DCM (5 mL) at 0°C was added TFA (1.25 mL, 16.22 mmol) dropwise and the reaction was stirred and warmed slowly to ambient temperature over 45 mins. The reaction mixture was concentrated in vacuo and the residue was adsorbed onto a pre-wetted (methanol/DCM (1:1), 10 mL) SCX-2 cartridge (10 g) and flushed with DCM/methanol (1:1, 50 mL) and then the basic components eluted with 2 M ammonia in methanol (50 mL). The basic eluent was evaporated to dryness to afford (S)-hexahydro-2H-isothiazolo[2,3-a]pyrazine 1,1-dioxide as a colourless oil (192 mg, 84%).

Step 4: (S)-5-(3-aminopyridin-4-yl)hexahydro-2H-isothiazolo[2,3-a]pyrazine 1,1-dioxide

[00426] **Preparation N-1** was followed. MS (ES+) 269.1

Preparation N-28: 4-(3-methyl-4*H*-1,2,4-triazol-4-yl)pyridin-3-amine



Step 1: 3-bromo-4-isothiocyanatopyridine

[00427] 3-bromopyridin-4-amine (5 g, 28.90 mmol) was suspended in dry toluene (100 mL) and cooled in an ice-bath. A solution of thiophosgene (6.646 g, 4.407 mL, 57.80 mmol) in dry toluene (100 mL) was added dropwise over 25mins. The resulting orange/red suspension was stirred at reflux overnight. The red suspension was allowed to cool to RT and concentrated under reduced pressure to give a dark brown/red solid. This material was partitioned between saturated $NaHCO_3$ and DCM. The aqueous layer was extracted with further DCM (3 x 50mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a dark red solid/gum. This material was suspended in MeOH/DCM, adsorbed onto silica under reduced pressure and purified by column chromatography (75% EtOAc in hexanes, ~300 mL silica) to give 3-bromo-4-

isothiocyanatopyridine as a red oil which solidified on standing (3.513g, 57% Yield). MS (ES+) 216.9.

Step 2: 2-acetyl-N-(3-bromopyridin-4-yl)hydrazinecarbothioamide

[00428] 3-bromo-4-isothiocyanato-pyridine (1 g, 4.650 mmol) and acetylhydrazine (344.5 mg, 4.650 mmol) were dissolved in dry 1,4-dioxane (10 mL) and stirred at 80°C for 0.75 hrs. The orange suspension was allowed to cool to RT. The viscous suspension was diluted with ether and the solid was collected by fitration and washed with ether (3 x 5mL) to give 2-acetyl-N-(3-bromopyridin-4-yl)hydrazinecarbothioamide as a salmon-pink solid (1.2187g, 91% Yield). MS (ES-) 288.9.

Step 3: 4-(3-bromopyridin-4-yl)-5-methyl-4H-1,2,4-triazole-3-thiol

[00429] 2-acetyl-N-(3-bromopyridin-4-yl)hydrazinecarbothioamide (200 mg, 0.6917 mmol) was dissolved in sodium hydrogen carbonate (4 mL,) and stirred at 50°C for 2hrs and at 100°C for 5 hrs. The reaction mixture was then allowed to stand at RT for 48h before it was carefully neutralised with dilute HCl and partitioned with 10% MeOH in DCM. The aqueous layer was extracted with further 10% MeOH in DCM (3 x 10mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-(3-bromopyridin-4-yl)-5-methyl-4H-1,2,4-triazole-3-thiol as an orange solid (152.6 mg). MS (ES+) 272.9.

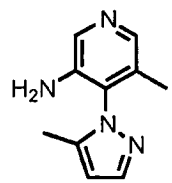
Step 4: 3-bromo-4-(3-methyl-4H-1,2,4-triazol-4-yl)pyridine

[00430] 4-(3-bromo-4-pyridyl)-5-methyl-1,2,4-triazole-3-thiol (145 mg, 0.5348 mmol) was suspended in dry DCM (4 mL) and cooled in an ice-bath. A solution of hydrogen peroxide (133.5 µL of 30 %w/v, 1.177 mmol) in AcOH (1.5 mL) was added slowly dropwise and the resulting mixture was stirred at RT for 2 hrs. The reaction mixture was cooled with an ice bath and quenched by slow addition of 2M NaOH and partitioned with DCM. The aqueous layer was extracted with further DCM (3 x 10mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow gum/solid (112.5mg). This material was redissolved in MeOH/DCM, adsorbed onto silica under reduced pressure and purified by column chromatography (7.5% MeOH in DCM, ~75 mL silica) to give 3-bromo-4-(3-methyl-4H-1,2,4-triazol-4-yl)pyridine as a cream solid (82.3mg, 64% Yield). MS (ES+) 240.9.

Step 5: 4-(3-methyl-4H-1,2,4-triazol-4-yl)pyridin-3-amine

[00431] Procedure similar to *Step 3a* of **Preparation N-14** was used.

Preparation N-29: 5-methyl-4-(5-methyl-1*H*-pyrazol-1-yl)pyridin-3-amine



Step 1: 3-bromo-4-hydrazinyl-5-nitropyridine

[00432] A solution of 3-bromo-4-chloro-5-nitro-pyridine (500 mg, 2.106 mmol), hydrazine hydrate (158.1 mg, 153.6 µL, 3.159 mmol) in ethanol (5.000 mL) was stirred at RT for 1h. The bright yellow precipitate was filtered, washed with methanol and dried under vacuum to leave 3-bromo-4-hydrazinyl-5-nitropyridine (390 mg, 79.5%). MS (ES-) 232.8.

Step 2: 3-bromo-4-(5-methyl-1H-pyrazol-1-yl)-5-nitropyridine

[00433] 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde (320 mg, 2.459 mmol) and (3-bromo-5-nitro-4-pyridyl)hydrazine (286.4 mg, 1.229 mmol) were heated under reflux in ethanol (2.864 mL) overnight. The reaction mixture was concentrated in vacuo and the residue was partitioned between DCM and a saturated aqueous sodium hydrogen carbonate solution. Combined organic extract was dried over $MgSO_4$ and concentrated in vacuo to leave 3-bromo-4-(5-methyl-1H-pyrazol-1-yl)-5-nitropyridine as a yellow oil. (200mg, 85%). MS (ES+) 284.9.

Step 3: 3-methyl-4-(5-methyl-1H-pyrazol-1-yl)-5-nitropyridine

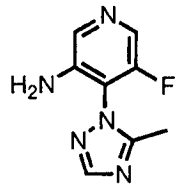
[00434] To an oven dried flask under nitrogen was added 3-bromo-4-(5-methylpyrazol-1-yl)-5-nitro-pyridine (200 mg, 0.6005 mmol), Pd_2dba_3 (8.249 mg, 0.009008 mmol) and X-Phos (8.590 mg, 0.01802 mmol). Anhydrous THF (1.700 mL) was added, followed by 1,4-diazabicyclo[2.2.2]octane; trimethylalumane (153mg, 0.6005 mmol). The reaction was heated at reflux for 2 hours then cooled to ambient temperature before it was quenched by the addition of water. The mixture was extracted with EtOAc (x 3) and the combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to leave a 3/1

mixture of 3-methyl-4-(5-methyl-1H-pyrazol-1-yl)-5-nitropyridine and 4-(5-methyl-1*H*-pyrazol-1-yl)-3-nitropyridine, that was used in the next step without further purification. (140 mg of product isolated as a mixture). MS (ES+) 219.0.

Step 4: 5-methyl-4-(5-methyl-1H-pyrazol-1-yl)pyridin-3-amine

[00435] Reduction was run according to *Step 2* of **Preparation N-1.** MS (ES+) 189.0.

Preparation N-30: 5-fluoro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine



Step 1: 3-bromo-5-fluoro-4-hydrazinylpyridine

[00436] 3-bromo-4-chloro-5-fluoro-pyridine (500 mg, 2.376 mmol), hydrazine (761.4 mg, 745.7 µL, 23.76 mmol), Na_2CO_3 (503.7 mg, 4.752 mmol) in cyclohexanol was heated at 100C overnight. The reaction mixture was filtered on celite and loaded on a SCX column, washed with DCM/MeOH mixtures and was eluted with a 2M solution of NH_3 in MeOH. The filtrate was concentrated in vacuo and the 3/1 mixture of 3-bromo-5-fluoro-4-hydrazinylpyridine and 3-bromo-4-chloro-5-hydrazinylpyridine was used in next step without further purification. MS (ES+) 205.9.

Step 2: 3-bromo-5-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)pyridine

[00437] Acetamide (136.7 mg, 2.315 mmol), 1,1-dimethoxy-N,N-dimethyl-methanamine (382.0 mg, 425.9 µL, 3.206 mmol), in dioxane was heated at 45-50°C under 150mm Hg vacuum for 2h. The reaction mixture was concentrated in vacuo. To the residue, (3-bromo-5-fluoro-4-pyridyl)hydrazine (367 mg, 1.781 mmol) and dioxane-acetic acid (1/1) was added and the mixture was heated at 130°C for 1h then at 160°C for 2h. At RT, the residue was loaded on a SCX column, washed with MeOH/DCM mixture. The filtrate is concentrated in vacuo yielding pure 3-bromo-5-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)pyridine as a dark oil. MS (ES+) 257.0.

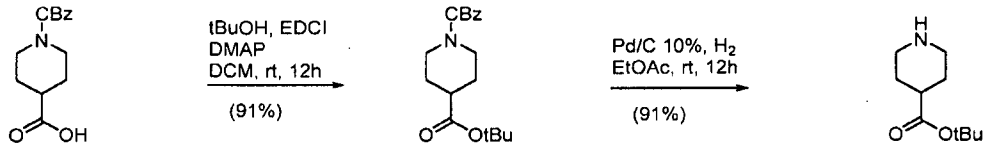
Step 3: 5-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)pyridin-3-amine

[00438] Amination reaction was run according to a procedure similar as *Step 3* of

Preparation N-14. MS (ES+) 194.0.

Preparation N-31: tert-butyl piperidine-4-carboxylate

Scheme 8



20 21 22

Step 1: O1-benzyl O4-tert-butyl piperidine-1,4-dicarboxylate **21**

[00439] In a 5L flange flask was charged 1-benzyloxycarbonylpiperidine-4-carboxylic acid **20** (200 g, 759.6 mmol) in DCM (500.0 mL) followed by additional DCM (2.000 L), t-butanol (140.8 g, 181.7 mL, 1.899 mol) and DMAP (46.40 g, 379.8 mmol). The mixture was cooled on ice/salt/water bath (internal -3.4°C). 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine (Hydrochloric Acid (1)) (145.6 g, 759.6 mmol) was added portionwise over 15 mins, with addition funnel rinsed with DCM (500.0 mL). Mixture was stirred on ice bath for approx. 2h. Ice bath was then removed (internal 3°C) and allowed to warm to room temperature overnight. Mixture was washed with 5% citric acid (2 x 500 mL), then saturated $NaHCO_3$ (500 mL), water (500 mL), and organics dried over $MgSO_4$, which was then filtered and concentrated *in vacuo* to leave product **21** as a viscous light yellow oil which turned to a white solid on standing. (246.1g, 101%). ^1H NMR (500 MHz, DMSO-d6) δ 7.40 – 7.31 (m, 5H), 5.08 (s, 2H), 3.90 (dt, 2H), 2.93 (br s, 2H), 2.43 (tt, 1H), 1.80 – 1.76 (m, 2H) and 1.45 – 1.37 (m, 11H).

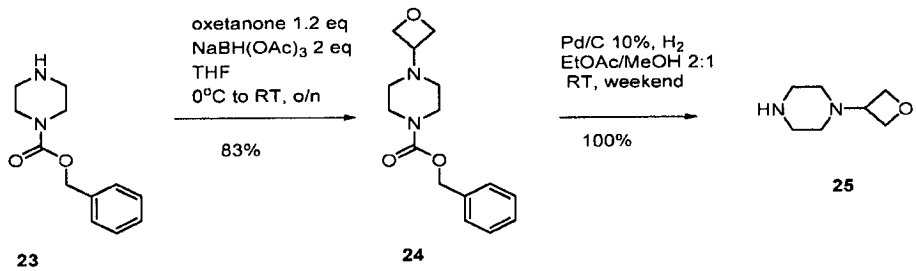
Step 2: tert-butyl piperidine-4-carboxylate **22**

[00440] To a 3L florentine under nitrogen was charged Pd on C, wet, Degussa (10%Pd, 50% WATER) (8.120 g, 76.30 mmol) then EtOAc (1.706 L). The mixture was degassed via N_2/vacuum cycles (3x), then a solution of O1-benzyl O4-tert-butyl piperidine-1,4-dicarboxylate **21** (243.7 g, 763.0 mmol) in EtOAc (243.7 mL) was added. Mixture was stirred under a hydrogen atmosphere overnight. Hydrogen was replenished and mixture was stirred for a further 3.5h. Methanol (60 mL) was added to aid dissolution of precipitate then filtered through celite, washing through with methanol. Filtrate concentrated *in vacuo* to leave a brown oil with a slight suspension of a white solid, 138.6g. Solid removed by filtration, and washed with minimal EtOAc. Filtrate was concentrated *in vacuo* to leave desired product as a

light brown oil (129g, 91%). ^{1}H NMR (500 MHz, DMSO-d6) δ 2.88 (dt, 2H), 2.44 (td, 2H), 2.23 (tt, 1H), 1.69 – 1.64 (m, 2H) and 1.41 – 1.33 (m, 11H).

Preparation N-32: 1-(oxetan-3-yl)piperazine

Scheme 9



Step 1: benzyl 4-(oxetan-3-yl)piperazine-1-carboxylate **24**

[00441] Benzyl piperazine-1-carboxylate **23** (27.3 mL, 142.2 mmol) was dissolved in dry THF (313.1 mL) and oxetan-3-one (12.29 g, 10.93 mL, 170.6 mmol) was added. The resulting solution was cooled in an ice-bath. $NaBH(OAc)_3$ (59.99 g, 284.4 mmol) was added portionwise over 30 mins, about a quarter was added. Mixture removed from ice bath, allowed to warm to room temperature then continued adding the $NaBH(OAc)_3$ portionwise over 30 mins. On complete addition, an exotherm from 22°C slowly to 32°C was observed, whereby the mixture was subsequently cooled on an ice bath until an internal of 22°C was reached. The ice bath was removed and the reaction mixture's internal temp was steady at 22°C. The mixture was stirred at room temperature overnight.

[00442] The resulting white suspension was quenched by addition of 2M sodium carbonate solution (approx 150 mL) (pH = 8) and concentrated under reduced pressure to remove THF. Product was then extracted with EtOAc (3 x 250 mL). Organics were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to leave product **24** as a white solid (32.7g 83% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.39 – 7.30 (m, 5H), 5.07 (s, 2H), 4.52 (t, 2H), 4.42 (t, 2H), 3.43 – 3.39 (m, 5H) and 2.22 (t, 4H). MS (ES+) 276.8.

Step 2: 1-(oxetan-3-yl)piperazine **25**

[00443] In a 1L florentine was added $Pd(OH)_2$ (1.661 g, 2.366 mmol) under nitrogen. MeOH (130.8 mL) and EtOAc (261.6 mL) were added and the mixture degassed via vacuum/nitrogen cycles (3x). Benzyl 4-(oxetan-3-yl)piperazine-1-carboxylate **24** (32.7 g, 118.3 mmol) was then added and the mixture stirred under a hydrogen atmosphere over the

weekend. Mixture was filtered through a pad of celite, washing through with EtOAc then methanol. Filtrate was concentrated *in vacuo* to leave product **25** as an orange oil 1(8.1g, quantitative yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 4.51 (t, 2H), 4.41 (t, 2H), 3.36 – 3.30 (masked signal, 1H), 2.69 (t, 4H) and 2.14 (br s, 4H).

[00444] The following compounds were successfully prepared using a procedure similar to **Example 1 or Examples 3a-3e:**

2-amino-6-fluoro-N-(4-(4-isopropylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-4**);

2-amino-N-(5-cyclopropyl-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-5**);

2-amino-*N*-(5-chloro-4-(8-methylhexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-6**);

N-(4-(1*H*-imidazol-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-7**);

2-amino-6-fluoro-*N*-(4-(4-(2-(methylamino)ethyl)-1*H*-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-8**);

2-amino-N-(4-(4-(2-(dimethylamino)ethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-9**);

(R)-2-amino-6-fluoro-*N*-(4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-10**);

2-amino-6-fluoro-*N*-(4-(4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-11**);

(S)-2-amino-6-fluoro-*N*-(4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-12**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-13**);

2-amino-6-chloro-*N*-(5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-14**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-15**);

2-amino-6-fluoro-*N*-(5-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-16**);

2-amino-*N*-(4-(4-ethylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-17**);

N-(4-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-18**);

(R,S)-2-amino-6-fluoro-*N*-(4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-19**);

2-amino-6-fluoro-*N*-(4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-20**);

(*S*)-2-amino-6-fluoro-*N*-(4-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-21**);

2-amino-6-fluoro-*N*-(4-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-22**);

(R)- 2-amino-6-fluoro-*N*-(4-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-23**);

(S)-2-amino-6-fluoro-*N*-(4-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-24**);

2-amino-6-chloro-*N*-(4-(4-(3-methyloxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-25**);

N-(4-(1*H*-pyrazol-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-26**);

2-amino-6-fluoro-*N*-(4-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-27**);

2-amino-6-fluoro-*N*-(4-(2-methyl-1*H*-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-28**);

N-(4-(1*H*-imidazol-1-yl)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-29**);

2-amino-6-fluoro-*N*-(4-(2-methyl-4-(trifluoromethyl)-1*H*-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-30**);

2-amino-6-fluoro-*N*-(4-(5-(oxetan-3-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-31**);

2-amino-*N*-(5-cyclopropyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-32**);

2-amino-*N*-(4-(4-cyclopropylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-33**);

2-amino-*N*-(4-(4-(*tert*-butyl)piperazin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-34**);

2-amino-6-chloro-*N*-(4-((3*S*,4*S*)-4-(dimethylamino)-3-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-35**);

2-amino-6-chloro-*N*-(4-(4-((dimethylamino)methyl)-4-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-36**);

2-amino-6-chloro-*N*-(4-(4-(dimethylamino)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-37**);

2-amino-6-chloro-*N*-(4-(4-isopropylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-

carboxamide (**Compound I-N-39**);

2-amino-6-chloro-*N*-(4-(3-(dimethylamino)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-40**);

2-amino-6-chloro-*N*-(5-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-41**);

2-amino-6-chloro-*N*-(4-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-42**);

2-amino-6-chloro-*N*-(4-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-43**);

2-amino-6-chloro-*N*-(4-(5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-44**);

2-amino-6-chloro-*N*-(4-(4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-45**);

2-amino-6-chloro-*N*-(4-(4-((dimethylamino)methyl)-4-methoxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-46**);

2-amino-6-chloro-*N*-(4-(3-(methoxymethyl)-4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-47**);

2-amino-6-chloro-*N*-(4-(4-cyclobutylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-48**);

2-amino-6-chloro-*N*-(4-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-49**);

2-amino-*N*-(6-amino-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-50**);

2-amino-6-chloro-*N*-(4-(4-ethylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-51**);

2-amino-6-chloro-*N*-(6-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-52**);

2-amino-6-chloro-*N*-(4-(3,3,4-trimethylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-53**);

2-amino-6-chloro-*N*-(4-(3,4-dimethylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-54**);

2-amino-*N*-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-55**);

N-(4-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-56**);

2-amino-6-chloro-*N*-(5-methyl-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-57**);

2-amino-6-chloro-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-58**);

2-amino-6-chloro-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-59**);

2-amino-6-chloro-*N*-(4-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-60**);

2-amino-6-chloro-*N*-(4-(8-methylhexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-61**);

2-amino-6-fluoro-*N*-(4-(4-(3-methyloxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-62**);

2-amino-6-chloro-*N*-(4-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-63**);

2-amino-6-chloro-*N*-(4-(4-cyclopropylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-64**);

(*R*)-2-amino-6-chloro-*N*-(4-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-65**);

2-amino-6-chloro-*N*-(4-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-66**);

2-amino-6-chloro-*N*-(4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-67**);

2-amino-6-chloro-*N*-(4-(1-oxidothiomorpholino)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-68**);

2-amino-6-chloro-*N*-(4-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-69**);

2-amino-6-chloro-*N*-(4-(3-(trifluoromethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-70**);

(*S*)-2-amino-6-chloro-*N*-(4-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-71**);

2-amino-6-chloro-*N*-(4-(2,4-dimethylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-72**);

2-amino-6-chloro-*N*-(4-(4-methoxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-73**);

methyl-1-(3-(2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)piperidine-4-carboxylate (**Compound I-N-74**);

2-amino-6-chloro-*N*-(4-(5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-75**);

2-amino-6-(2-cyanopropan-2-yl)-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide (**Compound I-N-76**);

2-amino-6-(cyanomethyl)-*N*-(4-(pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-77**);

2-amino-6-(1-cyanoethyl)-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-78**);

2-amino-*N*-(4-(azepan-1-yl)pyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-79**);

2-amino-6-(cyanomethyl)-*N*-(5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-80**);

2-amino-6-(cyanomethyl)-*N*-(4-morpholinopyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-81**);

2-amino-6-(cyanomethyl)-*N*-(4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-82**);

2-amino-6-(cyanomethyl)-*N*-(4-(4-hydroxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-83**);

2-amino-6-(cyanomethyl)-*N*-(4-(piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-84**);

2-amino-*N*-(5-chloro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-85**);

2-amino-*N*-(5-(difluoromethyl)-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-111**)

2-amino-6-fluoro-*N*-(4-(5-(oxetan-3-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-112**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(8-methylhexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-114**);

(*S*)-2-amino-6-fluoro-*N*-(4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-115**);

(*R*)-2-amino-6-fluoro-*N*-(4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-116**);

2-amino-6-chloro-*N*-(5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-117**);

(S)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-125**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-127**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(quinuclidine-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-130**);

2-amino-6-fluoro-*N*-(4-(1-methyl-9-oxa-1,4-diazaspiro[5.5]undecan-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-133**);

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-135**);

2-amino-6-fluoro-*N*-(4-(4-oxohexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-136**);

(*S*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-137**);

2-amino-6-(2-cyanopropan-2-yl)-*N*-(5-fluoro-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-138**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-139**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-140**);

2-amino-6-fluoro-*N*-(4-morpholinopyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-141**);

2-amino-6-(2-cyanopropan-2-yl)-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-142**);

2-amino-6-(1-cyanoethyl)-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-143**);

2-amino-6-(1-cyanoethyl)-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-144**);

2-amino-6-(2-cyanopropan-2-yl)-*N*-(5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-145**);

2-amino-*N*-(4-(4-(*N*,*N*-dimethylsulfamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-146**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-147**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)sulfamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-148**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(morpholinomethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-149**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((4-methylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-150**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methyl-2-oxopiperazin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-151**);

2-amino-6-fluoro-*N*-(4-(piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-152**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(morpholinosulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-155**);

2-amino-6-fluoro-*N*-(4-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-161**);

2-amino-6-fluoro-*N*-(4-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-162**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-163**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(methylsulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-165**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((4-methylpiperazin-1-yl)sulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-166**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-(pyrrolidin-1-yl)ethoxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-167**);

2-amino-*N*-(4-(4-(azetidin-1-ylsulfonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-169**);

2-amino-6-fluoro-*N*-(4-(4-(morpholinosulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-170**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((4-methyl-3-oxopiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-171**);

2-amino-6-(1-cyanocyclopropyl)-*N*-(5-fluoro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-180**);

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-182**);

2-amino-6-fluoro-*N*-(4-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-183**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(thiazol-2-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-184**);

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-186**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-(pyrrolidin-1-yl)acetyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-187**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-morpholinopiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-189**);

2-amino-6-fluoro-*N*-(4-(4-(methylsulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-190**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(3-(4-methylpiperazine-1-carbonyl)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-191**);

2-amino-6-(1-cyanocyclopropyl)-*N*-(5-fluoro-4-(4-((4-methylpiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-192);**

2-amino-6-fluoro-N-(5-fluoro-4-(4-((4-methyl-2-oxopiperazin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-193**);

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonan-4-ylsulfonyl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-196**);

2-amino-N-(4-(4-((3,3-difluoropyrrolidin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-197**);

2-amino-6-fluoro-N-(4-(4-(oxetan-3-ylsulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-200**);

2-amino-N-(4-(2-cyclopropyl-1H-imidazol-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-202**);

2-amino-6-fluoro-N-(4-(4-((2-methoxyethyl)sulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-208**);

2-amino-6-fluoro-N-(4-(4-methyl-3-oxopiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-209**);

2-amino-N-(4-(1,1-dioxidothiomorpholino)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-210**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-methyl-3-oxopiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-212**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-((2-oxopyrrolidin-1-yl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-213**);

2-amino-6-fluoro-N-(4-(4-((methylsulfonyl)methyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-215**);

2-amino-6-fluoro-N-(4-(3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-216**);

(S)-2-amino-6-fluoro-N-(4-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-217**);

2-amino-N-(4-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-218**);

2-amino-6-fluoro-N-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-219**);

2-amino-N-(4-(2,2-dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-220**);

2-amino-6-fluoro-N-(4-(3-(methylsulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-221**);

2-amino-6-fluoro-N-(4-(4-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-222**);

2-amino-6-fluoro-N-(4-(5-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-223**);

2-amino-6-fluoro-N-(4-((3aR,7aR)-2-methyl-3-oxohexahydro-1H-pyrrolo[3,4-c]pyridin-5(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-224**);

2-amino-6-fluoro-N-(4-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-225**);

N-(4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-226**);

2-amino-6-fluoro-N-(5-fluoro-4-(3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-229**);

2-amino-6-fluoro-N-(4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-230**);

2-amino-6-fluoro-N-(4-(2-methyl-3-oxo-2,9-diazaspiro[5.5]undecan-9-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-231**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-232**);

2-amino-6-fluoro-N-(4-(8-methyl-9-oxohexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-233**);

4-(3-(2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamido)pyridin-4-yl)-N,N-

dimethylmorpholine-2-carboxamide (**Compound I-N-234**);

2-amino-6-fluoro-N-(4-(1-methyl-2-oxo-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-235**);

2-amino-6-fluoro-N-(4-(2-methyl-3-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-236**);

2-amino-6-fluoro-N-(4-(3-oxotetrahydro-1H-oxazolo[3,4-a]pyrazin-7(3H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-238**);

2-amino-6-fluoro-N-(5-fluoro-4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-239**);

2-amino-6-fluoro-N-(5-fluoro-4-(8-methyl-9-oxohexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-240**);

N-(4-(4-(1,2,4-oxadiazol-3-yl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-241**);

2-amino-6-fluoro-N-(5-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-242**);

2-amino-6-fluoro-N-(4-(4-methyl-4-(methylsulfonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-243**);

2-amino-6-fluoro-N-(4-(6-oxohexahydro-1H-pyrido[1,2-a]pyrazin-2(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-244**);

2-amino-6-fluoro-N-(4-(8-isopropyl-9-oxohexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-245**);

2-amino-6-fluoro-N-(5-fluoro-4-(pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-246**);

(S)-2-amino-N-(4-(1,1-dioxidotetrahydro-2H-isothiazolo[2,3-a]pyrazin-5(3H)-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-247**);

(S)-2-amino-6-fluoro-N-(5-fluoro-4-(3-oxotetrahydro-1H-oxazolo[3,4-a]pyrazin-7(3H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-248**);

2-amino-N-(4-(1,1-dioxidothiomorpholino)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-250**);

2-amino-N-(4-(2,2-dimethyl-1,1-dioxidothiomorpholino)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-252**);

N-(4-(2-oxa-6-azaspiro[3.5]nonan-6-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-253**);

2-amino-6-fluoro-N-(4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-256**);

(R)-2-amino-6-fluoro-N-(4-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-258**);

2-amino-6-fluoro-N-(1-methyl-1H-pyrrolo[3,2-c]pyridin-7-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-259**);

2-amino-6-fluoro-N-(4-(4-(4-methyl-1,2,5-oxadiazol-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-260**);

2-amino-6-fluoro-N-(4-(3-methyl-4H-1,2,4-triazol-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-263**);

2-amino-N-(4-(azepan-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-264**);

2-amino-6-fluoro-N-(4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-265**);

2-amino-6-fluoro-N-(4-(4-methoxypiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-266**);

2-amino-N-(4-(4-((dimethylamino)methyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-267**);

N-(4-(4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-268**);

2-amino-N-(4-(4,5-dimethyl-1H-imidazol-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-269**);

2-amino-6-fluoro-N-(5-fluoro-4-(piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-270**);

2-amino-N-(4-(4-(azetidin-1-ylsulfonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-271**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-272**);

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonan-4-ylsulfonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-273**);

2-amino-6-fluoro-N-(5-fluoro-4-(6-oxohexahydro-1H-pyrido[1,2-a]pyrazin-2(6H)-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-277**);

(*S*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(6-oxohexahydro-1*H*-pyrido[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-279)**;

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(6-oxohexahydro-1*H*-pyrido[1,2-*a*]pyrazin-2(6*H*)-

yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-280)**;

2-amino-*N*-(5-chloro-4-(pyrrolidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-281);**

2-amino-6-fluoro-*N*-(4-(4-(methoxymethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-282);**

2-amino-6-fluoro-*N*-(4-(5-methyl-1*H*-imidazol-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-283);**

2-amino-*N*-(5-chloro-4-(3-hydroxypyrrolidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-284);**

(*R*)-2-amino-*N*-(5-chloro-4-(3-cyanopyrrolidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-285);**

2-amino-*N*-(5-chloro-4-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-286);**

2-amino-*N*-(5-chloro-4-(3-(methylsulfonyl)pyrrolidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-287);**

N-(4-(4-(1*H*-imidazol-1-yl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-288)**

2-amino-6-fluoro-*N*-(5-fluoro-4-(3-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-289**);

2-amino-N-(4-(3-(dimethylcarbamoyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-290**);

2-amino-6-fluoro-*N*-(5'-methoxy-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-C-82);**

2-amino-6-fluoro-*N*-(4-(1-(2-methoxyethyl)-1*H*-imidazol-5-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-C-83);**

2-amino-*N*-(4-cyclopropyl-5-methoxypyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-C-84);**

2-amino-6-fluoro-*N*-(4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-1**);

2-amino-*N*-(4-(4-(dimethylcarbamoyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-2**);

2-amino-*N*-(5-chloro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-3**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-G-4**);

2-amino-6-chloro-*N*-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-5**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methyl-1,4-diazepane-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-6**);

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonane-4-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-7**);

2-amino-*N*-(4-(4-(4-cyclopropylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-13**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3,3,4-trimethylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-15**);

2-amino-*N*-(4-(4-cyano-4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-25**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-methyl-4-(4-methylpiperazine-1-carbonyl)piperidin-1-

yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-54**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(5-methyl-2,5-diazabicyclo[4.1.0]heptane-2-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-65**); and

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonane-4-carbonyl)piperidin-1-yl)-5-chloropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-66**).

[00445] The following compounds were prepared according to methods similar to the one depicted in the procedure described in **Example 2**:

2-amino-*N*-(4-(4-aminopiperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-86**);

2-amino-6-chloro-*N*-(4-(4-(methylamino)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-87**);

2-amino-6-chloro-*N*-(4-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-88**);

2-amino-6-(cyanomethyl)-*N*-(4-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-89**);

2-amino-*N*-(4-(2-(aminomethyl)morpholino)pyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-90**);

2-amino-*N*-(4-(4-(aminomethyl)piperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-91**);

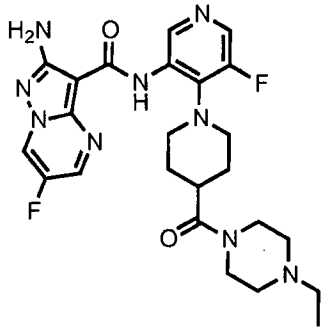
2-amino-6-fluoro-*N*-(5-fluoro-4-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-118**);

2-amino-*N*-(5-chloro-4-(piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-126**);

2-amino-6-fluoro-*N*-(6-(methylamino)-4-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-129**); and

N-(4-(2,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-255**).

Example 4: 2-amino-*N*-(4-(4-(4-ethylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (compound I-G-9)



Step 1: 1-(3-(2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylic acid (**Compound I-N-92**)

[00446] *tert*-butyl 1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)piperidine-4-carboxylate prepared according to methods similar to the one depicted in **Example 1** was dissolved in DCM (5mL). TFA (1 mL, 12.98 mmol) was added and the mixture was stirred at RT for 5 hr. The reaction mixture was concentrated to give 1-(3-(2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carboxylic acid as a beige solid that was used in next step without further purification. MS (ES+) 418.1.

Step 2: 2-amino-N-(4-(4-(4-ethylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide

[00447] A mixture of 1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)piperidine-4-carboxylic acid (Trifluoroacetic Acid (2)) (30 mg,), (benzotriazol-1-yloxy-dimethylamino-methylene)-dimethyl-ammonium (Boron Tetrafluoride Ion (1)) (46.17 mg, 0.1438 mmol) and TEA (33.07 mg, 45.55 µL, 0.3268 mmol) in DMF was stirred at room temperature for 5 minutes followed by the addition of 1-ethylpiperazine (13.68 mg, 0.1198 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was filtered and purified directly by fractionlynx yielding 2-amino-*N*-(4-(4-(4-ethylpiperazine-1-

carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide. yield 38% MS (ES+) 514.0.

[00448] The following compounds were successfully prepared using a procedure similar to **Example 4:**

2-amino-*N*-(4-(4-(azetidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-8**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(octahydropyrrolo[1,2-*a*]pyrazine-2-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-10**);

(R)-2-amino-*N*-(4-(4-(3-(dimethylamino)pyrrolidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-11**);

N-(4-(4-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-G-14**);

2-amino-*N*-(4-(4-((3-(dimethylamino)propyl)(methyl)carbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-16**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(5-methyloctahydropyrrolo[3,4-*c*]pyrrole-2-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-18**);

2-amino-*N*-(4-(4-(*tert*-butylcarbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-19**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((1-methylpiperidin-4-yl)carbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-20**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-methoxyazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-21**);

2-amino-*N*-(4-(4-(3-(dimethylamino)azetidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-22**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((1-methylazetidin-3-yl)carbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-23**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((1-methylpyrrolidin-3-yl)carbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-24**);

2-amino-*N*-(4-(4-((3-(dimethylamino)propyl)carbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-26**);

2-amino-*N*-(4-(4-(dimethylcarbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-29**);

2-amino-*N*-(4-(4-((2-(dimethylamino)ethyl)carbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-30**);

2-amino-*N*-(4-(4-((2-(dimethylamino)ethyl)(methyl)carbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-31**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-(oxetan-3-yl)piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-32**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(methylcarbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-33**);

2-amino-*N*-(4-(4-(4-cyclobutylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-35**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(morpholine-4-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-36**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(oxetan-3-ylcarbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-37**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methyl-4,7-diazaspiro[2.5]octane-7-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-38**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((2-methoxyethyl)(methyl)carbamoyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-40**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-hydroxyazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-41**);

2-amino-*N*-(4-(4-((2-(azetidin-1-yl)ethyl)carbamoyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-42**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(pyrrolidin-1-yl)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-43**);

N-(4-(4-(1,4-diazabicyclo[3.2.1]octane-4-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-46**);

(S)-2-amino-*N*-(4-(4-(3,4-dimethylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-47**);

N-(4-(4-([1,3'-biazetidine]-1'-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-49**);

(*R*)-2-amino-*N*-(4-(4-(3,4-dimethylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-50**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(8-methyl-3,8-diazabicyclo[3.2.1]octane-3-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-52**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-53**);

2-amino-6-fluoro-*N*-(5-methyl-4-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-55**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(piperidin-1-yl)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-57**);

(*S*)-*N*-(4-(4-([1,3'-bipyrrolidine]-1'-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-58**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-(pyrrolidin-1-yl)piperidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-59**);

N-(4-(4-([1,4'-bipiperidine]-1'-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-60**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-hydroxy-3-methylazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-63**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(piperidin-1-yl)pyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-64**);

2-amino-6-fluoro-N-(5-fluoro-4-(4-(3-fluoroazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-G-67**);

2-amino-*N*-(4-(4-(4-(azetidin-1-yl)piperidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-68**);

N-(4-(4-(1,4-diazabicyclo[3.2.1]octane-4-carbonyl)piperidin-1-yl)-5-chloropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-69**);

N-(4-(4-((5*S*)-1,4-diazabicyclo[3.2.1]octane-4-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-70)**;

N-(4-(4-((5*R*)-1,4-diazabicyclo[3.2.1]octane-4-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-71)**;

N-(4-(4-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-72)**;

2-amino-*N*-(4-(4-(3,3-difluoroazetidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-73)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-fluoroazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-

yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-74)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-methoxy-3-methylazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-75)**;

2-amino-*N*-(4-(4-(3-cyanoazetidine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-76)**;

2-amino-*N*-(4-(4-(azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-77)**;

2-amino-6-fluoro-*N*-(4-(4-(3-methoxyazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-78)**;

2-amino-6-fluoro-*N*-(4-(4-(3-methoxy-3-methylazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-79)**;

2-amino-*N*-(4-(4-(3,3-difluoroazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-80)**;

2-amino-*N*-(4-(4-(3-cyanoazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-81)**;

2-amino-6-fluoro-*N*-(4-(4-(3-fluoroazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-82)**;

2-amino-6-fluoro-*N*-(4-(4-(pyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-83)**;

N-(4-(4-(2-oxa-6-azaspiro[3.4]octane-6-carbonyl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-84)**;

2-amino-6-fluoro-*N*-(4-(4-(morpholine-4-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-85)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(methylsulfonyl)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-G-86)**;

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonane-4-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-87**);

N-(4-(4-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-88**);

2-amino-6-fluoro-*N*-(4-(4-(3-(methylsulfonyl)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-89**);

N-(4-(4-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-90**);

2-amino-*N*-(4-(4-(3-ethoxyazetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-91**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-(3-methyloxetan-3-yl)piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-92**);

(*R*)-2-amino-6-fluoro-*N*-(4-(4-(3-methoxypyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-93**);

(*S*)-2-amino-6-fluoro-*N*-(4-(4-(3-methoxypyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-94**);

4-(1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carbonyl)-1-methylpiperazine 1-oxide (**Compound I-G-95**);

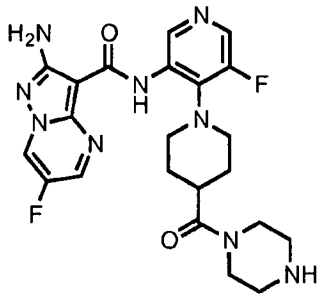
2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-(1-methylazetidin-3-yl)piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-96**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(methoxymethyl)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-98**); and

(*S*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-methoxypyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-99**).

Example 5: 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(piperazine-1-carbonyl)piperidin-1-

yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-G-12)



[00449] *tert*-butyl 4-(1-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperidine-4-carbonyl)piperazine-1-carboxylate prepared using procedure similar to **Example 4** was dissolved in a mixture of DCM (5 mL) / TFA (1 mL, 12.98 mmol) and stirred at RT for 90 min. then concentrated *in vacuo*. The residue was purified by fractionlynx. Clean fractions were freeze dried to yield 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. MS (ES+) 486.2.

[00450] The following compounds were successfully prepared using a procedure similar to **Example 5**:

2-amino-*N*-(4-(4-(3,3-dimethylpiperazine-1-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-27**);

N-(4-(4-(4,7-diazaspiro[2.5]octane-7-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-28**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-(methylamino)azetidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-34**);

N-(4-(4-(3,8-diazabicyclo[3.2.1]octane-3-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-44**);

(R)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-45**);

2-amino-*N*-(5-chloro-4-(4-(piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)-6-

fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-48**);

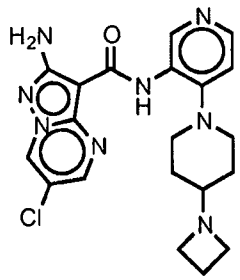
2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(octahydropyrrolo[3,4-*c*]pyrrole-2-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-51**);

2-amino-6-fluoro-*N*-(5-methyl-4-(4-(piperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-56**);

(S)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(3-methylpiperazine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-61**); and

N-(4-(4-(2,5-diazabicyclo[4.1.0]heptane-2-carbonyl)piperidin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-G-62**).

Example 6: 2-amino-N-(4-(4-(azetidin-1-yl)piperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-N-93)



Step 1: 2-amino-6-chloro-N-(4-(4-oxopiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00451] To a solution of 2-amino-6-chloro-N-[4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (prepared according to a procedure similar to **Example 1**) (420 mg, 0.9771 mmol) in tetrahydrofuran (10 mL) was added HCl (4.886 mL of 2 M, 9.771 mmol). The resulting mixture was stirred at room temperature overnight. The resulting reaction mixture was diluted with water (100 mL), made basic with 2.5 N aqueous sodium hydroxide, and extracted three times with dichloromethane (100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-amino-6-chloro-*N*-(4-(4-oxopiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a pale yellow solid which was used without

further purification. MS (ES+) 386.1.

Step 2: 2-amino-N-(4-(4-(azetidin-1-yl)piperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide

[00452] A solution of 2-amino-6-chloro-N-[4-(4-oxo-1-piperidyl)-3-pyridyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (50 mg, 0.1296 mmol), azetidine (Hydrochloric Acid (1)) (12.12 mg, 0.1296 mmol) and ammonium formate (8.172 mg, 0.1296 mmol) in toluene was heated at reflux for 1h with a Dean-Stark apparatus. The reaction was cooled to room temperature and evaporated. The resulting yellow solid was dissolved in DMSO and purified by fractionlynx to yield 2-amino-N-(4-(4-(azetidin-1-yl)piperidin-1-yl)pyridin-3-yl)-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide as a white solid. (27mg, 31%). MS (ES+) 427.2.

[00453] The following compounds were successfully prepared using a procedure similar to **Example 6**:

2-amino-6-chloro-*N*-(4-(4-(3-(dimethylamino)azetidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-94**);

2-amino-6-chloro-*N*-(4-(4-(3-methoxypyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-95**);

N-(4-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-96**);

2-amino-6-chloro-N-(4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-97**);

(*R*)-2-amino-6-chloro-*N*-(4-(4-(3-fluoropyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-98**);

N-(4-(4-(2-oxa-6-azaspiro[3.4]octan-6-yl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-99**);

2-amino-6-chloro-N-(4-(4-(1-oxidothiomorpholino)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide (**Compound I-N-100**);

2-amino-6-chloro-*N*-(4-(4-(5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-101**);

2-amino-6-chloro-N-(4-(4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-102**);

(*S*)-2-amino-6-chloro-*N*-(4-(4-(3-fluoropyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-103**);

2-amino-6-chloro-N-(4-(4-morpholinopiperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-104**);

2-amino-6-chloro-N-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-105**);

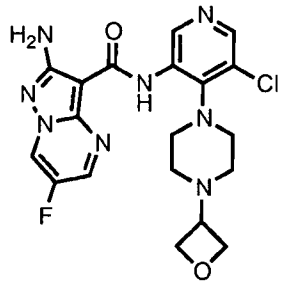
2-amino-6-chloro-N-(4-(4-(3-(dimethylamino)pyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-106**);

2-amino-6-chloro-N-(4-(4-(3-methoxyazetidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-107**);

2-amino-6-chloro-N-(4-(4-(3,3-difluoroazetidin-1-yl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-108**); and

N-(4-(4-(6-oxa-1-azaspiro[3.3]heptan-1-yl)piperidin-1-yl)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-109**).

Example 7: 2-amino-N-(5-chloro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-N-110)



[00454] To a solution of 2-amino-*N*-(5-chloro-4-(piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (51mg, 0.13mmol) (synthesized according to a procedure similar to **Example 2**) in THF (4 mL) was added oxetan-3-one (14.31 mg, 11.63 μL, 0.1986 mmol) and triacetoxyborohydride (Sodium Ion (1)) (56.12 mg, 0.2648 mmol), and the mixture was stirred at rt for 4h. The reaction mixture was partitioned between an aqueous saturated solution of $NaHCO_3$ and ethyl acetate. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by fractionlynx to yield 2-amino-N-(5-chloro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide. MS (ES+) 447.2.

[00455] The following compounds were synthesized according to a procedure similar to **Example 7**:

2-amino-*N*-(5-chloro-4-(8-(oxetan-3-yl)hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2(6*H*)-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-38**);

(*R*)-2-amino-*N*-(5-cyclopropyl-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-119**);

(*S*)-2-amino-*N*-(5-cyclopropyl-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-120**);

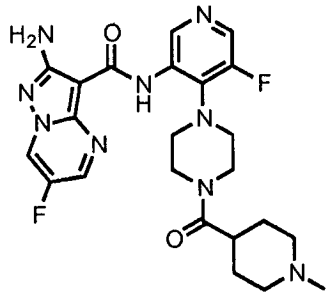
2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-121**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-122);**

2-amino-6-fluoro-*N*-(5-methyl-4-(4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-123**); and

2-amino-*N*-(5-chloro-4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-124**).

Example 8: 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpiperidine-4-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-128)



[00456] A microwave vial was charged with 2-amino-6-fluoro-N-(5-fluoro-4-piperazin-1-yl-3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (79 mg, 0.2110 mmol) (synthesized according to a procedure similar to **Example 2**), 1-methylpiperidine-4-carboxylic acid (Hydrochloric Acid (1)) (37.90 mg, 0.2110 mmol), TBTU (74.52 mg, 0.2321 mmol), Et_3N (46.97 mg, 64.70 μL, 0.4642 mmol) in NMP (0.5 mL) , the tube sealed and stirred at 100°C overnight. The mixture was cooled to RT and was loaded into a MeOH pre-washed SCX column, rinsed with MeOH and released with methanolic ammonia. The ammonia extracts were concentrated under reduced pressure to give 110 mg of a brown oil/gum, which was purified by Fraction Lynx reverse phase column chromatography. The clean fractions were combined and freeze dried, yielding 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpiperidine-4-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. MS (ES+) 500.2.

[00457] The following compounds were synthesized according to a procedure similar to **Example 8**:

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(quinuclidine-4-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-134**);

2-amino-*N*-(4-(4-(2-(dimethylamino)acetyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-153**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpyrrolidine-3-carbonyl)piperazin-1-

yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-156**);

(*S*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-157**);

2-amino-*N*-(4-(4-(2-(azetidin-1-yl)acetyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-160**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpiperidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-173**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methylmorpholine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-174**);

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-181**);

2-amino-*N*-(4-(4-(1-ethylpyrrolidine-2-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-185**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(2-(pyrrolidin-1-yl)acetyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-187**);

(*S*)-2-amino-6-fluoro-*N*-(4-(4-(1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-198)**;

(*R*)-2-amino-6-fluoro-*N*-(4-(4-(1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-199)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(octahydroindolizine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-203)**;

2-amino-*N*-(4-(4-(1-ethylpiperidine-2-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-204)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-isopropylpyrrolidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-205)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-isopropylpyrrolidine-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-206)**;

2-amino-*N*-(4-(4-(1-ethylpyrrolidine-3-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-207)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-(oxetan-3-yl)piperidine-4-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-211)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(1-methylpiperidine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-214)**;

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methylmorpholine-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-227)**;

2-amino-6-fluoro-*N*-(4-(4-(oxetane-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-254)**;

N-(4-(2-acetyl-2,7-diazaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-251);**

N-(4-(4-acetylpiperazin-1-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-254)**;

N-(4-(2-acetyl-2,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-257)**;

methyl-4-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperazine-1-carboxylate **(Compound I-N-261)**;

N-(4-(1-acetyl-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-N-262)**;

N-(4-(1-acetylpiperidin-4-yl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-C-69)**;

2-amino-*N*-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide **(Compound I-C-70)**;

2-amino-*N*-(4-(1-(1-cyanocyclopropanecarbonyl)piperidin-4-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-71**);

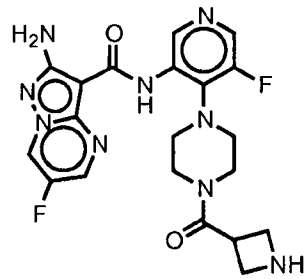
2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(tetrahydrofuran-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-274**);

N-(4-(4-acetylpiperazin-1-yl)-5-fluoropyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-275**);

2-amino-*N*-(4-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-276**); and

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(oxetane-3-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-278**).

Example 9: 2-amino-*N*-(4-(4-(azetidine-3-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-168)

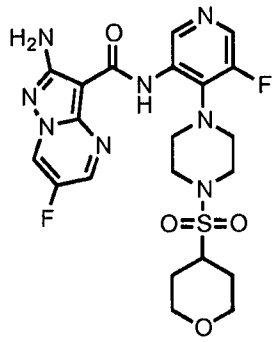


[00458] *Tert*-butyl 3-(4-(3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-5-fluoropyridin-4-yl)piperazine-1-carbonyl)azetidine-1-carboxylate (73 mg, 0.1309 mmol) (prepared using a procedure similar to **Example 8**) was dissolved in DCM (219.0 µL). TFA (298.5 mg, 201.7 µL, 2.618 mmol) was added and the mixture was stirred at RT for 2 hr. The reaction mixture was concentrated *in vacuo* and the residue was purified by fractionlynx yielding 2-amino-*N*-(4-(4-(azetidine-3-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a cream solid. MS (ES+) 458.1.

[00459] The following compounds were synthesized according to the procedure similar to **Example 9**:

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(morpholine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-172**).

Example 10: 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-158)



[00460] Tetrahydropyran-4-sulfonyl chloride (16.28 mg, 0.08815 mmol) was added to a suspension of 2-amino-6-fluoro-N-(5-fluoro-4-piperazin-1-yl-3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (30 mg, 0.08014 mmol) (synthesized according to the procedure similar to **Example 2**) and Et_3N (12.16 mg, 16.75 μL, 0.1202 mmol) in DMF (0.2 mL). The crude mixture was purified by Fractionlynx HPLC. The clean aqueous fractions were combined and lyophilised, yielding 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. MS (ES+) 523.1.

[00461] The following compounds were synthesized according to methods similar to the one depicted in the procedure described in **Example 10**:

2-amino-*N*-(4-(4-(cyclopropylsulfonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-159**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((1-methylpiperidin-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-175**);

2-amino-*N*-(4-(4-(cyclopropylsulfonyl)piperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-176**);

2-amino-6-fluoro-*N*-(4-(4-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-177**);

2-amino-6-fluoro-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-178**);

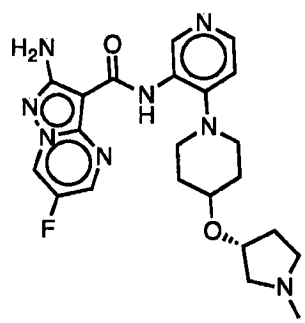
2-amino-6-fluoro-*N*-(4-(4-((tetrahydrofuran-3-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-179**);

2-amino-6-fluoro-N-(4-(4-((1-methylpiperidin-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-N-188**);

2-amino-6-fluoro-*N*-(4-(4-(oxetan-3-ylsulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-195**); and

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(oxetan-3-ylsulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-202**).

Example 11: 2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-131)



[00462] To a solution of (*R*)-2-amino-6-fluoro-*N*-(4-(4-(pyrrolidin-3-yloxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (synthesized according to a procedure similar to **Example 2)** was dissolved in a mixture of DCE (5.0 mL) and AcOH (0.050 mL). Formaldehyde (37% in water, 47.46mg, 0.5848 mmol) was added and the mixture was stirred at RT for 30 mins. Triacetoxyboranuide (Sodium Ion (1)) (186 mg, 0.8772 mmol) was added portionwise. The mixture was stirred at RT for 1 hour and was quenched by the addition of water and methanol. The mixture was concentrated under reduced pressure and the residue was purified by fractionlynx to yield 2-amino-6-fluoro-N-(5-fluoro-4-(4-((tetrahydro-2H-pyran-4-yl)sulfonyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

MS (ES+) 455.2.

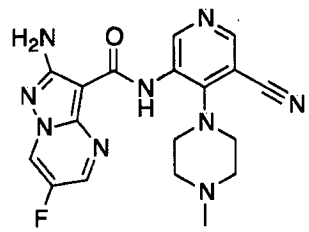
[00463] The following compounds were synthesized according to a procedure similar to **Example 11**:

(*R*)-2-amino-6-fluoro-*N*-(5-fluoro-4-(4-((1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-132**);

2-amino-6-fluoro-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-154**); and

2-amino-6-fluoro-*N*-(4-(4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-N-164**).

Example 12: 2-amino-*N*-(5-cyano-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-N-113)



[00464] A mixture of 2-amino-N-[5-bromo-4-(4-methylpiperazin-1-yl)-3-pyridyl]-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxamide (80.4 mg, 0.1790 mmol) synthesized according to a procedure similar to **Example 1**, $Pd_2(dba)_3$ (6.557 mg, 0.007160 mmol), zinc cyanide (18.92 mg, 10.23 μL, 0.1611 mmol) and xantphos (8.286 mg, 0.01432 mmol) was placed in a sealed microwave tube and evacuated and flushed with nitrogen. Solvent DMF (1.6 mL) was added and nitrogen bubbled through the reaction (with needle as outlet and inlet) for 5 mins. The reaction was heated at 120°C for 1 h. LCMS shows reaction near completion, so cooled to room temperature and loaded onto an SCX-2 cartidge, eluting with MeOH and then NH_3/MeOH. The basic fraction was evaporated and purified by fractionlynx and lyophilize to yield 2-amino-*N*-(5-cyano-4-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a white solid. MS (ES+) 396.2.

Example 13: 2-amino-N-(4-(4-(azetidine-3-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-N-194);

[00465] A solution of 2-amino-N-[4-[4-(azetidine-3-carbonyl)piperazin-1-yl]-5-fluoro-3-pyridyl]-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carboxamide (Trifluoroacetic Acid (2)) (20 mg, 0.02918 mmol), (synthesized according to **Example 9**), and formaldehyde (3.552 μL of 37 %w/v, 0.04377 mmol) in DMF (1 mL) was stirred for 1 h at RT. Triacetoxyboranuide (Sodium Ion (1)) (9.277 mg, 0.04377 mmol) was added and the reaction mixture was stirred at RT for 2 hr before it was quenched by the addition of methanol. The crude mixture was purified by Fractionlynx HPLC. The aqueous fractions were combined and lyophilised, yielding 2-amino-N-(4-(4-(azetidine-3-carbonyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (3mg, 21%). MS (ES+) 472.1.

Example 14: 2-amino-N-(4-(4-(2-(azetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-N-228)

[00466] 1-(azetidin-1-yl)-2-chloro-ethanone (12.03 mg, 0.09003 mmol) was added to a solution of 2-amino-6-fluoro-N-(5-fluoro-4-piperazin-1-yl-3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Trifluoroacetic Acid (3)) (50 mg, 0.06002 mmol) (synthesized according to a procedure similar to **Example 2**) and Et_3N (30.37 mg, 41.83 μL, 0.3001 mmol) in DMF (2 mL). The solution was stirred at RT for 18hr.

[00467] The crude mixture was purified by Fractionlynx HPLC. The aqueous fractions were combined and lyophilised yielding 2-amino-N-(4-(4-(2-(azetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-5-fluoropyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (30mg, 71%). MS (ES+) 472.1.

Compound Analytical Data

Cmpd No.	LCMS ES +	LCMS (Rt min)	HNMR
I-N-1	413.3	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.46 (dd, J = 4.8, 2.5 Hz, 1H), 9.42 (s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.19 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.58 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.1 Hz, 2H), 3.60 (p, J = 6.3 Hz, 1H), 2.98 (t, J = 4.7 Hz, 4H), 2.50 (t, J = 3.5 Hz, 4H).

I-N-2	392.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 9.47 (s, 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.20 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 5.3 Hz), 6.77 (s, 3H), 4.14 (s, 2H), 3.14 (dt, J = 12.9, 3.5 Hz, 2H), 2.77 (dd, J = 9.8, 5.2 Hz, 1H), 2.72 (td, J = 11.8, 11.4, 2.8 Hz, 2H), 1.91 - 1.82 (m, 2H), 1.67 - 1.55 (m, 2H).
I-N-3	371.2	1.82*	^{1}H NMR (500 MHz, Methanol-d4) δ 2.43 (3H, s), 2.75-2.75 (4H, m), 3.1-3.13 (4H, m), 7.22-7.23 (1H, d), 8.21-8.22 (1H, d), 8.72-8.73 (1H, d), 9.02-9.04 (1H, dd), 9.42 91H, s).
I-N-4	399.2	2.16*	----------
I-N-5	411.3	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.54 (s, 1H), 9.27 (s, 1H), 8.96 (s, 1H), 8.17 (s, 1H), 6.80 (br, 2H), 3.23 (m, 4H), 2.93 (s, 3H), 2.52 (br, 4H), 2.13 (m, 1H), 1.09 (m, 2H), 0.92 (m, 2H).
I-N-6	460.2	0.67	^{1}H NMR (500 MHz, Methanol-d4) δ 9.64 (s, 2H), 9.00 (s, 1H), 8.23 (s, 1H), 3.82 (td, J = 11.5, 2.9 Hz, 1H), 3.53 - 3.43 (m, 1H), 3.04 - 2.88 (m, 5H), 2.90 - 2.74 (m, 3H), 2.64 - 2.54 (m, 1H), 2.42 - 2.36 (m, 1H), 2.35 (s, 3H), 2.02 - 1.92 (m, 1H).
I-N-7	339.2	0.51	^{1}H NMR (500 MHz, Methanol-d4) δ 9.62 (d, J = 0.6 Hz, 1H), 9.35 (t, J = 1.4 Hz, 1H), 9.03 (dd, J = 4.4, 2.5 Hz, 1H), 8.62 (d, J = 5.3 Hz, 1H), 8.47 (dd, J = 2.6, 0.5 Hz, 1H), 7.98 (dd, J = 1.9, 1.5 Hz, 1H), 7.86 (dd, J = 1.9, 1.3 Hz, 1H), 7.74 (dd, J = 5.2, 0.6 Hz, 1H).
I-N-8	396.3	0.55	^{1}H NMR (500 MHz, Methanol-d4) δ 10.04 (d, J = 0.8 Hz, 1H), 8.89 (dd, J = 4.4, 2.6 Hz, 1H), 8.63 (d, J = 2.5 Hz, 1H), 8.48 (dd, J = 6.1, 0.8 Hz, 1H), 8.45 (d, J = 0.9 Hz, 1H), 8.06 (d, J = 0.7 Hz, 1H), 8.02 (d, J = 6.3 Hz, 1H), 3.35 (dd, J = 8.3, 7.0 Hz, 2H), 3.05 (dd, J = 8.0, 7.2 Hz, 2H), 2.78 (s, 3H).
I-N-9	410.3	0.67	^{1}H NMR (500 MHz, Methanol-d4) δ 10.06 (d, J = 0.9 Hz, 1H), 8.93 - 8.87 (m, 1H), 8.64 (dd, J = 2.6, 0.7 Hz, 1H), 8.49 (dd, J = 6.2, 0.8 Hz, 1H), 8.46 (d, J = 0.9 Hz, 1H), 8.07 (s, 1H), 8.02 (d, J = 6.2 Hz, 1H), 3.51 - 3.44 (m, 2H), 3.15 - 3.08 (m, 2H), 2.99 (s, 6H).

I-N-10	427.3	0.59	^{1}H NMR (500 MHz, Methanol-d4) δ 9.42 (s, 1H), 9.06 - 8.98 (m, 1H), 8.77 - 8.70 (m, 1H), 8.22 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 5.53 (s, 2H), 4.00 (td, J = 8.6, 4.1 Hz, 1H), 3.94 (dd, J = 8.8, 6.8 Hz, 1H), 3.83 (td, J = 8.5, 7.2 Hz, 1H), 3.73 (dd, J = 8.8, 6.5 Hz, 1H), 3.22 - 3.15 (m, 1H), 3.15 - 3.06 (m, 4H), 2.90 - 2.80 (m, 2H), 2.78 - 2.69 (m, 2H), 2.24 - 2.15 (m, 1H), 1.97 - 1.85 (m, 1H).
I-N-11			^{1}H NMR (500 MHz, Methanol-d4) δ 9.39 (d, J = 0.5 Hz, 1H), 9.05 (dd, J = 4.4, 2.6 Hz, 1H), 8.74 - 8.68 (m, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.23 (dd, J = 5.5, 0.5 Hz, 1H), 4.10 - 4.00 (m, 2H), 3.53 - 3.43 (m, 2H), 3.18 - 3.09 (m, 4H), 2.93 - 2.83 (m, 4H), 2.60 (tt, J = 11.3, 3.8 Hz, 1H), 1.93 (dm, 2H), 1.60 (qd, J = 12.2, 4.5 Hz, 2H).
I-N-12	427.3	0.59	^{1}H NMR (500 MHz, Methanol-d4) δ 9.42 (s, 1H), 9.06 - 8.98 (m, 1H), 8.77 - 8.70 (m, 1H), 8.22 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 5.53 (s, 2H), 4.00 (td, J = 8.6, 4.1 Hz, 1H), 3.94 (dd, J = 8.8, 6.8 Hz, 1H), 3.83 (td, J = 8.5, 7.2 Hz, 1H), 3.73 (dd, J = 8.8, 6.5 Hz, 1H), 3.22 - 3.15 (m, 1H), 3.15 - 3.06 (m, 4H), 2.90 - 2.80 (m, 2H), 2.78 - 2.69 (m, 2H), 2.24 - 2.15 (m, 1H), 1.97 - 1.85 (m, 1H).
I-N-13	431.0	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.49 (q, J = 2.3 Hz, 2H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H),6.79 (s, 2H), 4.60 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.63 (p, J = 6.3 Hz, 1H), 3.13 (m, 4H), 2.50 (m, 4H).
I-N-14	405.1	0.7	^{1}H NMR (500 MHz, DMSO-d6) δ 2.97 (3H, s), 3.21 (2H, m), 3.41 (4H, m), 3.60 (masked signal), 6.86 (2H, br s), 8.32 (1H, d), 8.83 (1H, m), 9.47 (2H, m) and 10.00 (2H, m) ppm.
I-N-15	389.0	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.49 (s, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.8 Hz, 1H), 6.80 (s, 2H), 3.10 (t, J = 4.6 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.33 (s, 3H).
I-N-16	427.2	1.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.1 (s, 1H), 9.47 (s, 1H), 9.36 (s, 1H), 8.80, (s, 1H), 8.05 (s, 1H), 6.78 (br, 2H), 4.59 (m, 2H), 4.45 (m, 2H), 3.57 (m, 1H), 3.12 (br, 4H) 2.52 (br, 4H), 2.40 (s, 3H).
I-N-17	385.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ1.26-1.28 (3H, m), 3.20-3.40 (4H, masked), 3.60-3.80 (6H, m), 6.80 (2H, s), 7.49-7.51 (1H, d), 8.44-8.45 (1H, d), 9.01-9.02 (1H, dd), 9.42 (1H, s), 9.54-9.55 (1H, dd), 9.65 (1H, s), 9.90-10.05 (1H, br s).

I-N-18	397.0	1.74*	----------
I-N-19			^{1}H NMR (500 MHz, Methanol-d4) δ 9.43 (d, J = 1.1 Hz, 1H), 9.14 (dd, J = 4.3, 2.5 Hz, 1H), 8.84 (dd, J = 2.6, 0.6 Hz, 1H), 8.43 (dd, J = 6.6, 1.1 Hz, 1H), 7.61 (d, J = 6.7 Hz, 1H), 4.23 (dd, J = 11.0, 3.4 Hz, 1H), 4.11 (td, J = 8.7, 4.3 Hz, 1H), 4.04 (d, J = 6.2 Hz, 1H), 3.92 (dd, J = 10.8, 6.1 Hz, 1H), 3.87 - 3.70 (m, 5H), 3.57 - 3.43 (m, 4H), 2.52 - 2.39 (m, 1H), 2.24 (ddd, J = 10.5, 6.2, 2.9 Hz, 1H).
I-N-20	439.2	2.52*	----------
I-N-21	397.2	2.04*	----------
I-N-22	415.4	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 2.61 (2H, t), 2.68 (4H, m), 2.95 (4H, m), 3.26 (3H, s), 3.48 (2H, t), 6.77 (2H, br s), 7.17 (1H, m), 8.22 (1H, d), 8.81 (1H, m), 9.42 (1H, s), 9.48 (1H, dd) and 9.79 (1H, s) ppm.
I-N-23	427.3	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.65 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.61 (dt, J = 17.9, 6.5 Hz, 2H), 4.52 (t, J = 6.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 3.61 (p, J = 6.3 Hz, 1H), 2.95 (d, J = 11.1 Hz, 1H), 2.86 - 2.73 (m, 2H), 2.71 - 2.59 (m, 1H), 2.41 - 2.27 (m, 1H), 2.12 - 2.02 (m, 1H), 0.83 (d, J = 6.2 Hz, 3H). 1H multiplet hidden under water peak.
I-N-24	427.3	0.64	^{1}H NMR (500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.65 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.61 (dt, J = 17.9, 6.5 Hz, 2H), 4.52 (t, J = 6.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 3.61 (p, J = 6.3 Hz, 1H), 2.95 (d, J = 11.2 Hz, 1H), 2.88 - 2.73 (m, 2H), 2.71 - 2.58 (m, 1H), 2.41 - 2.26 (m, 1H), 2.06 (t, J = 9.8 Hz, 1H), 0.82 (d, J = 6.1 Hz, 3H). 1H multiplet hidden under water peak.
I-N-25	443.0	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.21 (d, J = 1.1 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.82 (s, 2H), 4.69 (d, J = 6.8 Hz, 2H), 4.31 (d, J = 6.9 Hz, 2H), 3.59 (s, 4H), 3.01 (s, 4H), 1.54 (s, 3H).
I-N-26	339.1	0.61	^{1}H NMR (500 MHz, Acetone-d6) δ 11.17 (s, 2H), 9.80 (t, J = 0.5 Hz, 1H), 8.99 (dd, J = 4.6, 2.6 Hz, 1H), 8.70 (d, J = 2.6 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.30 (dd, J = 2.5, 0.6 Hz, 1H), 8.05 (dd, J = 1.9, 0.6 Hz, 1H), 7.57 (dd, J = 5.3, 0.5 Hz, 1H), 6.65 (dd, J = 2.5, 1.8 Hz, 1H), 6.37 (s, 1H).

I-N-27	407.1	0.69	^{1}H NMR (500 MHz, Methanol-d4) δ 9.79 (s, 1H), 9.02 (dd, J = 4.4, 2.5 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 1.2, 0.7 Hz, 1H), 8.10 (t, J = 1.3 Hz, 1H), 7.61 (d, J = 5.2 Hz, 1H).
I-N-28	353.2	0.55	^{1}H NMR (500 MHz, Methanol-d4) δ 9.66 (d, J = 0.6 Hz, 1H), 9.08 (dd, J = 4.4, 2.5 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.49 (dd, J = 2.5, 0.5 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 5.2, 0.6 Hz, 1H), 2.62 (s, 3H).
I-N-29	355.1	0.56	^{1}H NMR (500 MHz, Methanol-d4) δ 9.63 (d, J = 0.6 Hz, 1H), 9.14 (s, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.77 (t, J = 1.6 Hz, 1H), 7.71 (dd, J = 5.3, 0.6 Hz, 1H).
I-N-30	421.2	0.72	^{1}H NMR (500 MHz, Methanol-d4) δ 10.01 - 9.94 (m, 1H), 9.65 (s, 1H), 9.03 (dd, J = 4.4, 2.5 Hz, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.27 (ddd, J = 2.6, 1.2, 0.5 Hz, 1H), 7.89 (q, J = 1.4 Hz, 1H), 7.59 (dt, J = 5.1, 0.6 Hz, 1H), 2.32 (s, 3H).
I-N-31	425.3	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 9.18 (s, 1H), 8.80 (dd, J = 2.5, 0.5 Hz, 1H), 8.50 (s, 1H), 8.13 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 5.7 Hz, 1H), 6.65 (s, 2H), 4.60 - 4.50 (m, 4H), 3.70 (p, J = 6.4 Hz, 1H), 3.42 - 3.27 (m, 1H), 3.17 (ddd, J = 12.6, 10.4, 2.7 Hz, 1H), 2.76 (ddd, J = 8.1, 6.6, 4.2 Hz, 1H), 2.66 (ddd, J = 11.0, 4.1, 2.5 Hz, 1H), 2.59 - 2.51 (m, 1H), 2.31 - 2.16 (m, 1H), 0.61 (td, J = 5.6, 4.2 Hz, 1H), 0.37 (td, J = 6.8, 5.8 Hz, 1H).
I-N-32	453.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.31 (s, 1H), 8.81 (d, J = 2.5 Hz, 1H), 7.97 (d, J = 0.6 Hz, 1H), 6.77 (s, 2H), 4.59 (t, J = 6.5 Hz, 2H), 4.45 (t, J = 6.1 Hz, 2H), 3.66 - 3.51 (m, 1H), 3.31 - 3.18 (m, 4H), 2.51 (p, J = 1.9 Hz, 4H), 2.13 (tt, J = 8.4, 5.4 Hz, 1H), 1.11 - 1.01 (m, 2H), 0.90 - 0.78 (m, 2H).
I-N-33	397.2	2.25*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.55 (d, *J* = 4.0 Hz, 1H), 9.38 (s, 1H), 9.02 (s, 1H), 8.45 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 4.0 Hz, 1H), 6.80 (br, 2H), 2.90 (br, 8H), 0.87 (m, 2H), 0.80 (m, 2H).
I-N-34	429.3	0.8	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.37 (s, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.16 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 2.93 (t, J = 4.6 Hz, 4H), 2.72 (t, J = 4.7 Hz, 4H), 1.07 (s, 9H).

I-N-35	431.2	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.29 (s, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.15 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 4.52 - 4.42 (m, 1H), 3.77 (t, J = 4.7 Hz, 1H), 3.31 - 3.22 (m, 1H), 3.18 (d, J = 11.0 Hz, 1H), 2.76 - 2.60 (m, 1H), 2.59 - 2.53 (m, 1H), 2.48 - 2.40 (m, 1H), 2.32 (s, 6H), 1.81 - 1.57 (m, 2H).
I-N-36	445.2	0.7	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.53 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.22 (dd, J = 5.3, 0.6 Hz, 1H), 6.81 (s, 2H), 4.24 (s, 1H), 3.02 (td, J = 11.5, 10.3, 3.9 Hz, 2H), 2.87 (dd, J = 11.3, 4.2 Hz, 2H), 2.33 (s, 6H), 2.31 (s, 2H), 2.07 (td, J = 12.5, 4.2 Hz, 2H), 1.50 (d, J = 12.8 Hz, 2H).
I-N-37	415.2	0.7	----------
I-N-38	502.2	1.97*	^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.73 (s, 1H), 8.74 (s, 1H), 8.51 (dd, J = 3.8, 2.5 Hz, 1H), 8.25 (s, 1H), 5.92 (s, 2H), 4.66 (dt, J = 19.3, 6.5 Hz, 2H), 4.57 (s, 1H), 3.87 (s, 1H), 3.62 - 3.39 (m, 2H), 2.92 (s, 2H), 2.79 (s, 2H), 2.65 - 2.44 (m, 2H), 2.28 (s, 1H), 1.89 (s, 1H), 1.67 (s, 2H).
I-N-39	415.2	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.37 (s, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.95 (t, J = 4.7 Hz, 4H), 2.76 (s, 2H), 2.72 - 2.63 (m, 3H), 1.04 (d, J = 6.5 Hz, 6H).
I-N-40	415.2	0.72	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.34 (s, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.34 - 3.19 (m, 1H), 3.09 (d, J = 11.5 Hz, 1H), 2.69 - 2.47 (m, 3H), 2.09 (d, J = 5.2 Hz, 6H), 1.99 (d, J = 12.3 Hz, 1H), 1.90 - 1.70 (m, 2H), 1.28 (dd, J = 11.2, 6.4 Hz, 1H).
I-N-41	421.1	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 2.32 (3H, s), 2.60 (4H, m), 3.25 (4H, m), 6.85 (2H, br s), 8.26 (1H, s), 8.59 (1H, m), 9.44 (1H, m), 9.53 (1H, s) and 10.28 (1H, br s) ppm.
I-N-42	414.1	0.65	^{1}H NMR (500 MHz, Methanol-d4) δ 9.05 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 1.3 Hz, 1H), 8.09 (dd, J = 7.3, 1.4 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 4.92 (d, J = 2.4 Hz, 2H), 4.05 - 4.01 (m, 1H), 2.45 - 2.37 (m, 2H), 2.22 - 2.14 (m, 2H), 2.10 - 2.03 (m, 2H), 1.89 - 1.82 (m, 2H).

I-N-43	401.1	0.63	^{1}H NMR (500 MHz, Methanol-d4) δ 8.89 (d, J = 2.2 Hz, 1H), 8.62 (s, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 5.8 Hz, 1H), 6.96 (d, J = 5.8 Hz, 1H), 3.45 - 3.39 (m, 2H), 3.39 - 3.31 (m, 2H), 2.72 - 2.67 (m, 2H), 2.66 - 2.60 (m, 2H), 2.26 (s, 3H), 1.93 - 1.85 (m, 2H).
I-N-44	410.1	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.54 (s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.33 - 7.21 (m, 2H), 6.93 (d, J = 1.3 Hz, 1H), 6.78 (s, 2H), 4.24 - 4.10 (m, 4H), 3.62 - 3.50 (m, 2H).
I-N-45	429.2	2.29*	----------
I-N-46	459.2	0.8	^{1}H NMR (500 MHz, DMSO-d6) δ 10.02 (s, 1H), 9.50 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 3.16 (s, 3H), 2.94 - 2.83 (m, 4H), 2.40 (s, 2H), 2.31 (s, 6H), 2.06 - 1.95 (m, 2H), 1.84 - 1.73 (m, 2H).
I-N-47	431.2	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.38 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.4, 0.5 Hz, 1H), 6.82 (s, 2H), 3.50 (dd, J = 9.9, 4.1 Hz, 1H), 3.28 - 3.23 (m, 1H), 3.18 (dd, J = 11.0, 2.3 Hz, 1H), 3.12 (s, 3H), 3.07 - 3.00 (m, 1H), 2.89 - 2.77 (m, 2H), 2.61 - 2.53 (m, 1H), 2.50 - 2.45 (m, 2H), 2.31 (s, 3H).
I-N-48	427.2	0.79	^{1}H NMR (500 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.94 (t, J = 4.8 Hz, 4H), 2.91 - 2.82 (m, 1H), 2.50 - 2.46 (m, 4H), 1.99 (ddtd, J = 11.2, 8.7, 4.5, 2.6 Hz, 2H), 1.88 - 1.74 (m, 2H), 1.66 (tdd, J = 10.9, 6.0, 2.1 Hz, 2H).
I-N-49	444.2	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.74 (s, 1H), 9.46 - 9.36 (m, 2H), 8.63 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.94 (t, J = 4.7 Hz, 4H), 2.69 - 2.62 (m, 4H), 2.53 (d, J = 6.9 Hz, 2H), 2.38 (dd, J = 7.8, 5.8 Hz, 2H), 2.17 (s, 6H).
I-N-50	402.1	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 9.39 (d, J = 2.2 Hz, 1H), 9.28 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 6.75 (s, 2H), 6.20 (s, 1H), 5.66 (s, 2H), 2.92 - 2.84 (m, 4H), 2.50 (s, 4H), 2.24 (s, 3H).
I-N-51	401.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.62 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.97 (t, J = 4.8 Hz, 4H), 2.64 (d, J = 9.5 Hz, 4H), 2.50 - 2.43 (m, 2H), 1.05 (t, J = 7.1 Hz, 3H).

I-N-52	421.0	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.53 (s, 1H), 9.47 (d, J = 2.2 Hz, 1H), 9.25 (s, 1H), 8.92 (d, J = 2.2 Hz, 1H), 7.34 (s, 1H), 6.84 (s, 2H), 3.65 - 3.48 (m, 4H), 3.32 - 3.21 (m, 2H), 3.15 - 3.04 (m, 2H), 2.97 (s, 3H).
I-N-53	415.2	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.52 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.31 (s, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.12 (dd, J = 5.4, 0.5 Hz, 1H), 6.84 (s, 2H), 2.88 - 2.81 (m, 2H), 2.77 (s, 2H), 2.61 (t, J = 5.0 Hz, 2H), 2.19 (s, 3H), 1.14 (s, 6H).
I-N-54	401.2	0.39	^{1}H NMR (500 MHz, DMSO-d6) δ 9.74 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.11 - 2.99 (m, 2H), 2.90 - 2.75 (m, 2H), 2.60 - 2.52 (m, 1H), 2.49 - 2.42 (m, 1H), 2.43 - 2.34 (m, 1H), 2.27 (s, 3H), 0.99 (d, J = 6.2 Hz, 3H).
I-N-55	387.1	1.92*	^{1}H NMR (500 MHz, Methanol-d4) δ 9.27 (d, J = 0.9 Hz, 1H), 9.00 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.25 (dd, J = 6.3, 0.9 Hz, 1H), 7.39 (d, J = 6.3 Hz, 1H), 3.74 (d, J = 11.8 Hz, 1H), 3.59 - 3.50 (m, 1H), 3.46 (d, J = 12.5 Hz, 1H), 3.38 - 3.22 (m, 2H), 3.13 - 3.02 (m, 1H), 2.95 (dd, J = 11.9, 9.7 Hz, 1H), 2.20 - 2.06 (m, 2H), 1.95 - 1.80 (m, 3H), 1.57 (dtd, J = 12.9, 10.5, 5.0 Hz, 2H).
I-N-56	413.1	0.65	^{1}H NMR (500 MHz, Methanol-d4) δ 9.10 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 1.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 6.9, 1.2 Hz, 1H), 7.50 (d, J = 6.9 Hz, 1H), 4.59 (ddd, J = 5.8, 3.8, 1.9 Hz, 1H), 4.14 - 4.04 (m, 2H), 3.74 - 3.67 (m, 2H), 3.67 - 3.57 (m, 2H), 3.50 (ddd, J = 14.3, 11.3, 6.4 Hz, 2H), 2.51 - 2.41 (m, 2H), 2.35 - 2.24 (m, 2H).
I-N-57	401.2	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 2.30 (3H, s), 2.38 (3H, s), 2.57 (4H, m), 3.09 (4H, m), 6.83 (2H, br s), 8.05 (1H, s), 8.60 (1H, m), 9.34 (1H, s), 9.43 (1H, s) and 10.12 (1H, br s) ppm
I-N-58	429.1	0.62	^{1}H NMR (500 MHz, Methanol-d4) δ 9.40 (d, J = 0.5 Hz, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.25 (dd, J = 5.5, 0.5 Hz, 1H), 4.76 (t, J = 6.7 Hz, 2H), 4.65 (dd, J = 6.5, 5.9 Hz, 2H), 3.72 - 3.63 (m, 1H), 3.15 (t, J = 4.9 Hz, 5H), 2.65 (t, J = 4.8 Hz, 5H).
I-N-59	387.0	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H),7.18 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 2.96 (t, J = 4.8 Hz, 4H), 2.56 (t, J = 4.5 Hz, 4H), 2.28 (s, 3H).

I-N-60	431.2	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.44 - 9.39 (m, 2H), 8.63 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 3.49 (t, J = 5.6 Hz, 2H), 3.26 (s, 3H), 2.95 (t, J = 4.7 Hz, 4H), 2.68 (d, J = 4.2 Hz, 4H), 2.61 (t, J = 5.6 Hz, 2H).
I-N-61	442.3	0.59	^{1}H NMR (500 MHz, Methanol-d4) δ 9.39 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.40 (dd, J = 6.7, 1.2 Hz, 1H), 7.60 (d, J = 6.7 Hz, 1H), 3.92 (d, J = 12.7 Hz, 2H), 3.79 (d, J = 12.1 Hz, 2H), 3.60 (d, J = 12.3 Hz, 2H), 3.10 - 2.97 (m, 2H), 2.95 (s, 3H), 2.86 - 2.58 (m, 5H).
I-N-62	427.0	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.21 (d, J = 0.9 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.54 (d, J = 6.5 Hz, 1H), 6.78 (s, 2H), 4.68 (d, J = 7.0 Hz, 2H), 4.30 (d, J = 6.8 Hz, 2H), 3.58 (s, 4H), 2.98 (s, 4H), 1.54 (s, 3H).
I-N-63	417.1	0.47	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 4.43 (t, J = 5.5 Hz, 1H), 3.63 (ddd, J = 11.0, 5.6, 3.9 Hz, 1H), 3.28 - 3.20 (m, 1H), 3.08 - 2.97 (m, 1H), 2.93 - 2.75 (m, 2H), 2.54 (ddd, J = 11.1, 3.6, 1.8 Hz, 2H), 2.37 (h, J = 1.7 Hz, 1H), 2.31 (s, 3H).
I-N-64	413.2	0.77	^{1}H NMR (500 MHz, DMSO-d6) δ 9 .77 (s, 1H), 9.41 (d, J = 2.2 Hz, 1H), 9.39 (s, 1H), 8.67 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 5.4 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 6.80 (s, 2H), 2.90 (t, J = 4.9 Hz, 4H), 2.77 (d, J = 5.3 Hz, 4H), 1.80 (pd, J = 6.6, 4.2, 3.4 Hz, 1H), 0.45 (dq, J = 6.6, 4.3, 3.8 Hz, 2H), 0.36 - 0.29 (m, 2H).
I-N-65	413.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.46 - 9.39 (m, 2H), 8.58 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.4 Hz, 1H), 6.82 (s, 2H), 3.26 - 3.20 (m, 1H), 3.14 (d, J = 11.5 Hz, 1H), 3.05 - 2.96 (m, 2H), 2.78 (td, J = 11.4, 3.1 Hz, 1H), 2.63 (t, J = 10.3 Hz, 1H), 2.48 - 2.43 (m, 1H), 2.33 (d, J = 7.7 Hz, 1H), 2.20 (q, J = 7.9 Hz, 1H), 1.79 - 1.66 (m, 3H), 1.35 (tt, J = 14.8, 7.2 Hz, 1H).
I-N-66	402.1	0.67	^{1}H NMR (500 MHz, Methanol-d4) δ 9.42 (d, J = 0.5 Hz, 1H), 9.04 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 7.27 (dd, J = 5.5, 0.5 Hz, 1H), 3.24 - 3.14 (m, 2H), 3.06 (dd, J = 11.1, 5.6 Hz, 2H), 1.94 (ddd, J = 13.6, 9.8, 4.0 Hz, 2H), 1.85 (d, J = 13.2 Hz, 2H), 1.37 (s, 3H).
I-N-67	455.1	0.84	^{1}H NMR (500 MHz, DMSO-d6) δ 2.89 (4H, m), 2.97 (4H, m), 3.37 masked signal, 6.82 (2H, br s), 7.20 (1H, m), 8.22 (1H, m), 8.70 (1H, m), 9.43 (2H, m) and 9.75 (1H, s) ppm.

I-N-68	406.2	0.53	^{1}H NMR (500 MHz, Methanol-d4) δ 9.45 (d, J = 1.1 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.41 (dd, J = 6.6, 1.1 Hz, 1H), 7.68 (d, J = 6.6 Hz, 1H), 4.02 (ddd, J = 13.6, 11.1, 2.0 Hz, 2H), 3.83 - 3.75 (m, 2H), 3.33 - 3.28 (m, 2H), 3.16 - 3.08 (m, 2H).
I-N-69	430.2	0.75	^{1}H NMR (500 MHz, Methanol-d4) δ 9.23 (d, J = 1.3 Hz, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.30 (dd, J = 6.8, 1.3 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 4.00 (dt, J = 13.0, 2.8 Hz, 2H), 3.15 - 3.03 (m, 2H), 2.00 - 1.90 (m, 2H), 1.74 (qd, J = 12.6, 3.8 Hz, 2H), 1.66 - 1.60 (m, 1H), 1.25 (s, 6H).
I-N-70	441.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.50 - 9.40 (m, 2H), 8.77 (d, J = 2.2 Hz, 1H), 8.25 (d, J = 5.3 Hz, 1H), 7.25 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 3.84 - 3.65 (m, 1H), 3.22 (d, J = 11.0 Hz, 1H), 3.12 - 2.90 (m, 3H), 2.81 (dd, J = 10.9, 10.1 Hz, 1H), 2.76 - 2.59 (m, 1H).
I-N-71	413.1	0.72	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.44 - 9.38 (m, 2H), 8.58 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.20 (dd, J = 5.4, 0.5 Hz, 1H), 6.82 (s, 2H), 3.31 - 3.20 (m, 2H), 3.14 (dd, J = 10.8, 2.9 Hz, 1H), 3.07 - 2.96 (m, 2H), 2.78 (td, J = 11.4, 2.9 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.34 (s, 1H), 2.19 (q, J = 8.4 Hz, 1H), 1.73 (tdd, J = 13.4, 7.9, 4.2 Hz, 3H), 1.35 (td, J = 10.5, 5.8 Hz, 1H).
I-N-72	401.2	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.62 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 5.2 Hz, 1H), 6.82 (s, 2H), 3.00 - 2.89 (m, 1H), 2.90 - 2.81 (m, 1H), 2.81 - 2.73 (m, 1H), 2.72 - 2.62 (m, 1H), 2.47 - 2.39 (m, 1H), 2.30 (s, 3H), 2.24 - 2.11 (m, 1H), 0.82 (d, J = 6.2 Hz, 3H). (One proton hidden under DMSO peak).
I-N-73	402.1	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.50 - 9.35 (m, 2H), 8.58 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.44 (dt, J = 7.9, 4.0 Hz, 1H), 3.30 (s, 3H), 3.12 - 3.03 (m, 2H), 2.79 (ddd, J = 11.8, 8.8, 3.1 Hz, 2H), 2.07 - 1.98 (m, 2H), 1.75 (dtd, J = 12.2, 8.5, 3.4 Hz, 2H).
I-N-74	430.2	0.8	^{1}H NMR (500 MHz, Methanol-d4) δ 9.44 (d, J = 1.2 Hz, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.34 (dd, J = 6.7, 1.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 3.84 - 3.79 (m, 2H), 3.78 (s, 3H), 3.23 - 3.14 (m, 2H), 2.80 - 2.72 (m, 1H), 2.22 - 2.06 (m, 4H).

I-N-75	410.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.54 (s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 8.28 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 1.0 Hz, 1H), 7.57 (d, J = 2.2 Hz, 1H), 7.29 (dd, J = 5.3, 0.5 Hz, 1H), 6.78 (s, 2H), 6.66 (d, J = 1.0 Hz, 1H), 4.34 - 4.11 (m, 4H), 3.59 - 3.44 (m, 2H).
I-N-76	420.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85 (6H,s), 2.95 (3H,s), 3.2-3.4 (4H,m), 3.6-3.8 (4H,m), 6.8 (1H,brs), 7.47 (1H,d), 8.47 (1H,d), 9.05 (1H,s), 9.15 (1H,s), 9.45 (1H,s), 9.75 (1H,s), 10.0 (1H,brs).
I-N-77	363.1	1.89*	----------
I-N-78	406.2	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7 (3H,d), 2.95 (3H,s), 3.2-3.4 (4H,m), 3.6-3.8 (4H,m), 4.5 (1H,q), 6.8 (1H,brs), 7.49 (1H,d), 8.47 (1H,d), 8.95 (1H,s), 9.18 (1H,s), 9.40 (1H,s), 9.75 (1H,s), 10.1 (1H,brs).
I-N-79	391.2	2.32*	----------
I-N-80	410.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 2.99 (3H, br s), 3.18 (2H, m), 3.37-3.44 (4H, m), 3.67 (2H, m), 4.15 (2H, s), 6.80 (2H, br s), 8.32 (1H, d), 8.76 (1H, d), 9.12 (1H, d), 9.51 (1H, s), 9.86 (1H, br s) and 10.19 (1H, s) ppm.
I-N-81	379.2	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.36 (s, 1H), 9.10 (d, J = 2.0 Hz, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.44 (d, J = 6.4 Hz, 1H), 7.49 (d, J = 6.4 Hz, 1H), 6.78 (s, 2H), 4.15 (s, 2H), 3.87 - 3.83 (m, 4H), 3.33 - 3.29 (m, 4H).
I-N-82	92.2	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.42 (s, 1H), 9.12 (d, J = 1.9 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 6.2 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 6.80 (s, 2H), 4.15 (s, 2H), 3.90 - 3.68 (m, 4H), 3.68 - 3.55 (m, 3H), 2.96 (s, 3H).
I-N-83	393.2	0.53	^{1}H NMR (500 MHz, DMSO-d6) δ 9.92 (s, 1H), 9.46 (s, 1H), 9.06 (dt, J = 2.0, 0.8 Hz, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.21 - 7.16 (m, 1H), 6.77 (s, 2H), 4.73 (d, J = 4.3 Hz, 1H), 4.14 (d, J = 0.7 Hz, 2H), 3.71 (s, 1H), 3.12 (d, J = 11.5 Hz, 2H), 2.77 (t, J = 9.6 Hz, 2H), 1.92 (s, 2H), 1.73 (t, J = 9.2 Hz, 2H).
I-N-84	377.2	2.38*	----------
I-N-85	405.2	0.69	^{1}H NMR (500 MHz, Methanol-d4) δ 9.56 (s, 1H), 9.07 (dd, J = 4.3, 2.6 Hz, 1H), 8.82 - 8.77 (m, 1H), 8.25 (s, 1H), 3.38 - 3.36 (m, 4H), 2.84 (d, J = 4.4 Hz, 4H), 2.50 (s, 3H).

I-N-86	387.1	0.56	^{1}H NMR (500 MHz, Methanol-d4) δ 9.30 (s, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 2.81 (td, J = 10.9, 5.5 Hz, 1H), 2.71 (td, J = 12.0, 2.4 Hz, 2H), 1.87 (d, J = 12.4 Hz, 2H), 1.66 (qd, J = 12.1, 3.8 Hz, 2H), 3.26 - 3.23 (m, 2H).
I-N-87	401.1	1.85*	----------
I-N-88	373.0	1.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 2.93 (dd, J = 6.2, 3.3 Hz, 4H), 2.85 (dd, J = 6.1, 3.2 Hz, 4H).
I-N-89	378.1	0.97	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.44 (s, 1H), 9.06 (d, J = 1.9 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.15 (s, 2H), 2.95 (d, J = 4.7 Hz, 4H), 2.88 - 2.85 (m, 4H).
I-N-90	408.2	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (d, J = 14.9 Hz, 1H), 9.51 (d, J = 4.6 Hz, 1H), 9.04 (dd, J = 22.0, 2.2 Hz, 1H), 8.67 (dd, J = 24.9, 2.2 Hz, 1H), 8.24 (d, J = 5.3 Hz, 1H), 7.19 (dd, J = 13.7, 5.3 Hz, 1H), 6.76 (d, J = 10.4 Hz, 2H), 4.14 (d, J = 7.0 Hz, 2H), 3.99 - 3.79 (m, 2H), 3.77 - 3.68 (m, 1H), 3.20 (d, J = 11.4 Hz, 1H), 3.16 - 3.00 (m, 1H), 2.90 - 2.73 (m, 1H), 2.71 - 2.53 (m, 3H).
I-N-91	401.1	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 1.47 (2H, m), 1.82 (3H, m), 2.85 (2H, m), 2.96 (2H, m), 3.66 (2H, m), 6.83 (2H, br s), 7.46 (1H, d), 7.90 (3H, br s), 8.40 (1H, m), 8.76 (1H, s), 9.27 (1H, s), 9.47 (1H, m) and 9.57 (1H, s) ppm.
I-N-92			^{1}H NMR (500 MHz, DMSO-d6) δ 12.39 (s, 1H), 9.81 (s, 1H), 9.45 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 5.5 Hz, 1H), 3.45 - 3.40 (m, 2H), 7.40 (d, J = 6.1 Hz, 1H), 6.83 (s, 2H), 3.04 - 2.86 (m, 2H), 2.60 - 2.55 (m, 1H), 2.05 - 1.85 (m, 4H).
I-N-93	427.2	2.2*	----------
I-N-94	470.2	2.15*	----------
I-N-95	471.2	2.27*	----------
I-N-96	469.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.52 - 9.31 (m, 2H), 8.62 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 4.63 (s, 4H), 3.27 (s, 4H), 3.13 - 3.02 (m, 2H), 2.76 - 2.66 (m, 2H), 2.14 (dq, J = 8.3, 4.4, 3.8 Hz, 1H), 1.84 - 1.70 (m, 2H), 1.57 - 1.41 (m, 2H).

I-N-97	470.3	0.64	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.14 (s, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.39 (dd, J = 6.5, 1.1 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 3.77 (d, J = 12.8 Hz, 2H), 3.25 - 3.11 (m, 3H), 3.11 - 3.00 (m, 3H), 3.00 - 2.89 (m, 2H), 2.77 (s, 3H), 2.58 - 2.53 (m, 2H), 2.49 - 2.45 (m, 1H), 1.99 - 1.85 (m, 2H), 1.77 - 1.59 (m, 2H).
I-N-98	459.2	2.43*	----------
I-N-99	483.3	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.53 - 9.46 (m, 2H), 9.34 - 9.23 (m, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.5, 1.0 Hz, 1H), 7.50 (d, J = 6.5 Hz, 1H), 6.84 (s, 2H), 4.70 - 4.42 (m, 3H), 4.04 - 3.90 (m, 2H), 3.89 - 3.74 (m, 3H), 3.24 - 3.09 (m, 1H), 3.10 - 2.90 (m, 2H), 2.46 - 2.39 (m, 1H), 2.33 - 2.12 (m, 3H), 2.00 - 1.73 (m, 2H). 2 proton signals hidden by water.
I-N-100	489.2	0.61	^{1}H NMR (500 MHz, Methanol-d4) δ 9.35 (s, 1H), 9.06 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 7.27 - 7.20 (m, 1H), 3.12 - 3.00 (m, 2H), 3.00 - 2.90 (m, 2H), 2.90 - 2.79 (m, 2H), 2.74 - 2.63 (m, 2H), 2.11 - 2.04 (m, 1H), 2.04 - 1.86 (m, 4H), 1.36 (d, J = 19.8 Hz, 4H).
I-N-101	493.2	1.4*	^{1}H NMR (500 MHz, Methanol-d4) δ 9.18 (d, J = 1.3 Hz, 1H), 9.08 (d, J = 2.2 Hz, 1H), 8.86 (d, J = 1.3 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 6.8, 1.4 Hz, 1H), 7.54 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 4.44 - 4.35 (m, 2H), 4.10 - 3.98 (m, 4H), 3.29 - 3.17 (m, 4H), 3.03 - 2.92 (m, 1H), 2.19 - 2.10 (m, 2H), 1.99 - 1.88 (m, 2H), 1.39 - 1.26 (m, 1H), 0.92 (d, J = 7.0 Hz, 1H).
I-N-102	493.2	1.4*	^{1}H NMR (500 MHz, Methanol-d4) δ 9.16 (d, J = 1.3 Hz, 1H), 9.12 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 6.9, 1.3 Hz, 1H), 7.56 (q, J = 2.1 Hz, 2H), 7.54 (d, J = 6.9 Hz, 1H), 4.28 (t, J = 5.3 Hz, 2H), 4.06 (dm, J = 13.0 Hz, 2H), 3.33 - 3.19 (m, 4H), 2.99 - 2.93 (m, 1H), 2.14 (d, J = 12.4 Hz, 2H), 1.98 - 1.87 (m, 2H), 1.39 - 1.29 (m, 3H), 0.95 - 0.89 (m, 1H).
I-N-103	459.2	2.42*	----------
I-N-104	457.3	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.55 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.23 (d, J = 0.9 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H), 6.83 (s, 2H), 4.20 - 3.93 (m, 2H), 3.91 - 3.79 (m, 2H), 3.30 - 3.09 (m, 1H), 3.03 (t, J = 12.1 Hz, 2H), 2.27 - 2.13 (m, 2H), 1.86 (qd, J = 12.5, 3.7 Hz, 2H). Remaining signals for 6 protons under water peak.

I-N-105	441.0	2.26*	----------
I-N-106	484.3	2.29*	----------
I-N-107	457.2	2.24*	----------
I-N-108	463.2	2.55*	----------
I-N-109	469.3	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 - 9.45 (m, 2H), 9.31 (d, J = 1.1 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H), 6.94 - 6.73 (m, 2H), 5.51 - 4.98 (m, 1H), 4.85 (d, J = 9.2 Hz, 2H), 4.83 - 4.51 (m, 1H), 3.93 - 3.66 (m, 6H), 3.09 (t, J = 12.3 Hz, 2H), 2.76 - 2.54 (m, 1H), 2.32 - 1.57 (m, 4H). (Aliphatic signals broad and undefined).
I-N-110	447.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.56 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (s, 1H), 6.80 (s, 2H), 4.61 (t, J = 6.4 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.70 - 3.51 (m, 1H), 3.44 - 3.20 (m, 4H), 2.60 - 2.45 (m, 4H).
I-N-111	421.2	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (1H, br), 9.68 (1H, s), 9.54 (1H, d, *J* = 5.0 Hz), 8.95 (1 H, d, *J* = 5.0 Hz), 8.55 (1 H, s), 7.37 (1H, t, *J* = 55 Hz), 6.79 (2H, br), 2.88 (3H, s) 3.47-3.22 (8 H, br).
I-N-112	425.3	1.67*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 9.18 (s, 1H), 8.80 (dd, J = 2.5, 0.5 Hz, 1H), 8.50 (s, 1H), 8.13 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 5.7 Hz, 1H), 6.65 (s, 2H), 4.60 - 4.50 (m, 4H), 3.70 (p, J = 6.4 Hz, 1H), 3.42 - 3.27 (m, 1H), 3.17 (ddd, J = 12.6, 10.4, 2.7 Hz, 1H), 2.76 (ddd, J = 8.1, 6.6, 4.2 Hz, 1H), 2.66 (ddd, J = 11.0, 4.1, 2.5 Hz, 1H), 2.59 - 2.51 (m, 1H), 2.31 - 2.16 (m, 1H), 0.61 (td, J = 5.6, 4.2 Hz, 1H), 0.37 (td, J = 6.8, 5.8 Hz, 1H).
I-N-113	396.2	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (1H, br), 9.71 (1 H, d, *J* = 2.2 Hz), 9.54 (1H, dd, *J* = 5.0, 2.2 Hz), 9.46 (1 H, s), 8.98 (1H, s), 8.66 (1 H, s), 6.77 (2 H, br), 3.63-3.41 (6 H, br), 3.17 (2 H, br), 2.92 (3 H, s).
I-N-114	444.3	1.96*	^{1}H NMR (500 MHz, methanol-d4) δ 10.41 (s, 1H), 9.57 (d, J = 1.6 Hz, 1H), 9.08 (dd, J = 4.4, 2.4 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 3.0 Hz, 1H), 3.53 - 3.44 (m, 1H), 3.43 - 3.39 (m, 1H), 3.26 - 3.18 (m, 1H), 3.18 - 3.06 (m, 3H), 3.02 (dt, J = 11.3, 2.5 Hz, 1H), 2.99 - 2.92 (m, 1H), 2.92 - 2.85 (m, 1H), 2.85 - 2.78 (m, 1H), 2.74 (s, 3H), 2.71 - 2.66 (m, 1H), 2.63 (d, J = 17.2 Hz, 1H).

I-N-115	413.2	1.82*	^{1}H NMR (500 MHz, methanol-d4) δ 9.49 (s, 1H), 9.06 (d, J = 4.5 Hz, 1H), 8.77 (s, 1H), 8.24 (d, J = 5.6 Hz, 1H), 7.24 (d, J = 5.7 Hz, 1H), 3.93 (d, J = 11.2 Hz, 1H), 3.83 - 3.62 (m, 2H), 3.46 - 3.25 (m, 2H), 3.24 - 3.00 (m, 2H), 2.94 (d, J = 11.2 Hz, 1H), 2.83 (d, J = 11.6 Hz, 1H), 2.80 - 2.66 (m, 2H), 2.65 - 2.48 (m, 2H).
I-N-116	413.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (s, 1H), 8.83 - 8.78 (m, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.77 (s, 2H), 3.79 (dm, J = 10.9 Hz, 1H), 3.59 (dd, J = 10.8, 2.8 Hz, 1H), 3.53 (td, 1H), 3.16 - 3.08 (m, 2H), 2.97 (dm, 1H), 2.86 (td, 1H), 2.78 (dm, J = 11.1 Hz, 1H), 2.68 (dm, J = 11.5 Hz, 1H), 2.63 (p, J = 1.8 Hz, 1H), 2.59 - 2.53 (m, 1H), 2.40 (dd, J = 11.5, 3.3 Hz, 1H), 2.36 (p, J = 1.9 Hz, 1H).
I-N-117	447.1	2.10*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 2.54 - 2.51 (m, 2H), 9.47 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 2.8 Hz, 1H), 6.83 (s, 2H), 4.60 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 4.08 (q, J = 5.3 Hz, 2H), 3.62 - 3.54 (m, 1H), 3.15 - 3.08 (m, 4H).
I-N-118	375.1	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.34 (m, 8H), 6.83 (2H, br s), 8.32 (1H, m), 8.74 (2H, br s), 8.94 (1H, m), 9.55 (1H, m), 9.61 (1H, s) and 10.32 (1H, s) ppm.
I-N-119	467.3	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 0.6 Hz, 1H), 6.78 (s, 2H), 3.91 - 3.76 (m, 2H), 3.75 - 3.65 (m, 1H), 3.48 (t, J = 7.7 Hz, 1H), 3.32 - 3.12 (m, 4H), 3.09 - 2.92 (m, 1H), 2.80 - 2.66 (m, 2H), 2.65 - 2.54 (m, 2H), 2.19 - 1.97 (m, 2H), 1.84 - 1.63 (m, 1H), 1.09 - 0.97 (m, 2H), 0.90 - 0.77 (m, 2H).
I-N-120	467.3	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 0.6 Hz, 1H), 6.77 (s, 2H), 3.90 - 3.76 (m, 2H), 3.76 - 3.63 (m, 1H), 3.55 - 3.42 (m, 1H), 3.31 - 3.12 (m, 4H), 2.99 (t, J = 7.2 Hz, 1H), 2.77 - 2.66 (m, 2H), 2.63 - 2.54 (m, 2H), 2.17 - 1.95 (m, 2H), 1.79 - 1.64 (m, 1H), 1.08 - 0.99 (m, 2H), 0.89 - 0.78 (m, 2H).
I-N-121	459.2	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.65-1.73 (2H, m), 2.09 (2H, m), 3.16 (2H, m), 3.38 (5H, m), 3.49 (3H, m), 3.72 (1H, m), 4.02 (2H, m), 6.80 (2H, br s), 8.33 (1H, d), 8.96 (1H, d), 9.46 (1H, s), 9.54 (1H, m), 9.78 (1H, br s) and 10.09 (1H, s) ppm.

I-N-122	445.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.12-2.17 (1H, m), 2.35-2.42 (1H, m), 3.22-3.47 (6H, m), 3.73 masked signal, 3.95-4.09 (5H, m), 6.81 (2H, br s), 8.33 (1H, d), 8.97 (1H, m), 9.50 (1H, s), 9.54 (1H, d) and 10.09 (2H, m) ppm.
I-N-123	455.3	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (1 H, br), 9.48 (1 H, d, J = 5.2 Hz), 9.24 (1 H, m), 8.79 (1 H, br), 8.06 (1 H, d, J = 5.2 Hz), 6.77 (2 H, br), 3.92 (2 H, br), 3.35-3.32 (7 H, br), 2.70 (4 H, br), 2.39 (3 H, s), 1.78 (2 H, br), 1.55 (2 H, br).
I-N-124	461.2	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.1-2.12 (1H,m), 2.4-2.5 (1H,m), 3.2-3.4 (4H,m), 3.6-3.85 (5H,m), 3.9-4.1 (4H,m), 6.78 (2H,brs), 8.35 (1H,s), 8.92 (1H,s), 9.5-9.6 (2H,m), 10.0-10.15 (2H,m).
I-N-125	445.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.12-2.17 (1H, m), 2.35-2.42 (1H, m), 3.22-3.47 (6H, m), 3.73 masked signal, 3.95-4.09 (5H, m), 6.81 (2H, br s), 8.32 (1H, d), 8.98 (1H, m), 9.50 (1H, s), 9.54 (1H, d) and 10.09 (2H, m) ppm.
I-N-126	391.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.72 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.93 (dd, J = 2.5, 0.7 Hz, 1H), 8.85 (s, 2H), 8.32 (s, 1H), 6.85 (s, 2H), 3.43 - 3.27 (m, 4H), 2.58 - 2.45 (m, 4H).
I-N-127	433.2	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.64 (2H, t), 2.70 (4H, m), 3.09 (4H, m), 3.27 (3H, s), 3.51 (2H, t, J = 5 Hz), 6.80 (2H, br s), 8.25 (1H, d), 8.77 (1H, m), 9.50 (2H, m) and 10.30 (1H, s) ppm.
I-N-128	500.1	2.13*	^{1}H NMR (500 MHz, methanol-d4) δ 9.54 (bs, 1H), 9.07 (dd, J = 4.3, 2.5 Hz, 1H), 8.71 (d, J = 2.5 Hz, 1H), 8.34 (bs, 1H), 4.02 - 3.85 (m, 4H), 3.62 (dm, J = 12.6 Hz, 2H), 3.50 - 3.42 (m, 1H), 3.41 - 3.35 (m, 2H), 3.32 - 3.21 (m, 2H), 3.17 - 3.03 (m, 2H), 2.91 (s, 3H), 2.05 (2m, 4H).
I-N-129	400.2	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 9.05 (dd, J = 2.6, 0.6 Hz, 1H), 8.66 (s, 1H), 8.21 (s, 1H), 6.75 (s, 2H), 6.55 (s, 1H), 3.86 - 3.03 (m, 8H, under water peak), 2.95 (s, 3H), 2.94 (s, 3H).
I-N-130	512.2	2.18*	^{1}H NMR (500 MHz, methanol-d4) δ 10.26 (s, 1H), 9.50 (s, 1H), 9.03 (dd, J = 4.3, 2.5 Hz, 1H), 8.68 (dd, J = 2.5, 0.5 Hz, 1H), 8.35 (d, J = 4.1 Hz, 1H), 4.03 - 3.82 (m, 5H), 3.58 - 3.51 (m, 1H), 3.49 - 3.37 (m, 5H), 3.30 - 3.27 (m, 3H), 2.35 (d, J = 3.1 Hz, 1H), 2.18 - 2.09 (m, 1H), 2.09 - 2.01 (m, 2H), 2.01 - 1.87 (m, 2H).

I-N-131	455.2	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.43 (s, 1H), 8.73 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.18 (ddt, J = 7.6, 6.3, 3.7 Hz, 1H), 3.56 (tt, J = 7.9, 3.8 Hz, 1H), 3.13 - 3.01 (m, 2H), 2.79 (ddt, J = 12.2, 8.4, 3.1 Hz, 2H), 2.67 (dd, J = 9.7, 6.3 Hz, 1H), 2.54 - 2.51 (m, 1H), 2.44 - 2.31 (m, 2H), 2.23 (s, 3H), 2.13 - 1.94 (m, 3H), 1.83 - 1.70 (m, 2H), 1.70 - 1.61 (m, 1H).
I-N-132	473.2	2.52*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.55 (s, 1H), 9.54 - 9.46 (m, 1H), 8.70 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 6.80 (s, 2H), 4.23 (ddt, J = 7.4, 6.3, 3.6 Hz, 1H), 3.64 (dt, J = 8.8, 4.5 Hz, 1H), 3.19 - 3.08 (m, 2H), 3.07 - 2.97 (m, 2H), 2.72 (dd, J = 9.7, 6.2 Hz, 1H), 2.60 - 2.53 (m, 1H), 2.47 - 2.34 (m, 2H), 2.26 (s, 3H), 2.15 - 1.98 (m, 3H), 1.91 - 1.79 (m, 2H), 1.75 - 1.64 (m, 1H).
I-N-133	441.2	1.78*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 2H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 9.50 (s, 1H), 9.44 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.59 (d, J = 6.0 Hz, 1H), 4.00 - 3.81 (m, 4H), 3.54 (d, J = 28.4 Hz, 4H), 3.29 (d, J = 65.1 Hz, 2H), 2.96 (s, 3H), 2.15 (dd, J = 58.8, 17.3 Hz, 4H).
I-N-134	512.2	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.54 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.30 (s, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 3.98 - 3.81 (m, 4H), 3.38 - 3.25 (m, 6H), 3.09 (t, J = 4.9 Hz, 4H), 2.22 - 2.11 (m, 6H).
I-N-135	431.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.54 - 9.48 (m, 2H), 8.74 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.07 (q, J = 5.3 Hz, 1H), 3.80 (dd, J = 11.4, 2.9 Hz, 1H), 3.64 - 3.49 (m, 2H), 3.29 - 3.24 (m, 1H), 3.19 - 3.08 (m, 2H), 2.99 (dm, J = 11.9 Hz, 1H), 2.90 - 2.77 (m, 2H), 2.73 (dm, J = 11.8 Hz, 2H), 2.63 - 2.57 (m, 1H), 2.41 (td, J = 11.6, 3.3 Hz, 1H).
I-N-136	427.2	1.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.51 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.99 - 8.94 (m, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 6.76 (s, 2H), 4.51 - 4.43 (m, 1H), 4.07 (s, 2H), 3.98 (dd, J = 11.8, 4.7 Hz, 1H), 3.96 - 3.87 (m, 1H), 3.57 (dd, J = 11.8, 7.0 Hz, 1H), 3.25 - 3.15 (m, 2H), 3.04 (td, J = 12.5, 2.9 Hz, 1H), 2.73 - 2.65 (m, 2H).

I-N-137	431.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.54 - 9.48 (m, 2H), 8.74 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.07 (q, J = 5.3 Hz, 1H), 3.80 (dd, J = 11.4, 2.9 Hz, 1H), 3.64 - 3.49 (m, 2H), 3.29 - 3.24 (m, 1H), 3.19 - 3.08 (m, 2H), 2.99 (dm, J = 11.9 Hz, 1H), 2.90 - 2.77 (m, 2H), 2.73 (dm, J = 11.8 Hz, 2H), 2.63 - 2.57 (m, 1H), 2.41 (td, J = 11.6, 3.3 Hz, 1H).
I-N-138	438.2	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.84 (6H, s), 2.33 (3H, s), 2.64 (4H, br d), 3.11 (4H,br s), 6.81 (2H,s), 8.26 (1H,d), 8.815 (1H,d), 9.16 (1H, d), 9.52 (1H,d), 10.46 (1H,s).
I-N-139	447.1	2.35*	----------
I-N-140	501.1	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.10-2.15 (3H, s), 2.35-2.40 (2H, m), 2.50-2.60 (2H, masked), 2.66 (2H, br s), 2.81 (4H, br s), 3.15 (2H, br s), 7.51-7.52 (1H, d), 7.88-7.89 (1H, s), 8.21-8.23 (1H, d), 8.77 (1H, s).
I-N-141	357.0	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 9.31 (d, J = 1.1 Hz, 1H), 8.97 (dd, J = 2.5, 0.5 Hz, 1H), 8.47 (dd, J = 6.6, 1.1 Hz, 1H), 7.53 (d, J = 6.6 Hz,1H), 6.78 (s, 2H), 3.86 - 3.81 (m, 4H), 3.39 - 3.33 (m, 4H).
I-N-142	463.1	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (s, 1H), 9.34 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.92 (d, J = 2.3 Hz, 1H), 8.56 - 8.43 (m, 1H), 7.57 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.79 - 4.59 (m, 4H), 4.20 (s, 1H), 3.57 (d, J = 6.0 Hz, 5H), 3.08 (s, 4H), 1.85 (s, 6H).
I-N-143	448.2	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.32 (d, J = 1.0 Hz, 1H), 9.16 (dd, J = 2.1, 0.6 Hz, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.55 (d, J = 6.4 Hz, 1H), 6.88 - 6.70 (m, 2H), 4.65 - 4.69 (m, 5H), 4.51 (q, J = 7.2 Hz, 1H), 3.51 (s, 4H), 2.96 (br s, 3H), 1.71 (d, J = 7.2 Hz, 3H).
I-N-144	480.2	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.45 (s, 1H), 9.15 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 4.87 - 4.67 (m, 4H), 4.42 - 4.27 (br m, 9H), 1.87 (s, 6H).
I-N-145	466.1	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.48 (s, 1H), 9.19 (dd, J = 2.1, 0.6 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 6.81 (s, 2H), 4.86 - 4.70 (m, 4H), 4.52 (q, J = 7.2 Hz, 1H), 3.71 (5H), 3.41 (s, 4H), 1.73 (d, J = 7.3 Hz, 3H).

I-N-146	481.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.05-2.12 (4H,m), 2.9 (6H,s), 3.15-3.22 (4H,m), 3.55-3.62 (1H,m), 8.29 (1H,d), 8.96 (1H,d), 9.50-9.53 (1H,m), 9.65 (1H,s), 10.42 (1H,s).
I-N-147	457.1	2.1*	----------
I-N-148	564.2	2.42*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.88-1.92 (2H,m), 1.96-2.05 (2H,m), 2.06-2.15 (4H,m), 2.77-2.83 (6H,m), 3.1-3.22 (6H,m), 3.47-3.60 (3H,m), 3.85-3.95 (1H,m), 8.29 (1H,d), 8.96 (1H,d), 9.40 (1H,s), 9.50-9.53 (1H,m), 9.65 (1H,s), 10.42 (1H,s).
I-N-149	473.2	2.60*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.53 (dd, J = 4.9, 2.5 Hz, 1H), 9.51 (s, 1H), 9.40 (s, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 2.8 Hz, 1H), 6.82 (s, 2H), 4.01 (d, J = 12.9 Hz, 2H), 3.73 (t, J = 12.0 Hz, 2H), 3.56 (d, J = 12.4 Hz, 2H), 3.21 (t, J = 6.1 Hz, 2H), 3.13 (d, J = 7.7 Hz, 5H), 2.08 (d, J = 5.7 Hz, 2H), 1.90 (d, J = 11.8 Hz, 2H), 1.56 (q, J = 18.7, 14.9 Hz, 2H).
I-N-150	486.2	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.49 (s, 1H), 8.75 (d, J = 2.6 Hz, 1H), 8.28 (d, J = 2.9 Hz, 1H), 6.82 (s, 2H), 3.47 (br s, 6H), 3.19 - 2.94 (m, 5H), 2.86 - 2.78 (m, 2H), 2.82 (s, 3H), 1.86 (d, J = 12.8 Hz, 4H), 1.52 (dd, J = 16.7, 8.1 Hz, 2H).
I-N-151	486.2	1.96*	----------
I-N-152	354.0	2.59*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.61 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.20 (s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 6.77 (s, 2H), 3.32 (t, J = 5.4 Hz, 4H), 1.77 - 1.69 (m, 4H), 1.65 (td, J = 6.3, 3.5 Hz, 2H).
I-N-153	460.2	2.01*	----------
I-N-154	469.2	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.42-1.50 (2H, m), 1.72-1.81 (4H, m), 1.96-2.04 (5H, m), 2.14 (3H, s), 2.61 (2H, m), 2.81 (2H, m), 3.07 (2H, m), 3.40-3.47 (1H, m), 3.67-3.72 (1H, m), 6.77 (2H, br s), 7.17 (1H, d), 8.20 (1H, d), 8.73 (1H, d), 9.44 (1H, s), 9.49 (1H, m) and 9.91 (1H, br s) ppm.
I-N-155	523.2	2.37*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (4H,m), 3.12-3.22 (4H,m), 3.26-3.40 (8H,m), 3.57-3.63 (1H,m), 3.62-3.68 (4H,m), 8.27 (1H,d), 8.95 (1H,d), 9.48-9.52 (1H,m), 9.64 (1H,s), 10.42 (1H,s).

I-N-156	486.2	1.97*	^{1}H NMR (500 MHz, methanol-d4) δ 2.09-2.20 (2H, m), 2.41 (2H, s), 2.52-2.57 (1H, m), 2.70-2.82 (2H, m), 2.93-2.97 (1H, m), 3.17-3.22 (3H, m), 3.40-3.45 (1H, m), 3.88-3.97 (1H, m), 8.18 (1H, d), 8.71 (1H, dd), 9.58 (1H, s),
I-N-157	486.2	2.03*	----------
I-N-158	523.1	2.25*	^{1}H NMR (500 MHz, CDCl3) δ 1.92-2.05 (3H, m), 2.07-2.12 (2H, m), 3.26-3.28 (4H, m), 3.45 (2H, m), 3.61-3.63 (4H, m), 5.89 (2H, s), 8.25 (1H, d), 8.54 (1H, dd), 8.61 (1H, d), 9.70 (1H, s), 10.25 (1H, s).
I-N-159	479.1	2.34*	----------
I-N-160	472.1	1.96*	----------
I-N-161	354.0	1.70*	----------
I-N-162	354.0	1.63*	----------
I-N-163	429.1	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.52-1.62 (2H, m), 1.12-1.18 (1H, m), 2.22-2.25 (1H, m), 2.32-2.37 (1H, m), 2.85-2.92 (1H, m), 2.94-2.98 (1H, m), 3.03-3.18 (2H, m), 3.22-3.27 (1H, m), 3.95 (1H, masked), 6.85 (2H, br s), 8.29 (1H, d), 8.81 (1H, d), 9.48 (1H, dd), 9.55 (1H, s), 10.42 (1H, s).
I-N-164	441.2	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.70-1.76 (2H, m), 1.94-1.97 (2H, m), 2.24 (3H, s), 2.75-2.81 (4H, m), 3.04-3.08 (2H, m), 3.53-3.57 (3H, m), 4.10-4.15 (1H, m), 6.77 (2H, br s), 7.18 (1H, d), 8.21 (1H, d), 8.75 (1H, d), 9.42 (1H, s), 9.49 (1H, m) and 9.86 (1H, br s) ppm.
I-N-165	452.0	1.48*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.64 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 7.16 (s, 1H), 6.80 (s, 2H), 3.45 (ddt, J = 12.2, 7.5, 3.8 Hz, 1H), 3.25 - 3.10 (m, 4H), 3.07 (s, 3H), 2.23 - 2.16 (m, 2H), 2.10 - 1.98 (m, 2H).
I-N-166	536.1	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (5H,m), 2.47 (3H,s), 3.12-3.32 (7H,m), 3.48-3.53 (2H,m), 3.65-3.71 (1H,m), 3.85-3.92 (4H,m), 8.27 (1H,d), 8.91 (1H,d), 9.51-9.53 (1H,m), 9.65 (1H,s), 9.72 (1H,brs), 10.43 (1H,s).

I-N-167	487.2	2.38*	^{1}H NMR (500 MHz, methanol-d4) δ 9.60 (s, 1H), 9.05 (dd, J = 4.4, 2.5 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 2.9 Hz, 1H), 3.76 (t, J = 5.8 Hz, 2H), 3.65 (dt, J = 9.1, 4.8 Hz, 1H), 3.28 - 3.22 (m, 2H), 3.16 (dt, J = 11.4, 2.6 Hz, 2H), 2.83 (t, J = 5.8 Hz, 2H), 2.72 (d, J = 6.9 Hz, 4H), 2.19 (dt, J = 13.0, 4.0 Hz, 2H), 2.07 - 1.96 (m, 2H), 1.90 - 1.84 (m, 4H).
I-N-168	458.2	1.70*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.62 (s, 1H), 8.29 (d, J = 2.5 Hz, 1H), 6.81 (s, 2H), 4.30 - 4.08 (m, 4H), 4.07 - 3.92 (m, 1H), 3.77 (s, 2H), 3.08 (dt, J = 10.8, 4.7 Hz, 4H).
I-N-169	493.1	2.51*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.01-2.12 (2H,m), 2.12-2.18 (2H,m), 2.22-2.28 (2H,m), 3.16-3.21 (4H,m), 3.38-3.46 (1H,m), 3.92-3.97 (4H,m), 5.8 (2H,brs), 8.29 (1H,d), 8.93 (1H,d), 9.50-9.53 (1H,m), 9.63 (1H,s), 10.41 (1H,s).
I-N-170	505.1	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (3H,m), 2.98-3.08 (2H,m), 3.25-3.31 (4H,m), 3.57-3.71 (8H,m), 6.82 (2H,brs), 7.5 (1H,d), 8.42 (1H,d), 8.81 (1H,d), 9.44 (1H,s), 9.54-9.57 (1H,m), 9.80 (1H,s).
I-N-171	500.1	2.31*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.57 - 9.47 (m, 2H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H), 6.82 (s, 2H), 4.12 (s, 2H), 3.86 (s, 2H), 3.56 (s, 2H), 3.42 (s, 1H), 3.24 (s, 1H), 3.12 (s, 4H), 2.92 (s, 3H), 2.11 (s, 1H), 1.88 (s, 2H), 1.63 - 1.45 (m, 2H).
I-N-172	488.1	1.8*	----------
I-N-173	501.0	2.26*	----------
I-N-174	502.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.15-2.30 (4H, m), 2.65-2.75 (1H, br s), 2.78-2.88 (1H, br s), 3.02-3.14 (5H, m), 3.55-3.65 (2H, br s), 3.70-3.75 (1H, br s), 3.82-3.90 (3H, br s), 4.30-4.38 (1H, br s), 6.80 (2H, s), 8.27 (1H, d), 8.82 (1H, d), 9.49 (1H, dd), 9.55 (1H, d), 10.40 (1H, s).
I-N-175	536.0	2.26*	----------
I-N-176	461.0	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 0.94-1.03 (4H, m), 2.80-2.83 (1H, m), 3.37 (4H, m), 3.42 (4H, m), 6.79 (2H, s), 7.51-7.52 (1H, d), 8.44-8.45 (1H, d), 8.88 (1H, d), 9.32 (1H, s), 9.55 (1H, dd), 9.77 (1H, s).
I-N-177	505.0	2.08*	----------

I-N-178	435.0	1.9*	----------
I-N-179	491.0	2.03*	----------
I-N-180	478.0	1.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.66 - 1.70 (2H, m), 1.80 - 1.85 (2H, m), 2.59 (4H, brs), 3.12 (4H, brs), 3.58 - 3.64 (1H, m), 4.48 - 4.52 (2H, m), 3.58 - 3.62 (2H, m), 6.78 (2H, s), 8.24 (1H, s), 8.71 (1H, s), 9.08 (1H, s), 9.49 (1H, s), 10.36 (1H, s).
I-N-181	486.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85-2.03 (2H, m), 2.06-2.13 (1H, m), 2.86 (3H, d), 3.11-3.13 (4H, m), 3.19-3.24 (1H, m), 3.63-3.68 (3H, m), 3.75-3.80 (1H, m), 3.82-3.85 (1H, m), 4.63-4.65 (2H, m), 6.80 (2H, br s), 8.30 (1H, d), 8.90 (1H, d), 9.51-9.53 (1H, dd), 9.56 (2H, m), 10.37 (1H, s).
I-N-182	429.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.52-1.62 (2H, m), 1.12-1.18 (1H, m), 2.22-2.25 (1H, m), 2.32-2.37 (1H, m), 2.85-2.92 (1H, m), 2.94-2.98 (1H, m), 3.03-3.18 (2H, m), 3.22-3.27 (1H, m), 3.95 (1H, masked), 6.85 (2H, br s), 8.29 (1H, d), 8.81 (1H, d), 9.48 (1H, dd), 9.55 (1H, s), 10.42 (1H, s).
I-N-183	441.4	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.77-1.82 (2H, m), 1.99 (2H, m), 2.23 (3H, m), 2.37 (3H, m), 2.93 (4H, m), 3.68 (2H, m), 6.77 (2H, br s), 7.19 (1H, d, J = 5Hz), 8.20 (1H, d), 8.80 (1H, m), 9.41 (1H, s), 9.41 (1H, m) and 9.79 (1H, br s) ppm.
I-N-184	457.1	2.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.60 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 8.99 (dd, J = 2.6, 0.7 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 7.83 (d, J = 3.3 Hz, 1H), 7.68 (d, J = 3.3 Hz, 1H), 6.80 (s, 2H), 3.40 - 3.32 (m, 1H), 3.27 - 3.22 (m, 2H), 3.16 (d, J = 11.7 Hz, 2H), 2.30 - 2.20 (m, 2H), 2.12 (d, J = 12.5 Hz, 2H).
I-N-185	500.0	2.16*	----------
I-N-186	429.0	1.97*	^{1}H NMR (500MHz, DMSO-d6) δ 1.52-1.62 (1H, m), 2.11-2.17 (1H, m), 2.22-2.25 (1H, m), 2.32-2.37 (1H, m), 2.85-2.88 (1H, m), 2.90-2.92 (1H, m), 3.02-3.05 (1H, m), 3.10-3.13 (1H, m), 3.22-3.27 (1H, m), 3.93-3.95 (2H, m), 6.79 (2H, br s), 8.29 (1H, d), 8.81 (1H, d), 9.48 (1H, dd), 9.55 (1H, s), 10.42 (1H, s).
I-N-187	486.0	2.19*	^{1}H NMR (500 MHz, CDCl3) δ 10.34 (s, 1H), 9.69 (s, 1H), 8.54-8.55 (dd, 1H), 8.46 (d, 1H), 8.23 (d, 1H), 5.89 (s, 2H), 3.90 (s, 4H), 3.48 (s, 2H), 3.18 (s, 4H), 2.71 (s, 4H). 1.86 (s, 4H).

I-N-188	518.0	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.80-1.87 (2H, m), 2.20-2.25 (2H, m), 2.81 (3H, s), 2.92-2.97 (2H, m), 3.33 (3H, s), 3.48-3.56 (8H, m), 6.80 (2H, s), 7.45 (1H, m), 8.41 (1H, d), 8.90 (1H, d), 9.31 (1H, s), 9.53-9.55 (1H, d), 9.73 (1H, s).
I-N-189	459.0	2.36*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85-1.88 (2H, m), 2.17-2.19 (2H, m), 3.14-3.21 (3H, m), 3.27-3.30 (2H, m), 3.53-3.55 (2H, m), 3.73-3.76 (2H, m), 4.04-4.07 (2H, m), 6.75-6.6.85 (2H, s), 7.41-7.44 (1H, m), 7.54-7.56 (1H, m), 7.72-7.74 (1H, d), 7.99-8.00 (1H, d), 8.29 (1H, d), 8.94 (1H, d), 9.41 (1H, s), 9.52-9.54 (1H, m), 9.60-9.80 (1H, m), 10.05 (1H, s).
I-N-190	434.0	0.6	^{1}H NMR (500 MHz, Methanol-d4) δ 9.90 (s, 0.5H), 9.62 (d, 1H), 9.1-9.07 (m, 1H), 8.88 (d, 1H), 8.38 (d, 1H), 7.62 (d, 1H), 3.92-3.85 (m, 2H), 3.51-3.45 (m, 1H), 3.15 - 3.08 (m, 2H), 3.06 (s, 3H), 2.35 - 2.26 (m, 4H)
I-N-191	486.2	1.89*	----------
I-N-192	533.0	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (1H, s), 9.48 (1H, s), 9.08 (1H, d), 8.68 (1H, d), 8.28 (1H, d), 6.77 (2H, brs), 3.08 – 3.19 (6H, m), 2.80 (3H, s), 1.85 – 1.88 (2H, m), 1.76 – 1.81 (2H, m), 1.70 – 1.73 (2H, m), 1.52 – 1.55 (2H, m) (n.b some signals masked by broad water peak).
I-N-193	500.1	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.53 (s, 1H), 9.51 (dd, J = 4.7, 2.5 Hz, 1H), 8.94 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 3.92 (s, 2H), 3.59 (d, J = 4.7 Hz, 4H), 3.45 (s, 2H), 3.17 - 3.00 (m, 4H), 2.88 (s, 3H), 1.93 (dtd, J = 15.7, 8.3, 7.6, 3.8 Hz, 1H), 1.74 (d, J = 12.1 Hz, 2H), 1.55 (qd, J = 12.1, 4.4 Hz, 2H).
I-N-194	472.1	1.85*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 9.04-9.05 (dd, 1H), 9.70 (d, 1H), 8.18 (d, 1H), 3.92 (s, 2H), 3.68-3.71 (m, 5H), 3.49 (m, 2H), 3.18-3.20 (m, 4H), 2.42 (s, 3H).
I-N-195	477.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.50-9.51 (dd, 1H), 9.39 (s, 1H), 8.91 (d, 1H), 8.26 (d, 1H), 7.23-7.24 (d, 1H), 6.76 (s, 2H), 4.93-4.97 (m, 1H), 4.84-4.88 (m, 2H), 4.73-4.76 (m, 2H), 3.35 (s, 4H), 3.03 (s, 4H).
I-N-196	544.1	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.97-2.18 (9H,m), 2.92-3.00 (2H,m), 3.30-3.50 (5H,m), 3.55-3.65 (3H,m), 3.67-3.72 (2H,m), 4.22-4.26 (1H,m), 6.70-6.88 (2H,m), 7.45 (1H,d), 8.40 (1H,d), 8.78 (1H,s), 9.45 (1H,s), 9.52-9.54 (1H,m), 9.8 (1H,brs), 10.35 (1H,s).

I-N-197	475.1	2.83*	^{1}H NMR (500 MHz, Methanol-d4) δ 9.69 (s, 1H), 9.20 (dd, 1H), 9.11 (dd, 1H), 8.76 (dd, 1H), 8.36 - 8.22 (m, 1H), 7.51 (dd, 1H), 3.98 (d, 2H), 3.71 (br t, 2H), 3.52 (s, 2H), 3.19 - 3.16 (m, 2H), 3.13 (dd, 2H), 2.59 (tt, 2H), 2.11 - 2.05 (m, 1H), 1.98 (d, 2H), 1.62 (qd, 2H).
I-N-198	468.1	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.46-9.49 (m, 2H), 8.94 (d, 1H), 7.20 (d, 1H), 6.76 (s, 2H), 3.90-3.95 (m, 1H), 3.80-3.87 (m, 2H), 3.60-3.67 (m, 1H), 3.29 (s, 3H), 3.15-3.25 (m, 1H), 2.85-3.00 (m, 4H), 2.20-2.30 (m, 2H), 2.10-2.15 (m, 1H), 1.80-1.90 (m, 2H).
I-N-199	468.2	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.46-9.49 (m, 2H), 8.94 (d, 1H), 7.20 (d, 1H), 6.76 (s, 2H), 3.90-3.95 (m, 1H), 3.80-3.87 (m, 2H), 3.60-3.67 (m, 1H), 3.29 (s, 3H), 3.15-3.25 (m, 1H), 2.85-3.00 (m, 4H), 2.20-2.30 (m, 2H), 2.10-2.15 (m, 1H), 1.80-1.90 (m, 2H).
I-N-200	476.1	1.9*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.97-2.12 (4H,m), 2.92-3.00 (2H,m), 3.44-3.56 (1H,m), 3.60-3.67 (2H,m), 4.75-4.79 (2H,m), 4.83-4.86 (2H,m), 6.80 (2H,brs), 7.50 (1H,d), 8.42 (1H,d), 8.81-8.83 (1H,m), 9.47 (1H,s), 9.54-9.58 (1H,m), 9.8 (1H,brs).
I-N-201	495.0	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.46 (s, 1H), 8.84 - 8.80 (m, 1H), 8.30 (d, J = 2.6 Hz, 1H), 6.79 (s, 2H), 5.07 - 4.97 (m, 1H), 4.85 (dd, J = 8.1, 7.0 Hz, 2H), 4.75 (dd, J = 7.1, 6.1 Hz, 2H), 3.45 (dd, J = 6.1, 3.4 Hz, 4H), 3.18 - 3.12 (m, 4H).
I-N-202	379.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.42 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.83 (dd, J = 18.1, 2.1 Hz, 2H), 7.79 (d, J = 5.1 Hz, 1H), 6.74 (s, 2H), 1.87 (ddd, J = 10.6, 8.2, 5.3 Hz, 1H), 1.11 - 0.93 (m, 4H).
I-N-203	526.1	2.26*	----------
I-N-204	514.0	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.55 (s, 1H), 9.51-9.52 (dd, 1H), 9.38-9.46 (m, 1H), 8.88 (d, 1H), 8.30 (d, 1H), 6.80 (s, 2H), 4.56-4.61 (m, 1H), 3.92-3.95 (m, 1H), 3.82-3.85 (m, 1H), 3.70-3.80 (m, 2H), 3.55-3.58 (m, 1H), 3.08-3.20 (m, 5H), 2.98-3.05 (m, 1H), 2.89-2.95 (m, 1H), 212-2.15 (m, 1H), 1.78-1.90 (m, 3H), 1.50-1.65 (m, 2H), .25-1.28 (t, 3H).
I-N-205	514.0	2.23*	----------

I-N-206	514.1	2.18*	----------
I-N-207	500.1	2.09*	----------
I-N-208	478.2	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.99-2.10 (2H,m), 2.18-2.25 (2H,m), 2.95-3.05 (2H,m), 3.32 (3H,s), 3.40-3.50 (4H,m), 3.62-3.68 (2H,m), 3.75-3.78 (2H,m), 6.80 (2H,brs), 7.55 (1H,d), 8.43 (1H,d), 8.81-8.82 (1H,m), 9.48 (1H,s), 9.54-9.57 (1H,m), 9.8 (1H,brs).
I-N-209	385.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.53 (dd, 1H), 9.09 (s, 1H), 8.74 (d, 1H), 8.40 (dd, 1H), 7.42 (d, 1H), 6.75 (s, 2H), 4.02 (s, 2H), 3.75 (br t, 2H), 3.48 (br t, 1H), 2.94 (s, 3H).
I-N-210	406.0	1.65*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 9.33 (d, J = 0.9 Hz, 1H), 8.86 - 8.81 (m, 1H), 8.47 (dd, J = 6.2, 0.9 Hz, 1H), 7.64 (d, J = 6.3 Hz, 1H), 6.80 (s, 2H), 3.77 - 3.71 (m, 4H), 3.46 - 3.40 (m, 8H).
I-N-211	542.1	2.02*	----------
I-N-212	403.1	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.51 (s, 1H), 9.50 (t, 1H), 8.54 (d, 1H), 8.31 (d, 1H), 6.76 (br s, 2H), 3.71 (s, 2H), 3.53 - 3.50 (m, 2H), 3.46 - 3.44 (m, 2H), 3.01 (s, 3H).
I-N-213	471.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.52 (s, 1H), 9.50 (dd, 1H), 8.99 (d,1H), 8.28 (d, 1H), 6.79 (br s, 2H), 3.38 (t, 2H), 3.22 (d, 2H), 3.12 - 3.02 (m, 4H), 2.26 (t, 2H), 1.98 - 1.92 (m, 2H), 1.89 - 1.82 (m, 1H), 1.68 (dd, 2H), 1.52 (qd, 2H).
I-N-214	500.1	2.49*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.49-9.56 (m, 2H), 8.77 (d, 1H), 8.27 (d, 1H), 6.80 (s, 2H), 4.02-4.25 (m, 2H), 3.80-3.90 (m, 1H), 3.70-3.80 (m, 2H), 3.35-3.45 (m, 1H), 3.05-3.20 (m, 4H), 2.88-2.90 (m, 1H), 2.19 (s, 2H), 1.90-205 (m, 2H), 1.60-1.80 (m, 3H), 1.50-1.55 (s, 1H), 1.30-1.40 (m, 1H).
I-N-215	448.1	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.62-1.70 (2H,m), 1.96-2.03 (2H,m), 2.20-2.28 (1H,m), 3.00-3.08 (5H,m), 3.28 (2H,d), 3.62-3.68 (2H,m), 6.80 (2H,brs), 7.48 (1H,d), 8.42 (1H,d), 8.97 (1H,d), 9.32 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs).

I-N-216	441.0	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.53 (dd, 1H), 9.29 (s, 1H), 8.88 (d, 1H), 8.43-8.45 (dd, 1H), 7.57-7.58 (d, 1H), 6.79 (s, 2H), 3.45-3.50 (m, 2H), 3.45 (s, 2H), 3.30-3.45 (m, 2H), 2.78 (s, 3H), 1.97-2.08 (m, 4H).
I-N-217	411.1	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.40 - 9.34 (m, 1H), 8.99 - 8.92 (m, 1H), 8.43 (dd, J = 6.3, 0.9 Hz, 1H), 7.52 (d, J = 6.4 Hz, 1H), 6.78 (s, 2H), 3.95 - 3.85 (m, 2H), 3.77 - 3.70 (m, 1H), 3.62 (d, J = 12.5 Hz, 1H), 3.15 - 3.05 (m, 1H), 2.87 (td, J = 12.3, 3.5 Hz, 1H), 2.77 (dd, J = 12.1, 10.9 Hz, 1H), 2.37 - 2.21 (m, 2H), 2.09 (dddd, J = 12.8, 9.8, 7.7, 4.0 Hz, 1H), 1.63 - 1.52 (m, 1H).
I-N-218	368.1	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.73 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.46 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 5.1, 0.6 Hz, 1H), 2.38 (s, 3H), 2.36 (s, 3H).
I-N-219	407.0	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.85 (s, 1H), 9.48 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.24 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.59 (d, J = 1.3 Hz, 1H), 6.66 (s, 2H).
I-N-220	370.1	2.63*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.48 (dd, J = 4.8, 2.6 Hz, 1H), 9.26 (d, J = 0.9 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 1.5, 0.7 Hz, 1H), 8.10 (dd, J = 7.4, 1.4 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.65 (s, 2H), 3.80 (t, J = 6.5 Hz, 2H), 1.90 - 1.77 (m, 4H), 1.54 (s, 6H).
I-N-221	434.0	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (1H, s), 9.53 (1H, dd), 9.35 (1H, s), 9.00 (1H, dd), 8.45 (1H, dd), 7.57 (1H, d), 6.79 (2H, brs), 3.92 (1H, d), 3.52 – 3.58 (2H, m), 3.16 – 3.21 (1H, t), 2.99 (3H, s), 2.88 – 2.93 (1H, m), 2.30 – 2.33 (1H, m), 1.83 – 1.93 (2H, m), 1.67 – 1.71 (1H, m).
I-N-222	411.1	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.52 (dd,1H), 9.01 (s, 1H), 8.74 (d, 1H), 8.38 (dd, 1H), 7.44 (d, 1H), 6.74 (s, 2H), 4.24 (d, 1H), 4.20 (d, 1H), 3.87 (d, 1H), 3.84 - 3.78 (m, 1H), 3.53 - 3.48 (m, 1H), 3.41 - 3.36 (m, 1H), 3.18 (dd, 1H), 1.95 - 1.90 (m, 2H), 1.84 - 1.74 (m, 1H), 1.47 - 1.38 (m, 1H).
I-N-223	353.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.26 (3H, s), 6.47 (1H, m), 6.70 (2H, br s), 7.59 (1H, m), 7.94 (1H, m), 8.48 (1H, m), 8.60 (1H, m), 9.41 (1H, m), 9.79 (1H, s) and 10.14 (1H, s) ppm.

I-N-224	425.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (s, 1H), 8.92 (d, J = 1.1 Hz, 1H), 8.71 (d, J = 2.5 Hz, 1H), 8.33 (dd, J = 6.9, 1.2 Hz, 1H), 7.45 (d, J = 6.9 Hz, 1H), 6.73 (s, 2H), 3.97 - 3.90 (m, 1H), 3.72 - 3.63 (m, 1H), 3.50 (ddd, J = 13.8, 11.4, 5.6 Hz, 2H), 3.10 (ddd, J = 13.4, 10.7, 2.7 Hz, 1H), 3.00 (dd, J = 9.9, 1.7 Hz, 1H), 2.74 (d, J = 0.7 Hz, 3H), 2.71 (dt, J = 7.5, 4.1 Hz, 1H), 2.63 - 2.53 (m, 1H), 1.94 - 1.84 (m, 1H), 1.59 (dtd, J = 13.7, 10.1, 3.6 Hz, 1H).
I-N-225	352.9	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.32 (3H, s), 6.46 (1H, m), 6.73 (2H, br s), 7.64 (1H, m), 8.37-8.40 (2H, m), 8.76 (1H, m), 9.40-9.42 (2H, m) and 11.10 (1H, s) ppm.
I-N-226	398.1	2.0*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 9.44 (s, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.14 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.39 (s, 4H), 2.86 - 2.80 (m, 4H), 2.02 (t, J = 5.5 Hz, 4H).
I-N-227	502.0	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 10.20 (s, 1H), 9.56 (s, 1H), 9.51 (dd, 1H), 8.91 (d, 1H), 8.30 (d, 1H), 6.80 (br s, 2H), 4.80-4.85 (m, 1H), 4.32 (m, 1H), 4.01-4.09 (m, 2H), 3.88-3.91 (m, 1H), 3.70-3.76 (m, 2H), 3.57-3.62 (m, 1H), 3.49-3.53 (t, 1H), 3.42-3.45 (d, 1H), 3.20 (m, 3H), 3.11 (s, 2H), 2.83 (s, 3H).
I-N-228	472.0	2.06*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.11 (s, 1H), 9.52-9.54 (m, 2H), 9.07 (dd, 1H), 8.32 (d, 1H), 6.80 (br s, 2H), 4.22-4.24 (m, 2H), 4.15 (s, 2H), 3.99-4.00 (t, 2H), 3.25-3.70 (m, 8H), 2.29-237 (s, 2H).
I-N-229	459.0	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.51-9.52 (dd, 2H), 8.67 (d, 1H), 8.30 (d, 1H), 6.80 (br s, 2H), 3.54 (s, 2H), 3.22-3.28 (m, 2H), 3.02-3.08 (m, 2H), 2.81 (s, 3H), 2.02-2.07 (m, 4H).
I-N-230	439.0	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.36 (s, 1H), 8.93 - 8.88 (m, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.19 (d, J = 5.4 Hz, 1H), 6.76 (d, J = 4.5 Hz, 2H), 4.34 (t, J = 5.1 Hz, 1H), 3.84 (tt, J = 12.1, 3.9 Hz, 1H), 3.48 - 3.44 (m, 1H), 3.27 - 3.21 (m, 2H), 2.80 (td, J = 12.2, 2.2 Hz, 2H), 2.25 (dd, J = 8.6, 7.5 Hz, 2H), 2.09 - 1.91 (m, 4H), 1.69 - 1.62 (m, 2H).
I-N-231	453.1	2.01*	1H NMR (500 MHz, DMSO-d6) δ 9.52-9.55 (m, 2H), 9.15 (d, 1H), 8.90 (d, 1H), 8.41-8.43 (m, 1H), 7.50 (d, 1H), 6.77 (s, 2H), 3.40 (m, 4H), 3.23 (s, 2H), 2.80 (s, 3H), 2.20-2.25 (m, 2H), 1.74-1.77 (m, 2H), 1.63-1.71 (m, 4H).

I-N-232	429.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.54 (s, 1H), 9.50 (dd, 1H), 8.48 (d, 1H), 8.30 (d, 1H), 6.76 (s, 2H), 3.78 - 3.56 (m, 5H), 3.50 - 3.45 (m, 1H), 3.29 - 3.23 (m, 1H), 2.02 - 1.94 (m, 2H), 1.92 - 1.84 (m, 1H), 1.54 - 1.45 (m, 1H).
I-N-233	440.1	1.7*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.52-9.53 (dd, 1H), 9.32 (d, 1H), 8.93 (d, 1H), 8.47-8.48 (dd, 1H), 7.57-7.58 (d, 1H), 6.80 (s, 2H), 4.03-4.06 (dd, 1H), 3.66-3.69 (m, 1H), 3.45-3.50 (m, 1H), 3.23-3.26 (m, 1H), 3.06-3.15 (m, 4H), 2.97-3.03 (m, 1H), 2.95-2.97 (m, 4H), 2.62-2.65 (m, 1H).
I-N-234	429.1	1.75*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.66 (s, 1H), 9.52-9.53 (dd, 1H), 9.24 (d, 1H), 8.96-8.97 (dd, 1H), 8.40-8.42 (dd, 1H), 7.51-7.52 (d, 1H), 6.80 (s, 2H), 4.51-4.54 (dd, 1H), 3.96-3.98 (m, 1H), 3.56-3.58 (m 2H), 3.18-3.23 (m, 2H), 3.02 (s, 3H), 2.77 (s, 3H).
I-N-235	439.1	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.26 (s, 1H), 8.85 (dd, J = 2.6, 0.5 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.21 (dd, J = 5.3, 0.5 Hz, 1H), 6.77 (s, 2H), 3.23 - 3.16 (m, 2H), 2.89 (dd, J = 13.1, 11.0 Hz, 2H), 2.72 (t, J = 0.7 Hz, 3H), 2.26 (dd, J = 8.4, 7.4 Hz, 2H), 2.14 (td, J = 12.7, 4.2 Hz, 2H), 1.97 (t, J = 7.9 Hz, 2H), 1.47 (d, J = 12.4 Hz, 2H).
I-N-236	439.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.61 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.21 (d, J = 1.1 Hz, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.42 (dd, J = 6.7, 1.1 Hz, 1H), 7.51 (d, J = 6.7 Hz, 1H), 6.78 (s, 2H), 3.41 - 3.32 (m, 4H), 3.27 (s, 2H), 2.73 (s, 3H), 2.29 (d, J = 1.1 Hz, 2H), 1.77 (dtdd, J = 17.2, 10.7, 7.1, 3.8 Hz, 4H).
I-N-237	367.1	2.11*	----------
I-N-238	413.1	1.72*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.84 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.47 - 9.40 (m, 1H), 9.00 (dd, J = 2.6, 0.6 Hz, 1H), 8.45 (dd, J = 6.2, 0.9 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 6.78 (s, 2H), 4.42 - 4.34 (m, 1H), 4.18 (dddd, J = 10.9, 8.6, 5.0, 3.7 Hz, 1H), 3.98 - 3.94 (m, 1H), 3.75 - 3.64 (m, 2H), 3.52 (d, J = 12.4 Hz, 1H), 3.35 (ddd, J = 13.3, 12.0, 3.5 Hz, 1H), 3.02 - 2.89 (m, 2H).
I-N-239	416.1	2.27*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.49 (q, J = 2.3 Hz, 2H), 8.61 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 3.0 Hz, 1H), 6.79 (s, 2H), 4.44 (s, 4H), 3.00 (dd, J = 6.8, 4.1 Hz, 4H), 2.04 (t, J = 5.4 Hz, 4H).

I-N-240	458.1	1.88*	^{1}H NMR (500 MHz, Methanol-d4) δ 9.48 (s, 1H0, 9.07-9.09 (d, 1H), 8.77 (d, 1H), 8.43-8.44 (d, 1H), 3.91-3.96 (m, 1H), 3.62-3.68 (m, 1H), 3.53-3.56 (m, 1H), 3.30-3.45 (m, 4H), 3.25-3.28 (m, 1H), 2.88-3.04 (m, 5H).
I-N-241	424.1	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.05-2.15 (4H,m), 3.15-3.20 (2H,m), 3.23-3.32 (1H,m), 3.62-3.68 (2H,m), 6.80 (2H,brs), 7.52 (1H,d), 8.42 (1H,d), 8.87 (1H,d), 9.38 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs), 9.79 (1H,s).
I-N-242	372.0	1.85*	----------
I-N-243	448.0	1.96*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (1H, s), 9.54 (1H, dd), 9.44 (1H, s), 8.88 (1H, d), 8.50 (1H, dd), 7.62 (1H, d), 6.81 (2H, brs), 3.59 – 3.63 (2H, m), 3.17 – 3.22 (2H, m), 2.97 (3H, s), 2.37 – 2.42 (2H, m), 1.78 – 1.81 (2H, m), 1.53 (3H, s).
I-N-244	425.0	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.52-9.53 (dd, 1H),9.34 (s, 1H), 8.99 (d, 1H), 8.43-8.44 (d, 1H), 7.50-7.52 (d, 1H),6.78 (s, 2H), 4.47-4.50 (m, 1H), 3.62-3.78 (m, 2H), 2.94-2.97 (m, 2H), 2.86 (t, 1H), 2.18-2.22 (m, 2H),2.81-2.83 (m, 1H), 2.64-2.78 (m, 2H), 1.35-1.47 (m, 1H).
I-N-245	468.1	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.51-9.53 (dd, 1H), 9.31 (d, 1H), 8.94 (d, 1H), 8.44-8.45 (dd,1H), 7.54-7.55 (d, 1H), 4.50-4.55 (m, 1H) 3.91-3.96 (m, 1H), 3.62-3.68 (m, 1H), 3.25-3.30 (m, 1H), 2.90-3.15 (m, 4H), 2.50-2.80 (m, 4H). 1.03-1.06 (t, 6H).
I-N-246	360.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.82-1.92 (4H,m), 3.6-3.7 (4H,m), 6.85 (2H,s), 8.45 (1H,d), 8.59 (1H,s), 8.80-8.82 (1H,m), 9.48-9.53 (2H,m).
I-N-247	447.1	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.48 (s, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.1, 0.7 Hz, 1H), 7.54 (d, J = 6.1 Hz, 1H), 6.81 (s, 2H), 3.70 - 3.63 (m, 1H), 3.57 (d, J = 12.1 Hz, 1H), 3.47 (tdd, J = 9.8, 6.7, 3.0 Hz, 1H), 3.40 - 3.33 (m, 2H), 3.33 - 3.29 (m, 1H), 3.12 (td, J = 11.5, 3.0 Hz, 1H), 3.02 (td, J = 12.0, 3.0 Hz, 1H), 2.95 (dd, J = 12.0, 10.2 Hz, 1H), 2.36 (dddd, J = 12.6, 9.3, 5.8, 3.6 Hz, 1H), 1.97 (dtd, J = 12.5, 10.3, 8.2 Hz, 1H).

I-N-248	431.0	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.55 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.30 (d, J = 2.5 Hz, 1H), 6.79 (s, 2H), 4.43 (t, J = 8.6 Hz, 1H), 4.20 (ddd, J = 12.1, 9.5, 4.4 Hz, 1H), 3.99 (dd, J = 8.9, 5.0 Hz, 1H), 3.73 (dt, J = 13.0, 2.6 Hz, 1H), 3.42 - 3.31 (m, 1H), 3.23 (dd, J = 11.4, 3.9 Hz, 1H), 3.07 - 2.99 (m, 3H).
I-N-249	441.0	1.76*	----------
I-N-250	424.0	1.90*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.58 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.68 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 1.8 Hz, 1H), 6.85 (s, 2H), 3.60 - 3.42 (m, 8H).
I-N-251	439.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.47-9.48 (dd, 1H), 9.45 (s, 1H), 8.80 (d, 1H), 8.22 (d, 1H), 7.17 (d, 1H), 6.77 (s, 2H), 3.93 (s, 2H), 3.63 (s, 2H), 2.87 (m, 4H), 1.93-1.95 (m, 4H), 1.78 (s, 3H).
I-N-252	434.1	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 9.51 (s, 1H), 9.26 (s, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.41 (d, J = 6.1 Hz, 1H), 7.54 (d, J = 6.2 Hz, 1H), 6.81 (s, 2H), 3.51 (m, 6H), 1.46 (s, 6H).
I-N-253	397.9	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.51-9.52 (d, 1H), 9.48 (s, 1H), 9.25 (s, 1H), 8.83 (d, 1H), 7.51-7.53 (d, 1H), 6.78 (s, 2H), 4.43 (d, 2H), 4.31 (d, 2H), 3.55 (s, 2H), 3.08 (m, 2H), 1.87-1.89 (m, 2H), 1.65-1.67 (m, 2H).
I-N-254	399.1	1.72*	----------
I-N-255	411.2	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.54 (dd, 1H), 9.27 (s, 1H), 8.90 (d, 1H), 8.88 (br s, 2H), 8.40 (dd, 1H), 7.46 (d, 1H), 6.80 (s, 2H), 3.34 - 3.25 (m, 6H), 3.12 (t, 2H), 1.91 (t, 2H), 1.83 - 1.73 (m, 4H).
I-N-256	439.1	1.89*	1H NMR (500 MHz, DMSO-d6) (TFA salt) δ 2.37 (3H,s), 3.43-3.48 (4H,m), 3.63-3.67 (4H,m), 6.80 (2H,brs), 7.57 (1H,d), 8.48 (1H,d), 9.02 (1H,d), 9.37 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs), 9.77 (1H,s).
I-N-257	453.1	2.05*	^{1}H NMR (500 MHz, DMSO) δ 9.60 (d, 1H), 9.53 (ddd, 1H), 9.19 (t, 1H), 8.90 (t, 1H), 8.41 (dt, 1H), 7.50 (dd, 1H), 6.78 (s, 2H), 3.50 (t, 1H), 3.43 - 3.31 (m, 6H), 3.27 (s, 1H), 1.94 (d, 3H), 1.90 (t, 1H), 1.81 (t, 1H), 1.74 - 1.70 (m, 4H).
I-N-258	411.1	1.8*	^{1}H NMR (500 MHz, DMSO) δ 9.79 (s, 1H), 9.52 (dd, 1H), 9.37 (s, 1H), 8.96 (d, 1H), 8.43 (d, 1H), 7.51 (d,1H), 6.78 (s, 2H), 3.92 - 3.87 (m, 2H), 3.72 (d, 1H), 3.60 (d, 1H), 3.10 (td, 1H), 2.87 (td, 1H), 2.77 (t, 1H), 2.35 - 2.23 (m, 2H), 2.13 - 2.06 (m, 1H), 1.61 - 1.54 (m, 1H).

I-N-259	326.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.99 (s, 1H), 9.52-9.54 (d, 1H), 9.16 (d, 1H), 8.87 (m, 1H), 8.81 (s, 1H), 7.90 (d, 1H), 7.08 (d, 1H), 6.74 (s, 2H), 4.22 (d, 3H).
I-N-260	439.1	2.4*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.41 (3H,s), 3.43-3.47 (4H,m), 3.53-3.57 (4H,m), 6.80 (2H,brs), 7.51 (1H,d), 8.45 (1H,d), 8.87 (1H,d), 9.37 (1H,s), 9.52-9.56 (1H,m), 9.63 (1H,brs), 9.77 (1H,s).
I-N-261	433.1	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.53 (s, 1H), 9.47-9.49 (dd, 1H), 8.86 (d, 1H), 8.27 (s,1H), 6.79 (s, 2H), 3.64-3.66 (m, 7H), 3.05-3.07 (m, 4H).
I-N-262	453.2	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.51 (dd, J = 4.7, 2.6 Hz, 1H), 9.40 (d, J = 1.1 Hz, 1H), 9.19 (dd, J = 2.6, 0.8 Hz, 1H), 8.44 (dd, J = 6.7, 1.1 Hz, 1H), 7.53 (d, J = 6.7 Hz, 1H), 6.79 (s, 2H), 3.71 - 3.60 (m, 2H), 3.51 (t, J = 6.7 Hz, 2H), 3.21 (td, J = 12.8, 3.9 Hz, 2H), 3.08 - 2.94 (m, 2H), 2.01 (d, J = 6.9 Hz, 5H), 1.81 (p, J = 6.8 Hz, 2H), 1.42 (dd, J = 12.6, 2.2 Hz, 2H).
I-N-263	354.1	1.34*	^{1}H NMR (500 MHz, DMSO) δ 9.74 (s, 1H), 9.60 (s, 1H), 9.46 (dd, J = 4.8, 2.5 Hz, 1H), 8.84 (s, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.27 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H), 6.67 (s, 1H), 2.27 (s, 3H).
I-N-264	371.0	2.49*	run in d6-DMSO
I-N-265	438.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (4H,m), 2.37 (3H,s), 3.21-3.27 (2H,m), 3.30-3.37 (1H,m), 3.68-3.75 (2H,m), 6.80 (2H,brs), 7.58 (1H,d), 8.48 (1H,d), 8.87 (1H,d), 9.33 (1H,s), 9.53-9.56 (1H,m), 9.72 (1H,brs).
I-N-266	387.2	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.63 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.22 (d, J = 1.1 Hz, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.40 (dd, J = 6.6, 1.1 Hz, 1H), 7.49 (d, J = 6.6 Hz, 1H), 6.77 (s, 2H), 3.49 (dtt, J = 11.8, 7.5, 3.6 Hz, 3H), 3.26 (s, 3H), 3.26 - 3.12 (m, 2H), 2.09 - 1.92 (m, 2H), 1.80 - 1.61 (m, 2H).
I-N-267	413.1	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.41 (s, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 3.32 (s, 2H), 3.16 (dt, J = 12.0, 3.3 Hz, 2H), 2.68 (td, J = 11.8, 2.4 Hz, 2H), 2.18 (s, 6H), 1.79 (dd, J = 13.3, 3.6 Hz, 2H), 1.63 (s, 1H), 1.49 - 1.41 (m, 2H).

I-N-268	424.1	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.13 (2H,m), 2.14-2.24 (2H,m), 3.21-3.27 (2H,m), 3.38-3.42 (1H,m), 3.68-3.75 (2H,m), 6.80 (2H,brs), 7.58 (1H,d), 8.48 (1H,d), 8.85 (1H,d), 9.22 (1H,s), 9.33 (1H,s), 9.53-9.55 (1H,m), 9.72 (1H,brs).
I-N-269	367.1	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.36 (s, 1H), 9.33 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.73 (d, J = 5.1 Hz, 1H), 6.74 (s, 2H), 2.38 (d, J = 1.0 Hz, 3H), 2.04 (d, J = 1.0 Hz, 3H).
I-N-270	374.1	2.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.51 (s, 1H), 9.49 (dd, 1H), 8.77 (d, 1H), 8.24 (d, 1H), 6.79 (s, 2H), 3.03 (br t, 4H), 1.80 - 1.76 (m, 4H), 1.669 - 1.65 (m, 2H).
I-N-271	475.1	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.01-2.12 (2H,m), 2.12-2.18 (2H,m), 2.22-2.28 (2H,m), 2.92-3.02 (2H,m), 3.38-3.46 (2H,m), 3.52-3.60 (3H,m), 3.92-3.97 (4H,m), 6.82 (2H,brs), 7.45-7.48 (1H,m), 8.40 (1H,brs), 8.80 (1H,d), 9.45-9.50 (1H,m),9.53- 9.56 (1H,m), 9.83 (1H,s).
I-N-272	459.1	2.38*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.83 (2H, m), 2.02 (2H, m), 3.19 (3H, s), 2.30 (4H, m), 2.89-2.91 (2H, m), 3.25 (2H, m), 3.70 (2H, m), 6.80 (2H, br s), 8.24 (1H, d), 8.71 (1H, d), 9.49 (2H, m) and 10.31 (1H, br s) ppm.
I-N-273	562.1	2.25*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.0-2.2 (10H,m), 2.90-3.05 (3H,m), 3.35-3.42 (2H,m), 3.42-3.53 (3H,m), 3.60-3.68 (1H,m), 3.75-3.79 (2H,m), 4.30-4.33 (1H,m), 8.28 (1H,d), 8.94 (1H,d), 9.50-9.53 (1H,m), 9.66 (1H,s), 10.23 (1H,brs), 10.43 (1H,s).
I-N-274	473.0	2.03*	----------
I-N-275	417.1	1.96*	^{1}H NMR (500 MHz, Methanol-d4) δ1.03 (s, 1H), 9.52 (d, 1H), 9.05 (d, 1H), 8.72 (d, 1H), 8.36 (d, 1H), 3.85-3.91 (m, 4H), 3.35-3.40 (masked , 4H), 2.15 (s, 3H).
I-N-276	443.0	2.24*	----------
I-N-277	443.1	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.60 (dd, J = 12.1, 2.7 Hz, 1H), 3.75 (d, J = 8.1 Hz, 1H), 3.15 - 3.06 (m, 2H), 3.05 - 2.89 (m, 3H), 2.33 - 2.26 (m, 2H), 1.93 (dt, J = 13.5, 4.7 Hz, 1H), 1.75 (p, J = 4.1 Hz, 2H), 1.51 - 1.40 (m, 1H).

I-N-278	459.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.53-9.55 (d, 1H), 9.48-9.49 (dd, 1H), 8.88 (d, 1H), 8.29 (d, 1H), 6.80 (s, 2H), 4.71-4.76 (m, 4H), 4.17-4.23 (m, 1H), 3.75(m, 2H), 3.741-3.43 (m, 2H), 3.05-3.07 (m, 2H).
I-N-279	443.1	2.09*	^{1}H NMR (500 MHz, DMSO) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 2.7 Hz, 1H), 6.84 - 6.74 (m, 2H), 4.63 - 4.56 (m, 1H), 3.74 (d, J = 11.3 Hz, 1H), 3.15 - 3.06 (m, 2H), 3.05 - 2.89 (m, 3H), 2.29 (dd, J = 9.7, 4.8 Hz, 2H), 1.93 (dt, J = 13.5, 4.6 Hz, 1H), 1.75 (dq, J = 10.2, 4.4 Hz, 2H), 1.51 - 1.40 (m, 1H).
I-N-280	443.1	2.1*	^{1}H NMR (500 MHz, DMSO) δ 10.38 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 2.7 Hz, 1H), 6.78 (s, 2H), 4.63 - 4.56 (m, 1H), 3.75 (q, J = 8.5 Hz, 1H), 3.17 - 3.06 (m, 2H), 3.06 - 2.89 (m, 3H), 2.29 (t, J = 7.3 Hz, 2H), 1.93 (dq, J = 13.4, 4.5, 4.0 Hz, 1H), 1.81 - 1.71 (m, 2H), 1.45 (dtd, J = 14.2, 9.5, 4.7 Hz, 1H).
I-N-281	376.0	2.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.28 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.35 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.41 (s, 1H), 3.52 - 3.45 (m, 4H), 2.12 - 2.04 (m, 4H).
I-N-282	400.0	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (d, J = 1.1 Hz, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.39 (dd, J = 6.6, 1.0 Hz, 1H), 7.48 (d, J = 6.5 Hz, 1H), 6.78 (s, 2H), 3.65 (dt, J = 13.2, 3.4 Hz, 2H), 3.30 (d, J = 13.4 Hz, 6H), 2.98 (td, J = 12.5, 2.5 Hz, 2H), 1.91 - 1.67 (m, 3H), 1.66 - 1.46 (m, 2H).
I-N-283	353.1	1.75*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (d, J = 0.6 Hz, 1H), 9.58 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.80 (d, J = 1.1 Hz, 1H), 7.50 (dd, J = 5.0, 0.6 Hz, 1H), 7.08 (t, J = 1.1 Hz, 1H), 6.70 (s, 2H), 2.01 (d, J = 1.1 Hz, 3H).
I-N-284	392.1	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.48-9.49 (m, 1H), 9.19 (s, 1H), 8.78 (d, 1H), 8.36 (s, 1H), 6.80 (s, 2H), 4.45-4.48 (m, 1H), 3.78-3.80 (m, 1H), 3.70-3.73 (m, 1H), 3.41-3.45 (m, 1H), 3.35-3.37 (m, 1H), 2.10-2.15 (m, 1H), 1.88-1.93 (m, 1H).
I-N-285	401.0	2.4*	----------
I-N-286	431.1	2.25*	----------
I-N-287	454.0	2.11*	----------

I-N-288	440.3	2.16*	----------
I-N-289	500.0	2.2*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.50-1.60 (1H, m), 1.75-1.95 (2H, m), 2.01-2.12 (2H, m), 2.70-2.90 (5H, m), 3.00-3.15 (5H, m), 3.20-3.45 (2H, m), 3.85-3.97 (2H, m), 4.40-4.45 (1H, m), 6.85-6.93 (2H, br s), 8.28 (1H, d), 8.94 (1H, d), 9.51-9.53 (2H, dd), 9.60-9.70 (1H, s), 10.30-10.33 (1H, s).
I-N-290	427.0	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.52-9.54 (dd, 1H), 9.09 (d, 1H), 8.94 (dd, 1H), 8.36-8.38 (dd, 1H), 6.77 (s, 2H), 3.74-3.77 (m, 2H), 3.11-3.18 (m, 1H), 2.90-3.05 (m, 2H), 2.71 (s, 3H), 2.55 (s, 3H), 1.95-1.98 (m, 1H), 1.77-1.79 (m, 2H), 1.46-1.51 (m, 1H).
I-G-1	482.3	0.63	^{1}H NMR (500 MHz, MeOD) δ 9.52 (d, J = 1.2 Hz, 1H), 9.06 (dd, J = 4.3, 2.5 Hz, 1H), 8.88 (dd, J = 2.6, 0.5 Hz, 1H), 8.34 (dd, J = 6.6, 1.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 4.77 (s, 2H), 4.36 (s, 2H), 3.78 (dm, J = 13.0 Hz, 2H), 3.57 (s, 2H), 3.22 - 3.01 (m, 5H), 2.95 (s, 3H), 2.20 (dm, J = 12.2 Hz, 2H), 1.91 (dm, 2H).
I-G-2	427.2	0.65	^{1}H NMR (500 MHz, MeOD) δ 9.60 (s, 1H), 9.02 (dd, J = 2.6, 0.6 Hz, 1H), 9.00 (dd, J = 4.3, 2.5 Hz, 1H), 8.21 (d, J = 5.4 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 3.29 (dt, J = 11.6, 2.6 Hz, 2H), 3.20 (s, 3H), 3.03 (s, 3H), 2.95 (tt, J = 11.7, 3.8 Hz, 1H), 2.87 (td, J = 12.1, 2.3 Hz, 2H), 2.25 (qd, 2H), 1.87 (dm, 2H).
I-G-3	516.2	0.77	^{1}H NMR (500 MHz, MeOD) δ 10.65 (s, 1H), 9.81 (d, J = 1.3 Hz, 1H), 9.21 (dd, J = 2.6, 0.8 Hz, 1H), 9.04 (dd, J = 4.3, 2.6 Hz, 1H), 8.30 (s, 1H), 4.57 - 4.28 (m, 2H), 3.75 - 3.65 (m, 2H), 3.69 - 3.45 (m, 4H), 3.25 - 3.07 (m, 4H), 3.03 (dt, J = 12.2, 3.6 Hz, 1H), 3.00 (s, 3H), 2.40 - 2.23 (m, 2H), 1.91 (dm, J = 12.7 Hz, 2H).
I-G-4	500.2	0.72	^{1}H NMR (500 MHz, MeOD) δ 10.67 (s, 1H), 9.69 (d, J = 0.6 Hz, 1H), 9.20 (dd, J = 2.7, 0.6 Hz, 1H), 9.01 (dd, J = 4.3, 2.6 Hz, 1H), 8.16 (d, J = 3.0 Hz, 1H), 7.58 (d, J = 2.8 Hz, 1H), 3.74 (t, J = 5.1 Hz, 2H), 3.72 - 3.65 (m, 2H), 3.34 - 3.28 (m, 2H), 3.18 (tt, J = 12.0, 2.4 Hz, 2H), 3.06 - 2.95 (m, 1H), 2.60 - 2.45 (m, 4H), 2.38 (s, 3H), 2.36 - 2.25 (m, 2H), 1.91 - 1.79 (m, 2H).

I-G-5	516.2	2.34*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.66 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.32 - 8.24 (m, 1H), 6.85 (s, 2H), 4.47 (dd, J = 115.4, 12.9 Hz, 2H), 3.48 (d, J = 10.4 Hz, 2H), 3.40 (t, J = 13.5 Hz, 1H), 3.20 (d, J = 10.8 Hz, 2H), 3.10 - 2.94 (m, 6H), 2.85 (d, J = 2.9 Hz, 3H), 2.12 (dd, J = 43.1, 13.1 Hz, 2H), 1.84 - 1.73 (m, 2H).
I-G-6	514.2	2.28*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7-1.8 (2H,m), 2.1-2.25 (4H,m), 2.85-3.0 (4H,m), 3.05-3.12 (3H,m), 3.2-3.3 (3H,m), 3.4-3.55 (3H,m), 3.6-3.75 (2H,m), 4.05-4.15 (1H,m), 6.8 (2H,brs), 8.28 (1H,d), 9.25 (1H,d), 9.5-9.6 (2H,m), 9.7 (1H,d), 10.63-10.66 (1H,m).
I-G-7	526.2	2.21*	^{1}H NMR (500 MHz, DMSO-d6, 370 K) δ 10.50 (s, 1H), 9.62 (s, 1H), 9.27 (dd, J = 4.7, 2.4 Hz, 1H), 8.19 (d, J = 2.7 Hz, 1H), 6.53 (s, 2H), 3.78 - 3.67 (m, 2H), 3.22 (tm, J = 11.6 Hz, 2H), 3.09 (dm, 2H), 3.02 - 2.83 (m, 8H), 2.29 - 2.14 (m, 3H), 1.96 - 1.84 (m, 2H), 1.83 - 1.64 (m, 2H).
I-G-8	457.1	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7-1.75 (2H,m), 2.05-2.15 (2H,m), 2.2-2.28 (2H,m), 2.4-2.5 (1H,m), 3.03-3.18 (4H,m), 3.95 (2H,t), 4.25 (2H,t), 8.28 (1H,d), 9.38 (1H,d), 9.47-9.50 (1H,m), 9.7 (1H,s), 10.65 (1H,s).
I-G-9	514.0	2.40*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.23 (3H,t), 1.75-1.81 (2H,m), 2.05-2.20 (2H,m), 2.97-3.1 (5H,m), 3.15-3.25 (4H,m), 3.4-3.57 (3H,m), 4.35-4.4 (1H,m), 4.6-4.65 (1H,m), 8.28 (1H,d), 9.18 (1H,d), 9.48-9.56 (2H,m), 9.68 (1H,s), 10.65 (1H,s).
I-G-10	526.2	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.5-1.6 (1H,m), 1.70-1.81 (3H,m), 1.90-2.25 (5H,m), 2.90-3.1 (4H,m), 3.18-3.37 (4H,m), 3.4-3.5 (1H,m), 3.6-3.9 (3H,m), 3.9-4.0 (1H,m), 6.6-6.85 (2H,m), 8.26 (1H,d), 9.1-9.2 (1H,m), 9.47-9.51 (2H,m), 9.68 (1H,s), 10.1 (1H,brs), 10.67 (1H,s).
I-G-11	514.2	2.30*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.78-1.84 (2H,m), 2.00-2.18 (4H,m), 2.28-2.4 (2H,m), 2.45-2.55 (1H,m), 2.70-2.80 (1H,m), 2.80-2.90 (6H,m), 3.05-3.12 (2H,m), 3.12-3.22 (3H,m), 4.35-4.4 (1H,m), 4.6-4.65 (1H,m), 6.78 (2H,brs), 8.28 (1H,d), 9.35 (1H,d), 9.48-9.50 (1H,m), 9.70 (1H,s), 9.75-9.85 (1H,m), 10.67-10.69 (1H,m).
I-G-12	486.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.80 (2H,m), 2.08-2.15 (2H,m), 2.92-3.00 (1H,m), 3.05-3.25 (8H,m), 3.72-3.78 (2H,m), 3.80-3.85 (2H,m), 6.79 (2H,brs), 8.23 (1H,d), 8.72 (2H,brs), 9.15 (1H,d), 9.48 (1H,d), 9.65 (1H,s), 10.63 (1H,s).

I-G-13	526.1	2.62*	^{1}H NMR (500 MHz, CDCl3) δ 0.57 (4H, br s), 1.82-1.85 (2H, d), 2.03 (21H, s), 2.33-2.35 (2H, m), 2.60-2.85 (4H, m), 3.13-3.15 (2H, m), 3.24-3.29 (2H, m), 3.70 (4H, br s), 5.84 (2H, s), 8.20 (2H, d), 8.48-8.49 (1H, d), 9.34 (1H, d), 9.80 (1H, s), 10.6 (1H, s).
I-G-14	498.4	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.68 (s, 1H), 9.47-9.48 (dd, 1H), 9.35 (dd, 1H), 8.25-8.26 (d, 1H), 6.79 (s, 2H), 4.69 (s, 4H), 4.41 (s, 2H), 4.10 (s, 2H), 3.10-3.13 (m, 2H), 3.02-3.05 (m, 2H), 2.45-2.50 (m, 2H), 2.04-2.08 (m, 2H), 1.72- 1.75 (m, 2H).
I-G-15	528.2	2.43*	----------
I-G-16	516.3	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.95 (3H,m), 2.10-2.25 (2H,m), 2.78-2.85 (5H,m), 2.90-3.00 (1H,m), 3.02-3.15 (5H,m), 3.17-3.26 (2H,m), 3.43-3.52 (2H,m), 8.27-8.29 (1H,m), 9.22 (1H,s), 9.27 (1H,d), 9.48-9.53 (1H,m), 9.68-9.71 (1H,m), 10.64-10.68 (1H,s).
I-G-18	526.2	2.30*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.90 (2H,m), 2.10-2.22 (2H,m), 2.70-2.82 (1H,m), 2.85-2.93 (4H,m), 2.96-3.12 (3H,m), 3.12-3.22 (2H,m), 3.23-3.35 (2H,m), 3.40-3.55 (2H,m), 3.59-3.75 (2H,m), 3.78-3.90 (2H,m), 6.75-6.90 (1H,m), 8.28 (1H,d), 9.37 (1H,d), 9.48-9.53 (1H,m), 9.69 (1H,s), 9.74-9.88 (1H,m), 10.66 (1H,s).
I-G-19	473.2	2.78*	----------
I-G-20	514.2	2.14*	----------
I-G-21	487.1	2.31*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.68-1.75 (2H, m), 2.01-2.14 (2H, m), 2.35-2.40 (1H, masked), 3.05-3.15 (4H, m), 3.24 (3H, s), 3.71-3.74 (1H, m), 4.05-4.12 (2H, m), 4.22-4.24 (1H, m), 4.41-4.44 (1H, m), 6.70-7.00 (2H, br s), 8.29 (1H, d), 9.36 (1H, dd), 9.47-9.49 (1H, dd), 9.67 (1H, s), 10.62 (1H, s).
I-G-22	500.2	2.23*	----------
I-G-23	486.1	2.04*	----------
I-G-24	500.2	2.14*	----------
I-G-25	525.2	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.22-2.25 (2H, m), 2.35-2.50 (6H, masked), 2.87 (3H, s), 3.05-3.25 (4H, m), 3.30-3.35 (2H, m),4.70-4.80 (2H, m), 6.77-6.92 (2H, br s), 8.32 (1H, d), 8.69 (1H, dd), 9.51-9.53 (1H, dd), 9.64 (1H, s), 9.80-9.95 (1H, br s), 10.37 (1H, s).

I-G-26	502.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.77-1.83 (4H, m), 2.10-2.18 (2H, m), 2.36-2.42 (1H, m), 2.78-2.80 (6H, m), 3.05-3.09 (6H, m), 3.18-3.22 (2H, m), 6.80 (2H, br s), 8.16-8.18 (1H, m), 8.27 (1H, d), 9.34-9.36 (2H, m), 9.49-9.50 (1H, d), 9.67 (1H, s), 10.62 (1H, s).
I-G-27	514.2	2.19*	----------
I-G-28	512.2	2.2*	----------
I-G-29	445.0	2.37*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.74-1.77 (2H, m), 2.05-2.15 (2H, m), 2.88-2.91 (4H, m), 3.03-3.05 (2H, m), 3.11 (3H, s), 3.15-3.22 (2H, m), 6.79 (1H, s), 8.25 (1H, d), 9.34 (1H, dd), 9.47-9.49 (1H, dd), 9.68 (1H, s), 10.66 (1H, s).
I-G-30	489.2	2.12*	----------
I-G-31	502.1	2.33*	----------
I-G-32	542.3	2.14*	^{1}H NMR (500 MHz, methanol-d4) δ 1.87 (2H, m), 2.27-2.33 (2H, m), 2.55 (4H, m), 2.97-3.03 (1H, m), 3.18 (2H, m), 3.70-3.85 (4H, m), 4.67-4.70 (2H, m), 4.75-4.78 (2H, m), 8.16 (1H, d), 9.00 (1H, dd), 9.17 (1H, dd), 9.68 (1H, s), 10.65 (1H, s).
I-G-33	432.1	2.07*	----------
I-G-34	486.1	2.07*	----------
I-G-35	540.2	2.74*	----------
I-G-36	487.0	2.34*	----------
I-G-37	473.1	2.04*	----------
I-G-38	526.2	2.39*	----------
I-G-40	489.2	2.45*	----------
I-G-41	473.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.87 (2H, m), 2.25 (2H, m), 2.61 (1H, m), 3.84 (1H, m), 4.10 (1H, m), 4.28 (1H, m), 4.55 (1H, m), 4.62 (1H, m), 4.80 (3H, masked), 8.32 (1H, d), 9.05 (1H, dd), 9.24 (1H, d), 9.69 (1H, s), 10.56 (1H, s).
I-G-42	500.2	2.11*	----------
I-G-43	526.0	2.43*	----------

I-G-44	512.0	2.18*	----------
I-G-45	500.0	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.14-1.17 (3H, m), 1.83-1.86 (2H, m), 2.22-2.34 (2H, m), 2.37-2.45 (1H, m), 2.75-2.88 (3H, m), 2.92-3.12 (2H, m), 3.11-3.20 (3H, m), 3.28-3.335 (1H, masked), 4.01-4.08 (1H, m), 4.46-4.54 (1H, m), 8.14 (1H, s), 8.99-9.00 (1H, m), 9.19 (1H, m), 9.67 (1H, s).
I-G-46	512.1	2.15*	----------
I-G-47	514.2	2.37*	----------
I-G-48	504.1	2.15*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.81 (s, 1H), 9.46 (dd, J = 4.7, 2.5 Hz, 1H), 9.35 (s, 1H), 8.24 (s, 1H), 6.79 (s, 2H), 3.58 - 3.44 (m, 6H), 2.95 - 2.84 (m, 3H), 2.68 (dt, J = 22.8, 4.7 Hz, 4H), 2.40 (s, 1H), 2.21 - 2.11 (m, 2H), 1.77 - 1.70 (m, 2H).
I-G-49	512.1	2.29*	----------
I-G-50	514.2	2.38*	----------
I-G-51	512.1	2.03*	----------
I-G-52	526.2	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72-1.76 (1H, m), 1.83-1.85 (1H, m), 1.92-1.98 (3H, m), 2.05-2.12 (2H, m), 2.15-2.25 (1H, m), 2.80 (3H, s), 2.89 (1H, m), 3.05-3.25 (7H, m), 3.45-3.47 (2H, m), 4.78-4.80 (2H, m), 6.82 (2H, br s), 8.27 (1H, d), 9.27 (1H, d), 9.49-9.51 (1H, dd), 9.68 (1H, s), 10.65 (1H, s).
I-G-53	512.1	2.18*	----------
I-G-54	514.2	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.81 (s, 1H), 9.53 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 6.81 (s, 2H), 4.50 (d, J = 14.0 Hz, 2H), 3.46 (d, J = 11.7 Hz, 2H), 3.28 - 3.10 (m, 4H), 3.10 - 2.89 (m, 4H), 2.83 (s, 3H), 2.30 (ddd, J = 13.1, 8.9, 3.4 Hz, 2H), 1.86 - 1.67 (m, 2H), 1.40 (s, 3H).
I-G-55	496.2	2.17*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.67 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 9.25 (s, 1H), 8.04 (s, 1H), 6.78 (s, 2H), 3.64 (d, J = 37.4 Hz, 4H), 3.16 - 3.07 (m, 1H), 3.01 - 2.87 (m, 3H), 2.70 - 2.56 (m, 5H), 2.41 (s, 6H), 2.23 - 2.09 (m, 2H), 1.77 - 1.67 (m, 2H), 1.19 (t, J = 7.3 Hz, 1H).

I-G-56	482.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.73 (s, 1H), 9.50 (dd, J = 4.8, 2.6 Hz, 1H), 9.38 - 9.30 (m, 1H), 8.08 (d, J = 0.8 Hz, 1H), 6.83 (s, 2H), 3.61 (dt, J = 26.1, 5.2 Hz, 4H), 2.97 (tt, J = 11.8, 3.6 Hz, 3H), 2.85 (dt, J = 23.8, 5.0 Hz, 4H), 2.46 (s, 5H), 2.28 - 2.15 (m, 2H), 1.77 (dd, J = 12.2, 3.4 Hz, 2H).
I-G-57	540.0	2.69*	----------
I-G-58	540.0	2.57*	----------
I-G-59	554.0	2.45*	----------
I-G-60	568.0	2.58*	----------
I-G-61	500.2	2.14*	----------
I-G-62	498.0	2.17*	----------
I-G-63	487.0	2.17*	----------
I-G-64	554.0	2.75*	----------
I-G-65	512.0	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 0.64-0.78 (2H, m), 1.75-1.88 (2H, m), 2.05-2.24 (3H, m), 2.34-2.35 (3H, m), 2.50-2.55 (1H, masked), 2.61-2.63 (1H, m), 2.71-2.74 (1H, m), 3.05-3.20 (6H, m), 4.07-4.09 (1H, m), 6.79 (2H, s), 8.26 (1H, d), 9.45 (1H, d), 9.48 (1H, dd), 9.69 (1H, s), 10.68 (1H, s).
I-G-66	542.1	2.41*	^{1}H NMR (500 MHz, DMSO) δ 10.71 (d, J = 19.7 Hz, 1H), 9.82 (d, J = 12.7 Hz, 1H), 9.47 (dt, J = 4.7, 2.9 Hz, 1H), 9.31 (s, 1H), 8.24 (d, J = 1.0 Hz, 1H), 6.80 (s, 2H), 4.54 - 4.23 (m, 1H), 3.73 (dt, J = 31.9, 5.7 Hz, 2H), 3.59 - 3.50 (m, 2H), 2.96 - 2.79 (m, 9H), 2.20 (dd, J = 26.6, 13.3 Hz, 2H), 1.87 (d, J = 13.8 Hz, 3H), 1.76 (d, J = 12.7 Hz, 2H), 1.65 (tt, J = 10.1, 4.8 Hz, 1H).
I-G-67	474.4	2.42*	----------
I-G-68	542.0	2.42*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.05-1.25 (2H, m), 1.71-1.78 (2H, m), 1.95-1.98 (2H, m), 2.05-2.25 (3H, m), 2.340-2.45 (2H, masked), 2.60 (1H, m), 2.95-3.10 (4H, m), 3.15-3.22 (2H, m), 3.35-3.40 (1H, m), 4.04-4.08 (2H, m), 4.15-4.27 (3H, m), 4.52-4.55 (1H, m), 6.80 (2H, br s), 8.27 (1H, d), 9.22 (1H, dd), 9.48-9.50 (1H, dd), 9.67 (1H, s), 9.90-10.00 (1H, s), 10.62 (1H, s).

I-G-69	528.1	2.30*	^{1}H NMR (500 MHz, DMSO) δ 10.54 (s, 1H), 9.75 (s, 1H), 9.33 - 9.28 (m, 2H), 8.22 (s, 1H), 6.58 (s, 2H), 3.55 (t, J = 11.6 Hz, 2H), 2.26 - 2.11 (m, 4H), 3.01 - 2.93 (m, 3H), 2.80 (s, 2H), 2.47 (d, J = 11.4 Hz, 2H), 1.96 (s, 1H), 1.77 (d, J = 13.6 Hz, 3H), 2.39 - 2.34 (m, 1H), 2.68 - 2.60 (m, 2H).
I-G-70	512.0	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.70-1.80 (2H, m), 1.81-1.97 (2H, m), 2.05-2.15 (2H, m), 2.40-2.50 (2H, masked), 2.55-2.60 (1H, m), 2.78-2.83 (2H, m), 2.85-3.05 (2H, m), 3.10-3.20 (2H, m), 3.72-3.74 (1H, m), 3.96-3.98 (1H, m), 4.51 (1H, m), 5.05 (1H, m), 6.79 (2H, s), 8.25 (1H, m), 9.31 (1H, d), 9.35 (1H, d), 9.45 (1H, m), 9.67 (1H, d), 10.60 (1H, d).
I-G-71	512.0	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.70-1.80 (2H, m), 1.81-1.97 (2H, m), 2.05-2.15 (2H, m), 2.40-2.50 (1H, masked), 2.55-2.60 (1H, m), 2.78-2.83 (2H, m), 2.85-3.05 (2H, m), 3.72-3.74 (1H, m), 3.96-3.98 (1H, m), 4.51 (1H, m), 5.05 (1H, m), 6.79 (2H, s), 8.25 (1H, m), 9.31 (1H, d), 9.35 (1H, d), 9.45 (1H, m), 9.67 (1H, d), 10.60 (1H, d).
I-G-72	499.1	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.68 (s, 1H), 9.47-9.48 (dd, 1H), 9.35 (dd, 1H), 8.25-8.26 (d, 1H), 6.79 (s, 2H), 4.69 (s, 4H), 4.41 (s, 2H), 4.10 (s, 2H), 3.10-3.13 (m, 2H), 3.02-3.05 (m, 2H), 2.45-2.50 (m, 2H), 2.04-2.08 (m, 2H), 1.72- 1.75 (m, 2H).
I-G-73	493.0	2.63*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.67 (s, 1H), 9.48-9.50 (dd, 1H), 9.27 (dd, 1H), 8.28 (d, 1H), 6.80 (be s, 2H), 4.76 (m, 2H), 4.38 (m, 2H), 3.14 (m, 2H), 3.08-3.11 (m, 2H), 2.55-2.60 (m, 1H), 2.03-2.15 (m, 2H), 1.82-1.84 (m, 2H).
I-G-74	475.1	2.42*	----------
I-G-75	501.0	2.5*	----------
I-G-76	482.1	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.61 (s, 1H), 9.67 (s, 1H), 9.48-9.50 (dd, 1H), 9.30 (dd, 1H), 8.28 (d, 1H), 6.80 (br s, 2H), 4.55-4.56 (m, 1H), 4.46-4.49 (m, 1H), 4.21-4.25 (m, 1H),4.07-4.11 (m, 1H), 3.81-3.85 (m, 1H), 3.05-3.17 (m, 4H), 2.50-2.55 (masked, 1H), 2.03-2.09 (m, 2H), 1.75-1.81 (m, 2H).

I-G-77	439.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.45 (d, J = 1.0 Hz, 1H), 9.02 (dd, J = 2.6, 0.6 Hz, 1H), 8.44 (dd, J = 6.5, 1.1 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.21 (t, J = 7.6 Hz, 2H), 3.89 (t, J = 7.7 Hz, 2H), 3.58 (dt, J = 12.3, 3.2 Hz, 2H), 3.02 (td, J = 12.5, 2.5 Hz, 2H), 2.59 - 2.52 (m, 1H), 2.26 - 2.16 (m, 2H), 2.06 - 1.94 (m, 2H), 1.80 - 1.72 (m, 2H).
I-G-78	469.1	1.99*	----------
I-G-79	483.0	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (d, J = 1.0 Hz, 1H), 9.00 (dd, J = 2.5, 0.6 Hz, 1H), 8.46 (dd, J = 6.5, 1.1 Hz, 1H), 7.58 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.17 - 4.11 (m, 1H), 4.00 (dd, J = 8.8, 1.2 Hz, 1H), 3.80 (d, J = 9.9 Hz, 1H), 3.68 (dd, J = 10.0, 1.2 Hz, 1H), 3.60 (dt, J = 12.5, 3.3 Hz, 2H), 3.18 (s, 3H), 3.06 - 2.98 (m, 2H), 2.57 (ddt, J = 11.7, 8.3, 4.2 Hz, 1H), 2.06 - 1.94 (m, 2H), 1.83 - 1.75 (m, 2H), 1.42 (s, 3H).
I-G-80	475.1	2.24*	----------
I-G-81	464.1	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 9.44 (d, J = 1.0 Hz, 1H), 8.96 (dd, J = 2.5, 0.5 Hz, 1H), 8.46 (dd, J = 6.5, 1.1 Hz, 1H), 7.57 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.55 - 4.41 (m, 2H), 4.19 (t, J = 9.4 Hz, 1H), 4.05 (dd, J = 9.6, 6.1 Hz, 1H), 3.81 (tt, J = 9.1, 6.1 Hz, 1H), 3.64 - 3.56 (m, 2H), 3.02 (td, J = 12.4, 2.6 Hz, 2H), 2.61 - 2.52 (m, 1H), 2.04 - 1.90 (m, 2H), 1.80 (dd, J = 30.8, 12.9 Hz, 2H).
I-G-82	457.1	2.04*	----------
I-G-83	453.1	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (d, J = 1.5 Hz, 1H), 9.53 (ddd, J = 4.9, 2.6, 1.0 Hz, 1H), 9.46 (dd, J = 2.5, 1.1 Hz, 1H), 9.06 - 9.01 (m, 1H), 8.46 (ddd, J = 6.4, 2.5, 1.1 Hz, 1H), 7.57 (dd, J = 6.6, 1.7 Hz, 1H), 6.80 (s, 2H), 3.62 (dt, J = 12.8, 3.2 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 3.05 (td, J = 12.5, 2.4 Hz, 2H), 2.77 (tt, J = 11.5, 3.9 Hz, 1H), 2.05 (qd, J = 12.7, 3.9 Hz, 2H), 1.96 - 1.86 (m, 2H), 1.85 - 1.75 (m, 4H).
I-G-84	495.1	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.84 (q, J = 1.7 Hz, 1H), 9.54 (ddd, J = 4.7, 2.6, 2.0 Hz, 1H), 9.45 (q, J = 1.6 Hz, 1H), 9.06 - 8.96 (m, 1H), 8.46 (ddd, J = 6.5, 2.6, 1.2 Hz, 1H), 7.61 - 7.52 (m, 1H), 6.80 (s, 2H), 4.55 (d, J = 6.1 Hz, 1H), 4.52 - 4.34 (m, 2H), 3.82 (s, 1H), 3.71 - 3.24 (m, 6H), 3.11 - 2.99 (m, 2H), 2.76 (dddd, J = 21.0, 17.3, 12.3, 6.9 Hz, 1H), 2.21 (t, J = 6.9 Hz, 1H), 2.13 - 1.97 (m, 3H), 1.82 (td, J = 13.2, 6.7 Hz, 2H).

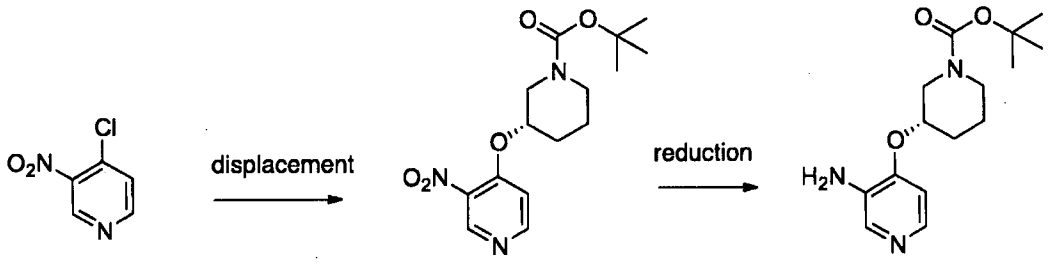
I-G-85	469.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.41 (d, J = 1.1 Hz, 1H), 8.97 - 8.90 (m, 1H), 8.45 (dd, J = 6.6, 1.1 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 6.80 (s, 2H), 3.68 - 3.54 (m, 8H), 3.50 (t, J = 4.5 Hz, 2H), 3.16 - 2.94 (m, 3H), 2.07 - 1.96 (m, 2H), 1.81 - 1.71 (m, 2H).
I-G-86	535.0	2.12*	----------
I-G-87	542.0	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 11.28 (1H, brs), 10.56 (0.4H, s), 10.52 (0.6H, s), 9.66 0.4H, s), 9.63 (0.6H, s), 9.44 (1H, d), 9.22 (0.4H, d), 8.99 (0.6H, d), 8.38 (1H, dd), 4.72 (0.6H, brs), 4.58 (0.4H, brs), 3.96 – 3.99 (2H, m), 3.20 – 3.40 (8H, m), 3.11 – 3.12 (2H, m), 1.98 – 2.15 (7H, m), 1.77 – 1.80 (2H, m).
I-G-88	481.1	1.86*	----------
I-G-89	517.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.16 (s, 1H), 9.64 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 9.06 (dd, J = 2.5, 0.6 Hz, 1H), 8.23 (d, J = 5.2 Hz, 1H), 7.21 (dd, J = 5.2, 0.6 Hz, 1H), 6.77 (s, 2H), 4.59 - 4.52 (m, 1H), 4.43 (dd, J = 9.5, 4.9 Hz, 1H), 4.31 (tt, J = 8.4, 5.0 Hz, 1H), 4.20 (dd, J = 10.4, 8.5 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.14 - 3.08 (m, 2H), 3.07 (s, 3H), 2.75 (tdd, J = 11.9, 6.5, 2.4 Hz, 2H), 2.48 (dt, J = 11.8, 4.0 Hz, 1H), 2.14 - 2.00 (m, 2H), 1.76 (dt, J = 12.5, 3.0 Hz, 2H).
I-G-90	481.1	1.96*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 9.44 (d, J = 1.1 Hz, 1H), 8.98 (d, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.5, 1.1 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.49 - 4.38 (m, 3H), 4.33 (dd, J = 10.0, 1.7 Hz, 1H), 4.14 (dd, J = 11.3, 1.7 Hz, 1H), 3.96 (dd, J = 11.2, 1.7 Hz, 1H), 3.61 - 3.54 (m, 2H), 3.01 (tt, J = 12.5, 3.2 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.59 - 2.52 (m, 1H), 1.97 (qq, J = 12.5, 4.8, 4.3 Hz, 2H), 1.81 - 1.73 (m, 2H).
I-G-91	483.1	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (d, J = 0.9 Hz, 1H), 9.04 - 8.98 (m, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.54 (d, J = 6.4 Hz, 1H), 6.80 (s, 2H), 4.40 (ddd, J = 9.1, 6.5, 1.3 Hz, 1H), 4.30 (tt, J = 6.5, 4.0 Hz, 1H), 4.11 - 3.99 (m, 2H), 3.70 - 3.66 (m, 1H), 3.56 (d, J = 12.5 Hz, 2H), 3.43 (qd, J = 7.0, 2.3 Hz, 2H), 3.05 - 2.96 (m, 2H), 2.61 - 2.52 (m, 1H), 1.99 (qt, J = 12.6, 3.5 Hz, 2H), 1.79 (q, J = 12.8, 11.8 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H).

I-G-92	556.0	2.37*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.67 (s, 1H), 9.49-9.50 (dd, 1H), 9.19 (d, 1H), 8.28 (d, 1H), 6.81 (s, 2H), 4.30-4.90 (m, 7H), 2.98-3.21 (m, 10H), 2.15-2.20 (m, 2H), 1.78-1.80 (m, 2H), 1.58 (m, 3H).
I-G-93	483.1	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 - 9.83 (m, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (dd, J = 2.2, 1.1 Hz, 1H), 9.02 (t, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.4, 1.1 Hz, 1H), 7.56 (dd, J = 6.5, 1.6 Hz, 1H), 6.79 (s, 2H), 3.99 (dtt, J = 37.7, 4.6, 2.3 Hz, 1H), 3.71 - 3.43 (m, 5H), 3.41 - 3.27 (m, 1H), 3.25 (d, J = 11.0 Hz, 3H), 3.05 (tq, J = 12.4, 2.5 Hz, 2H), 2.78 (qt, J = 11.6, 3.9 Hz, 1H), 2.12 - 1.76 (m, 6H).
I-G-94	483.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.87 (d, J = 1.5 Hz, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 9.46 (dd, J = 2.2, 1.0 Hz, 1H), 9.02 (t, J = 2.7 Hz, 1H), 8.44 (dd, J = 6.4, 1.0 Hz, 1H), 7.55 (dd, J = 6.5, 1.6 Hz, 1H), 6.80 (s, 2H), 3.99 (dtt, J = 37.8, 4.5, 2.3 Hz, 1H), 3.71 - 3.43 (m, 5H), 3.40 - 3.27 (m, 1H), 3.25 (d, J = 10.9 Hz, 3H), 3.03 (dddd, J = 12.9, 8.3, 3.9, 2.3 Hz, 2H), 2.77 (qt, J = 11.0, 3.7 Hz, 1H), 2.12 - 1.86 (m, 4H), 1.80 (dt, J = 13.6, 6.9 Hz, 2H).
I-G-95	516.1	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.48 (s, 1H), 10.64 (s, 1H), 9.68 (s, 1H), 9.50 (dd, 1H), 9.17 (dd, 1H), 8.28 (d, 1H), 6.81 (s, 2H), 4.54 (d, 1H), 4.31 (d, 1H), 3.79 - 3.69 (m, 5H), 3.53 (s, 3H), 3.36 - 3.30 (m, 1H), 3.24 - 3.18 (m, 2H), 3.09 - 3.01 (m, 3H), 2.21 - 2.07 (m, 2H), 1.79 (br d, 2H).
I-G-96	555.2	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.67 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.29 - 9.18 (m, 1H), 8.26 (d, J = 2.4 Hz, 1H), 6.79 (s, 2H), 3.65 - 3.50 (m, 4H), 3.38 (s, 1H), 3.19 (t, J = 11.7 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 11.7 Hz, 1H), 2.82 (d, J = 31.4 Hz, 3H), 2.65 (p, J = 1.9 Hz, 1H), 2.55 (s, 1H), 2.37 (p, J = 1.9 Hz, 1H), 2.30 - 2.19 (m, 7H), 2.18 - 2.06 (m, 2H), 1.78 - 1.69 (m, 2H), 1.25 (s, 2H).
I-G-98	501.0	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s,1H), 9.67 (s, 1H), 9.47-9.49 (dd, 1H), 9.38 (dd, 1H), 8.28 (d, 1H), 6.80 (s, 2H), 4.27-4.30 (m, 1H),3.93-3.97 (m, 2H), 3.61-3.64 (m, 1H), 3.49-3.51 (m, 2H), 3.30 (s, 3H), 3.15-3.16 (m, 2H), 3.10-3.11 (m, 2H), 2.80-2.83 (m, 1H), 2.35-2.40 (masked, 1H), 2.00-2.10 (m, 2H), 1.70-1.80 (m, 2H).
I-G-99	501.1	2.45*	----------

Retention times measured using HPLC Method B, described in the Experimental Methods and Materials section, above., are designated by (*). For all other compounds, the retention time was measured using the HPLC Method A.

Preparation O-1: (*S*)-*tert*-butyl 3-((3-aminopyridin-4-yl)oxy)piperidine-1-carboxylate

Scheme 7



Step 1: tert-butyl (3S)-3-[(3-nitro-4-pyridyl)oxy]piperidine-1-carboxylate

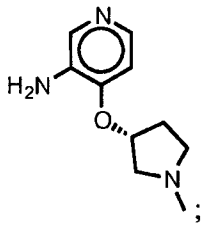
[00468] Sodium hydride (492.0 mg, 12.30 mmol) was added to a solution of tert-butyl (3S)-3-hydroxypiperidine-1-carboxylate (2.095 g, 10.41 mmol) in THF (20 mL) and the reaction stirred at 0°C for 15 minutes. A suspension of 4-chloro-3-nitro-pyridine (1.5 g, 9.461 mmol) in THF (10 mL) was added and the reaction allowed to warm slowly to ambient temperature over 2 hours. The reaction was quenched with water and the mixture was partitioned between EtOAc and brine. The combined organic extract was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO Companion, 80 g column, eluting with 0 to 100% EtOAc/Petroleum Ether) to give tert-butyl (3S)-3-[(3-nitro-4-pyridyl)oxy]piperidine-1-carboxylate as a pale yellow solid (2.65 g, 87% Yield, 93% ee). MS (ES+) 324.1.

Step 2: (S)-tert-butyl 3-((3-aminopyridin-4-yl)oxy)piperidine-1-carboxylate

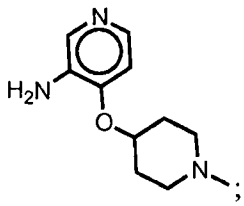
[00469] Pd on C, (10%, wet, Degussa) (1 g, 0.9397 mmol) was added to a stirred solution of tert-butyl (3S)-3-[(3-nitro-4-pyridyl)oxy]piperidine-1-carboxylate (2.65 g, 8.196 mmol) in EtOAc (30 mL) / EtOH (15 mL). The reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 16 hours. The catalyst was removed by filtration through a pad of celite and the filtrate concentrated *in vacuo* to give the sub-title compound as an off-white solid (2.46 g, >100 % Yield). MS (2ES+) 587.3.

[00470] The following aminopyridines were prepared using **Preparation O-1**:

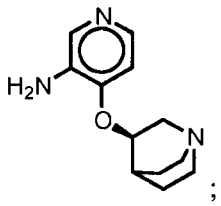
(R)-4-((1-methylpyrrolidin-3-yl)oxy)pyridin-3-amine:



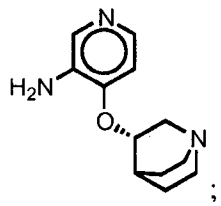
4-((1-methylpiperidin-4-yl)oxy)pyridin-3-amine:



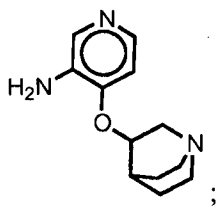
(*R*)-4-(quinuclidin-3-yloxy)pyridin-3-amine:



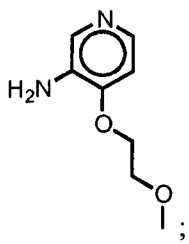
(*S*)-4-(quinuclidin-3-yloxy)pyridin-3-amine:



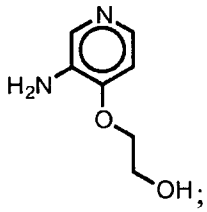
4-(quinuclidin-3-yloxy)pyridin-3-amine:



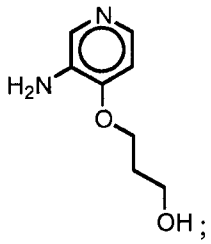
4-(2-methoxyethoxy)pyridin-3-amine:



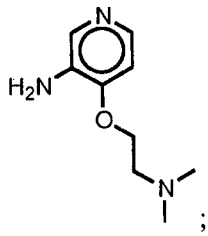
2-((3-aminopyridin-4-yl)oxy)ethanol:



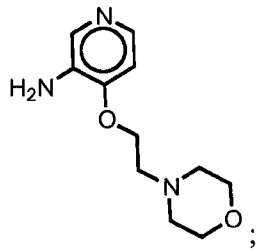
3-((3-aminopyridin-4-yl)oxy)propan-1-ol:



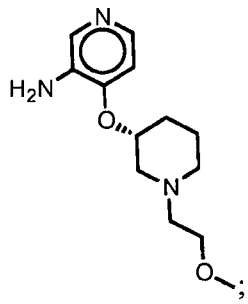
4-(2-(dimethylamino)ethoxy)pyridin-3-amine:



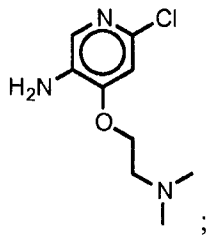
4-(2-morpholinoethoxy)pyridin-3-amine:



(*R*)-4-((1-(2-methoxyethyl)piperidin-3-yl)oxy)pyridin-3-amine:



6-chloro-4-(2-(dimethylamino)ethoxy)pyridin-3-amine:



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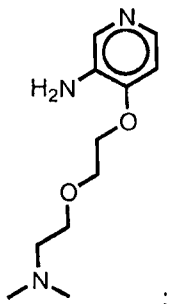
4-(2-(2-(dimethylamino)ethoxy)ethoxy)pyridin-3-amine:



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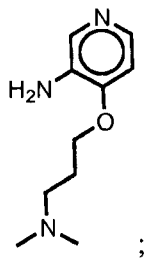
4-(3-(dimethylamino)propoxy)pyridin-3-amine:



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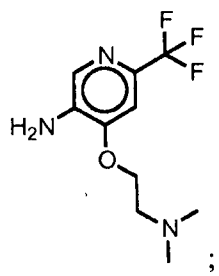
4-(2-(dimethylamino)ethoxy)-6-(trifluoromethyl)pyridin-3-amine:



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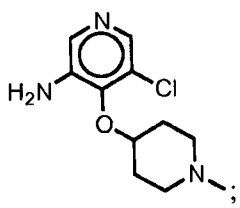
5-chloro-4-((1-methylpiperidin-4-yl)oxy)pyridin-3-amine:



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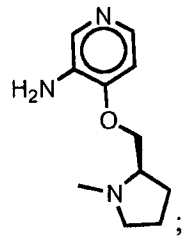
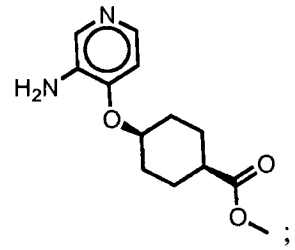
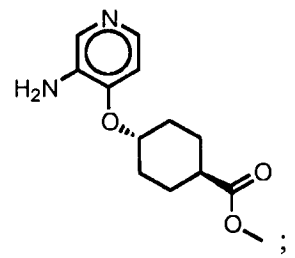
(*R*)-4-((1-methylpyrrolidin-2-yl)methoxy)pyridin-3-amine:



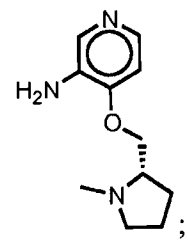
(1*s*,4*s*)-methyl 4-((3-aminopyridin-4-yl)oxy)cyclohexanecarboxylate:



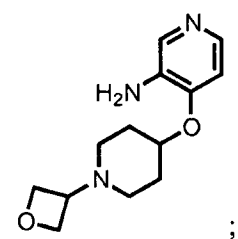
(1*r*,4*r*)-methyl 4-((3-aminopyridin-4-yl)oxy)cyclohexanecarboxylate:



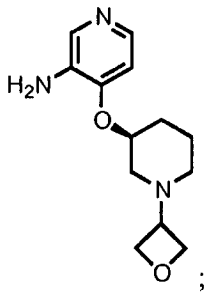
(*S*)-4-((1-methylpyrrolidin-2-yl)methoxy)pyridin-3-amine:



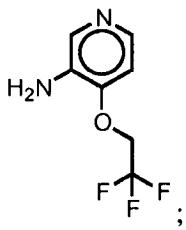
4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)pyridin-3-amine:



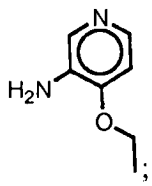
(S)-4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)pyridin-3-amine:



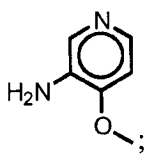
4-(2,2,2-trifluoroethoxy)pyridin-3-amine:



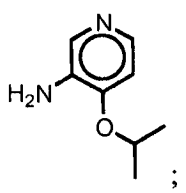
4-ethoxypyridin-3-amine:



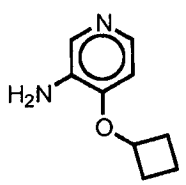
4-methoxypyridin-3-amine:



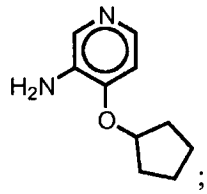
4-isopropoxypyridin-3-amine:



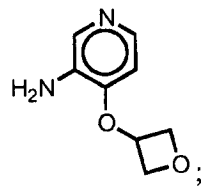
4-cyclobutoxypyridin-3-amine:



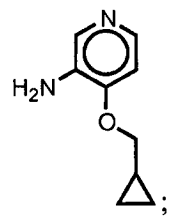
4-(cyclopentyloxy)pyridin-3-amine:



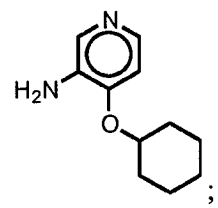
4-(oxetan-3-yloxy)pyridin-3-amine:



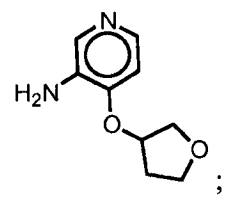
4-(cyclopropylmethoxy)pyridin-3-amine:



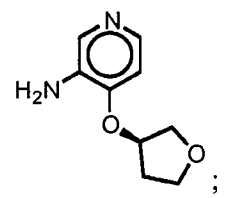
4-(cyclohexyloxy)pyridin-3-amine:



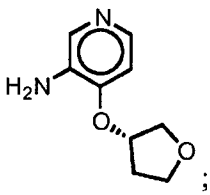
4-((tetrahydrofuran-3-yl)oxy)pyridin-3-amine:



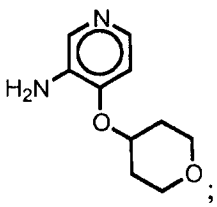
(*R*)-4-((tetrahydrofuran-3-yl)oxy)pyridin-3-amine:



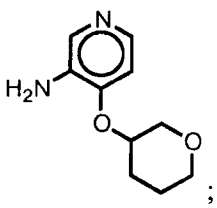
(*S*)-4-((tetrahydrofuran-3-yl)oxy)pyridin-3-amine:



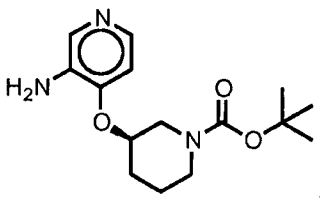
4-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-amine:



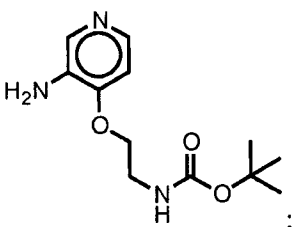
4-((tetrahydro-2*H*-pyran-3-yl)oxy)pyridin-3-amine:



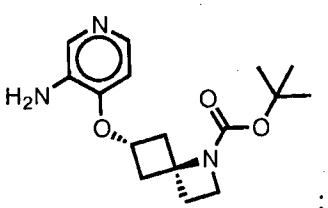
(*R*)-*tert*-butyl 3-((3-aminopyridin-4-yl)oxy)piperidine-1-carboxylate:



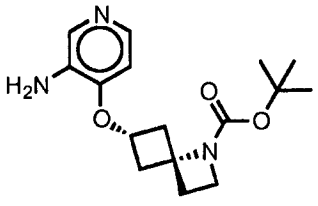
tert-butyl (2-((3-aminopyridin-4-yl)oxy)ethyl)carbamate:



(4*r*,6*s*)-*tert*-butyl 6-((3-aminopyridin-4-yl)oxy)-1-azaspiro[3.3]heptane-1-carboxylate:



(4*s*,6*r*)-*tert*-butyl 6-((3-aminopyridin-4-yl)oxy)-1-azaspiro[3.3]heptane-1-carboxylate:



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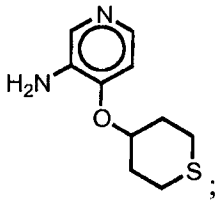
4-((tetrahydro-2*H*-thiopyran-4-yl)oxy)pyridin-3-amine:



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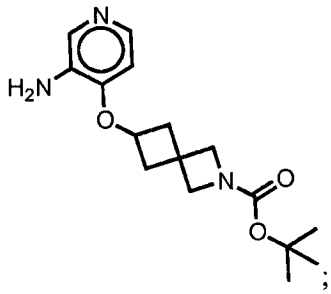
tert-butyl 6-((3-aminopyridin-4-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate:



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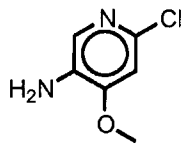
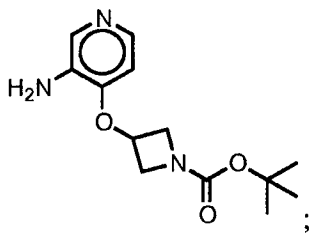
6-chloro-4-methoxypyridin-3-amine:



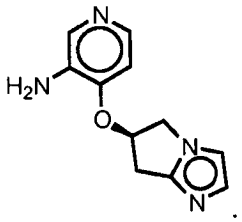
;

tert-butyl 3-((3-aminopyridin-4-yl)oxy)azetidine-1-carboxylate:



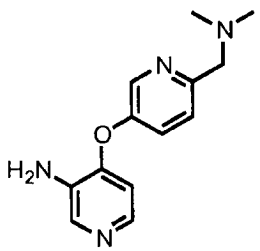
; and

(*R*)-4-((6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-6-yl)oxy)pyridin-3-amine:



Miscellanous preparation of aminopyridines

Preparation O-2: 4-((6-((dimethylamino)methyl)pyridin-3-yl)oxy)pyridin-3-amine



Step 1: 6-((dimethylamino)methyl)pyridin-3-ol

[00471] 6-(aminomethyl)pyridin-3-ol (150 mg, 1.208 mmol), formic acid (1 mL, 26.51 mmol), formaldehyde (1 mL, 36.30 mmol) was heated at 100°C overnight. The mixture was concentrated *in vacuo* to yield 6-((dimethylamino)methyl)pyridin-3-ol that was used in next step without further purification.

Step 2: N,N-dimethyl-1-(5-((3-nitropyridin-4-yl)oxy)pyridin-2-yl)methanamine

[00472] To a solution of 6-((dimethylamino)methyl)pyridin-3-ol in DMF (5 mL) was added, K_2CO_3 (834.8 mg, 6.040 mmol) and the mixture was stirred at RT for 10 min before 4-chloro-3-nitro-pyridine (191.5 mg, 1.208 mmol) was added. The mixture was stirred at RT for 60h. The reaction mixture was partitioned between EtOAc and NH_4Cl aq satd. Combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* yielding an oil that purified by SCX column, yielding *N,N*-dimethyl-1-(5-((3-nitropyridin-4-yl)oxy)pyridin-2-yl)methanamine as a colourless oil. MS (ES+) 275.1.

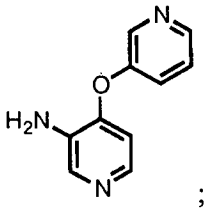
Step 3: 4-((6-((dimethylamino)methyl)pyridin-3-yl)oxy)pyridin-3-amine

[00473] *N,N*-dimethyl-1-(5-((3-nitropyridin-4-yl)oxy)pyridin-2-yl)methanamine (150 mg, 0.5469 mmol), Pd/C (10%) (58.20 mg, 0.5469 mmol) in MeOH (15 mL) was stirred overnight at RT under hydrogen (balloon). The catalyst was filtered off and the filtrate was concentrated

in vacuo to yield the title product as a clear oil. MS (ES+) 245.2.

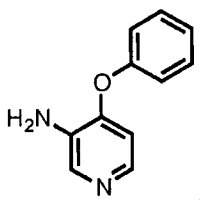
[00474] The following aminopyridine synthesized using **Step 2** and **Step 3** of **Preparation O-2:**

4-(pyridin-3-yloxy)pyridin-3-amine:

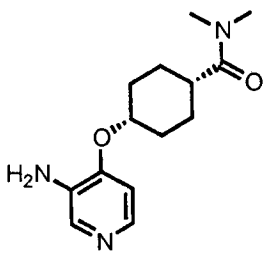


; and

4-phenoxypyridin-3-amine:



Preparation O-3: (1s,4s)-4-((3-aminopyridin-4-yl)oxy)-N,N-dimethylcyclohexanecarboxamide



Step 1: 4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxylic acid

[00475] Methyl 4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxylate (250.0 mg, 0.8920 mmol) (prepared according to methods similar to the one depicted in **Step 1** of **preparation O-1**) in THF (2.748 mL), Water (2.748 mL) and MeOH (1.5mL) solution was stirred at RT and treated with Lithium hydroxide monohydrate (Water (1)) (224.6 mg, 5.352 mmol). The mixture was stirred at RT overnight, then was concentrated under reduced pressure to remove

the organics. The aqueous solution was cooled in an ice bath then acidified with HCl (5.352 mL of 1 M, 5.352 mmol) to pH 4-5. Ethyl acetate was then added and the layers separated. Aqueous layer was extracted further with ethyl acetate (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to leave the 4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxylic acid as a yellow oil. Used in the next step without further purification. MS (ES+) 267.0.

Step 2: N,N-dimethyl-4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxamide

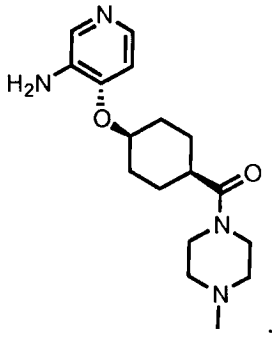
[00476] TBTU (630.0 mg, 1.962 mmol) and dimethylamine (1.784 mL of 2 M, 3.568 mmol) were added to a solution of 4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxylic acid (475 mg, 1.784 mmol) and DIPEA (253.6 mg, 341.8 µL, 1.962 mmol) in THF (9.500 mL) and the resulting solution was stirred at RT overnight. The reaction mixture was partitioned between EtOAc and water, and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 0-100% EtOAc/ petroleum ether using the ISCO column companion system (12 g column). Clean fractions were combined and concentrated *in vacuo* to yield N,N-dimethyl-4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxamide as a pale yellow oil. (180mg, 34%). MS (ES+) 294.3.

Step 3: (1s,4s)-4-((3-aminopyridin-4-yl)oxy)-N,N-dimethylcyclohexanecarboxamide

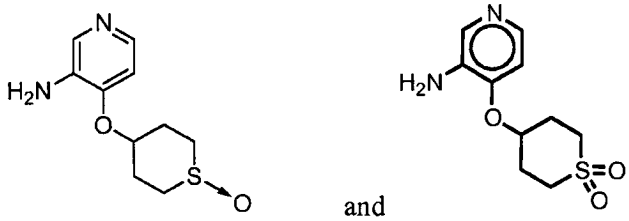
[00477] Pd on C, (10%, wet, Degussa) (65.31 mg, 0.06137 mmol) was added to a solution of N,N-dimethyl-4-[(3-nitro-4-pyridyl)oxy]cyclohexanecarboxamide (180 mg, 0.6137 mmol) in methanol (6.300 mL) and the reaction mixture was stirred under a hydrogen atmosphere overnight. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave the title product as a yellow oil. (160mg, 99%), MS (ES+) 264.3.

[00478] The following aminopyridine was synthesized according to methods similar to the one depicted in **Preparation O-3**:

((1*s*,4*s*)-4-((3-aminopyridin-4-yl)oxy)cyclohexyl)(4-methylpiperazin-1-yl)methanone:



Preparation O-4: 4-((3-aminopyridin-4-yl)oxy)tetrahydro-2H-thiopyran 1-oxide and 4-((3-aminopyridin-4-yl)oxy)tetrahydro-2H-thiopyran 1,1-dioxide



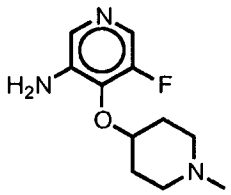
and

[00479] An amount of mCPBA (513.0 mg, 2.081 mmol) was added to a solution of 3-nitro-4-((tetrahydro-2*H*-thiopyran-4-yl)oxy)pyridine (prepared according to methods similar to the one depicted in **Preparation O-1**) (400 mg, 1.665 mmol) in DCM (10 mL) at RT. The mixture was stirred at RT overnight before 5 mL of an aqueous saturated solution of $NaHCO_3$ and 5mL of an aqueous saturated solution of $Na_2S_2O_3$ was added. The mixture was stirred at RT for 30min, partitioned between DCM and water. Combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* yielding an oil that was dissolved in MeOH (15mL). Pd/C 10% (177.2 mg, 1.665 mmol) was added and the mixture was hydrogenated (H^2 balloon) overnight. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to yield a 1/1 mixture of "sulfoxide and sulfone aminopyridine" intermediates that was used in next step without further purification.

MS (ES+) 227.1 (sulfoxide); and

MS (ES+) 243.1 (sulfone).

Preparation O-5: 5-fluoro-4-((1-methylpiperidin-4-yl)oxy)pyridin-3-amine



Step 1: 2-bromo-5-fluoro-4-((1-methylpiperidin-4-yl)oxy)-3-nitropyridine

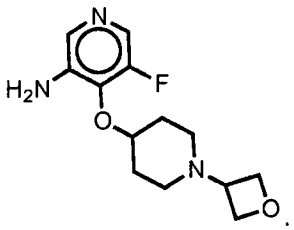
[00480] NaH (86.67 mg, 2.167 mmol) was added portionwise to a solution of 1-methylpiperidin-4-ol (192.0 mg, 1.667 mmol) in THF (5.000 mL) at 0°C and the resulting solution stirred for 15 min and then 2,4-dibromo-5-fluoro-3-nitro-pyridine (500 mg, 1.667 mmol) in THF (5.000 mL) was added and the reaction mixture stirred at RT overnight. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (10 mL). Combined organic extracts was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatograph on silica eluting with ethyl acetate/ petroleum ether (24 g column, 0-100% EtOAc) using the ISCO column companion system. Product fractions were combined and concentrated *in vacuo* to leave the product as a yellow oil that solidified on standing. (125mg). MS(ES+) 334.0 336.0.

Step 2: 5-fluoro-4-((1-methylpiperidin-4-yl)oxy)pyridin-3-amine

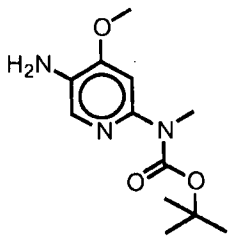
[00481] A solution of 2-bromo-5-fluoro-4-[(1-methyl-4-piperidyl)oxy]-3-nitro-pyridine (96 mg, 0.2873 mmol), $ZnBr_2$ (12.94 mg, 3.080 µL, 0.05746 mmol) and Pd on C, wet, Degussa (31 mg) in methanol (5 mL) was flushed with hydrogen and evacuated (3 x) and then stirred under a hydrogen atmosphere overnight. The catalyst was filtered off through a celite pad and washed with methanol and ethyl acetate mixtures and the filtrate was concentrated *in vacuo* to leave a pale yellow oil that was used in next step without further purification. MS (ES+) 226.1.

[00482] The following aminopyridine was prepared using **Step 1** and **Step 2** of **Preparation O-5:**

5-fluoro-4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)pyridin-3-amine:



Preparation O-6: *tert*-butyl (5-amino-4-methoxypyridin-2-yl)(methyl)carbamate



Step 1: tert-butyl (5-iodo-4-methoxypyridin-2-yl)(methyl)carbamate

[00483] Sodium hydride (37.70 mg, 0.9425 mmol) was added to a stirred suspension of tert-butyl N-(5-iodo-4-methoxy-2-pyridyl)carbamate (300 mg, 0.8568 mmol) in DMF (3 mL) and the reaction was stirred at 0°C for 15 minutes. MeI (145.9 mg, 63.99 µL, 1.028 mmol) was added and the reaction allowed to warm to ambient temperature over 1 hour. The mixture was quenched by the addition of water, diluted with EtOAc and the layers separated. The organic layer washed with saturated aqueous $NaHCO_3$ (x 1), brine (x 2), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 30% EtOAc/Petroleum Ether, loaded in DCM) to give tert-butyl (5-iodo-4-methoxypyridin-2-yl)(methyl)carbamate as a colourless oil (269 mg, 86% Yield). MS (ES+ -*t*-Bu) 309.4.

Step 2: tert-butyl (5-((diphenylmethylene)amino)-4-methoxypyridin-2-yl)(methyl)carbamate

[00484] $Pd_2(dba)_3$ (33.70 mg, 0.03680 mmol) and Xantphos (42.58 mg, 0.07359 mmol) were added to a sealed tube containing tert-butyl N-(5-iodo-4-methoxy-2-pyridyl)-N-methyl-carbamate (268 mg, 0.7359 mmol), diphenylmethanimine (173.4 mg, 160.6 µL, 0.9567 mmol) and Cs_2CO_3 (719.4 mg, 2.208 mmol) in dioxane (2.5 mL). The reaction was placed under an atmosphere of nitrogen and heated at 100°C for 4 hours. At RT, the reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The residue was purified by

column chromatography (ISCO Companion, 40 g column, eluting with 0 to 30% EtOAc/Petroleum Ether, loaded in DCM) to give tert-butyl (5-((diphenylmethylene)amino)-4-methoxypyridin-2-yl)(methyl)carbamate as a yellow solid (213 mg, 69% Yield). MS(ES+) 418.2.

Step 3: tert-butyl (5-amino-4-methoxypyridin-2-yl)(methyl)carbamate

[00485] HCl (100 μL of 2 M, 0.2000 mmol) was added to a stirred solution of tert-butyl N-[5-(benzhydrylideneamino)-4-methoxy-2-pyridyl]-N-methyl-carbamate (212 mg, 0.5078 mmol) in THF (2 mL) and the reaction was stirred at ambient temperature for 18 hours. The resultant precipitate was isolated by filtration and the filtrate stirred at ambient temperature for a further 6 hours. The reaction was diluted with 1M HCl and extracted with Et_2O (x 3). The aqueous layer was made basic by the addition of saturated aqueous $NaHCO_3$ and extracted with DCM (x 3). The combined organic extratcs were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give tert-butyl (5-amino-4-methoxypyridin-2-yl)(methyl)carbamate as a red oil (98.2 mg, 76% Yield). MS(ES+) 254.1.

[00486] The following compounds were synthesized using a procedure similar to **Example 1** or **Example 3a**:

(*S*)-2-amino-6-fluoro-*N*-(4-((1-methylpyrrolidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-1**);

(R,S)-2-amino-6-(cyanomethyl)-*N*-(4-(piperidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-2**);

2-amino-*N*-(4-((6-((dimethylamino)methyl)pyridin-3-yl)oxy)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-3**);

2-amino-6-fluoro-*N*-(4-methoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-4**);

(*R*)-2-amino-6-fluoro-*N*-(4-(quinuclidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-5**);

(R,S)-2-amino-6-fluoro-*N*-(4-(quinuclidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-6**);

2-amino-6-fluoro-*N*-(4-(pyridin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-7**);

4-((3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)oxy)cyclohexanecarboxylic acid (**Compound I-O-8**);

(*S*)-2-amino-6-fluoro-*N*-(4-((1-(oxetan-3-yl)piperidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-9**);

(*S*)-2-amino-6-fluoro-*N*-(4-(quinuclidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-10**);

2-amino-6-fluoro-*N*-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-11**);

2-amino-6-fluoro-*N*-(4-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-12**);

(1*r*,4*r*)-methyl 4-((3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)oxy)cyclohexanecarboxylate (**Compound I-O-13**);

2-amino-*N*-(4-ethoxypyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-14**);

(R,S)-2-amino-6-fluoro-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-15**);

(*S*)-2-amino-*N*-(4-((6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-6-yl)oxy)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-16**);

2-amino-*N*-(4-(((1*s*,4*s*)-4-(dimethylcarbamoyl)cyclohexyl)oxy)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-17**);

(1*s*,4*s*)-methyl 4-((3-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)pyridin-4-yl)oxy)cyclohexanecarboxylate (**Compound I-O-18**);

2-amino-6-fluoro-*N*-(4-(((1*s*,4*s*)-4-(4-methylpiperazine-1-carbonyl)cyclohexyl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-19**);

2-amino-6-(1-cyanopropyl)-*N*-(4-methoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-20**);

2-amino-6-(1-cyanoethyl)-*N*-(4-methoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-21**);

(R,S)-2-amino-6-(cyanomethyl)-*N*-(4-(quinuclidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-22**);

2-amino-6-(cyanomethyl)-*N*-(4-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-23**);

2-amino-6-(cyanomethyl)-*N*-(4-(2-(dimethylamino)ethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-24**);

2-amino-6-(cyanomethyl)-*N*-(4-phenoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-25**);

2-amino-6-(cyanomethyl)-*N*-(4-methoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-26**);

2-amino-*N*-(6-chloro-4-methoxypyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-27**);

2-amino-6-(cyanomethyl)-*N*-(4-ethoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-28**);

2-amino-6-(cyanomethyl)-*N*-(4-(2-methoxyethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-29**);

2-amino-6-(cyanomethyl)-*N*-(4-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-30**);

(*R*)-2-amino-6-(cyanomethyl)-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide (**Compound I-O-31**);

2-amino-6-(cyanomethyl)-*N*-(4-(cyclopropylmethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-32**);

2-amino-6-(cyanomethyl)-*N*-(4-(2-hydroxyethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-33**);

2-amino-6-(cyanomethyl)-*N*-(4-(2,2,2-trifluoroethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-34**);

2-amino-6-(cyanomethyl)-*N*-(4-isopropoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-35**);

2-amino-6-(cyanomethyl)-*N*-(4-cyclobutoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-36**);

(R,S)-2-amino-6-(cyanomethyl)-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-37**);

2-amino-6-(cyanomethyl)-*N*-(4-(oxetan-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-38**);

2-amino-6-(cyanomethyl)-*N*-(4-(cyclohexyloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-39**);

2-amino-6-(cyanomethyl)-*N*-(4-(3-hydroxypropoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-40**);

2-amino-6-(cyanomethyl)-*N*-(4-((tetrahydro-2*H*-pyran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-41**);

(*S*)-2-amino-6-(cyanomethyl)-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-42**);

2-amino-6-(cyanomethyl)-*N*-(4-(cyclopentyloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-43**);

2-amino-6-fluoro-*N*-(4-((1-oxidotetrahydro-2*H*-thiopyran-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-44**);

2-amino-*N*-(4-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-45**);

2-amino-6-chloro-*N*-(5-chloro-4-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-46**);

2-amino-6-chloro-*N*-(4-(2-(2-(dimethylamino)ethoxy)ethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-47**);

2-amino-6-chloro-*N*-(4-(2-(dimethylamino)ethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-48**);

(*R*)-2-amino-6-chloro-*N*-(4-((1-methylpyrrolidin-2-yl)methoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-49**);

(*S*)-2-amino-6-chloro-*N*-(4-((1-methylpyrrolidin-2-yl)methoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-50**);

2-amino-6-chloro-*N*-(4-((1-methylpiperidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-51**);

2-amino-6-chloro-*N*-(4-(3-(dimethylamino)propoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-52**);

2-amino-6-chloro-*N*-(4-(3-hydroxypropoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-53**);

(*R*)-2-amino-6-chloro-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-54**);

2-amino-6-chloro-*N*-(4-(2-methoxyethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-55**);

2-amino-6-chloro-*N*-(4-ethoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

(**Compound I-O-56**);

2-amino-6-chloro-*N*-(4-methoxypyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-57**);

(*S*)-2-amino-6-chloro-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-58**);

2-amino-6-chloro-*N*-(4-(2,2,2-trifluoroethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-59**);

2-amino-6-chloro-*N*-(4-(2-morpholinoethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-60**);

2-amino-6-chloro-*N*-(4-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-61**);

2-amino-6-chloro-*N*-(4-(quinuclidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-62**);

(*R*)-2-amino-6-chloro-*N*-(4-((1-methylpyrrolidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-63**);

2-amino-6-chloro-*N*-(4-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-64**);

2-amino-6-chloro-*N*-(4-((tetrahydro-2*H*-pyran-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-65**);

2-amino-6-chloro-*N*-(4-(2-hydroxyethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-66**);

(*S*)-2-amino-6-chloro-*N*-(4-((1-(2-methoxyethyl)piperidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-67**);

2-amino-6-chloro-*N*-(6-chloro-4-(2-(dimethylamino)ethoxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-68**);

(*S*)-2-amino-6-chloro-*N*-(4-((1-methylpyrrolidin-3-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-69**);

2-amino-6-chloro-*N*-(4-(pyridin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-70**);

2-amino-6-chloro-*N*-(4-(2-(dimethylamino)ethoxy)-6-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-71**);

2-amino-*N*-(4-(*tert*-butoxy)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-88**);

2-amino-6-fluoro-*N*-(5-fluoro-4-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-89**);

2-amino-6-fluoro-*N*-(5-fluoro-4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-91**); and

2-amino-6-fluoro-*N*-(4-(oxetan-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-92**).

[00487] The following compounds were prepared using a procedure similar to **Example 2:**

N-(4-(2-azaspiro[3.3]heptan-6-yloxy)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-72**);

2-amino-*N*-(4-(azetidin-3-yloxy)pyridin-3-yl)-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-73**);

(*S*)-2-amino-6-chloro-*N*-(4-(piperidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-74**);

2-amino-6-chloro-*N*-(4-(piperidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-75**);

(*S*)-2-amino-6-chloro-*N*-(4-(pyrrolidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-76**);

(*R*)-2-amino-6-chloro-*N*-(4-(pyrrolidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-77**);

N-(4-((4*s*,6*r*)-1-azaspiro[3.3]heptan-6-yloxy)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-78**);

N-(4-((4*r*,6*s*)-1-azaspiro[3.3]heptan-6-yloxy)pyridin-3-yl)-2-amino-6-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-79**);

2-amino-6-chloro-*N*-(4-(piperidin-4-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-80**);

(*R*)-2-amino-6-chloro-*N*-(4-(piperidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-81**);

2-amino-*N*-(4-(azetidin-3-yloxy)pyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-82**);

2-amino-*N*-(4-(2-aminoethoxy)pyridin-3-yl)-6-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-83**);

2-amino-6-(cyanomethyl)-*N*-(4-(piperidin-4-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-84**);

(*S*)-2-amino-6-fluoro-*N*-(4-(piperidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-85**);

(*S*)-2-amino-6-(cyanomethyl)-*N*-(4-(pyrrolidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-86**);

(*R*)-2-amino-6-(cyanomethyl)-*N*-(4-(pyrrolidin-3-yloxy)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-87**); and

2-amino-6-fluoro-*N*-(4-methoxy-6-(methylamino)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-O-90**).

Compound Analytical Data

Cmpd No.	LCMS ES +	LCMS (Rt min)	HNMR
I-O-1	372.2	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 10.4-10.6 (s, 1H), 10.05-10.15 (s, 1H), 9.64 (s, 1H), 9.54-9.56 (dd, 1H), 8.91 (s, 1H), 8.47-8.48 (d, 1H), 7.52 (s, 1H), 6.79 (s, 2H), 5.50-5.60 (m, 1H), 4.10-4.15 (s< 1H), 3.85-3.95 (s, 2H), 3.20-3.60 (m, 3H), 2.93 (s, 3H), 2.80-2.90 (s, 1H).
I-O-2	393.1	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 2.0, 0.7 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.75 (s, 2H), 4.63 - 4.53 (m, 1H), 4.15 (d, J = 0.7 Hz, 2H), 3.20 - 3.11 (m, 1H), 2.85 - 2.75 (m, 2H), 2.69 - 2.61 (m, 1H), 2.17 - 2.05 (m, 1H), 1.86 - 1.70 (m, 2H), 1.59 - 1.44 (m, 1H).
I-O-3	423.0	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.71 (s, 1H), 9.50 (dd, J = 4.7, 2.5 Hz, 1H), 8.77 (dd, J = 2.9, 0.6 Hz, 1H), 8.73 - 8.66 (m, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.91 (dd, J = 8.5, 2.9 Hz, 1H), 7.69 (dd, J = 8.6, 0.7 Hz, 1H), 7.22 (d, J = 5.8 Hz, 1H), 6.77 (s, 2H), 4.50 (s, 2H), 2.84 (s, 6H).
I-O-4	303.1	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 4.03 (2H, s), 6.71 (2H, s), 7.15-7.16 (1H, dd), 8.22-8.23 (1H, s), 8.87 (1H, d), 9.44 91H, s), 9.45-9.46 (1H, m), 9.96 (1H, s).
I-O-5	398.0	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.83 - 8.79 (m, 1H), 8.50 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 6.82 (s, 2H), 5.30 (d, J = 4.2 Hz, 1H), 3.98 (ddd, J = 14.0, 8.3, 2.2 Hz, 1H), 3.50 - 3.24 (m, 5H), 2.68 - 2.63 (m, 1H), 2.28 (s, 1H), 2.10 - 2.01 (m, 1H), 1.95 (d, J = 7.2 Hz, 2H).
I-O-6	398.2	0.64	----------
I-O-7	366.1	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 6.80-6.90 (2H, s), 7.23-7.24 (1H, d), 7.62-7.65 (1H, dd), 7.87-7.89 (1H, m), 8.43-8.44 (1H, d), 8.61-8.63 (1H, d), 8.72-8.76 (1H, m), 9.50 (1H, d), 8.78 (1H, (1H, s), 10.48 (1H, s)
I-O-8	415.3	0.43	^{1}H NMR (500 MHz, DMSO-d6) δ 12.20 (s, 1H), 10.34 (s, 1H), 9.62 (d, J = 0.9 Hz, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 6.3 Hz, 1H), 7.74 (d, J = 6.3 Hz, 1H), 6.76 (s, 2H), 6.51 (s, 1H), 4.90 (s, 1H), 2.22 (dd, J = 12.4, 4.0 Hz, 2H), 2.15 - 2.01 (m, 2H), 1.81 - 1.53 (m, 4H).

I-O-9	428.3	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.68 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 8.82 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 6.5 Hz, 1H), 7.77 (d, J = 6.8 Hz, 1H), 6.80 (s, 2H), 5.16 (s, 1H), 4.68 - 4.65 (m, 5H), 4.57 (s, 1H), 4.15 (s, 1H), 3.30 (s, 1H), 2.96 (s, 1H), 2.20 (s, 2H), 1.92 (s, 2H).
I-O-10	398.0	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.54 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.07 (d, J = 5.5 Hz, 1H), 6.76 (s, 2H), 4.72 (dt, J = 7.3, 3.1 Hz, 1H), 3.38 (ddd, J = 14.3, 7.9, 2.1 Hz, 1H), 2.92 - 2.82 (m, 1H), 2.82 - 2.64 (m, 3H), 2.22 (q, J = 3.2 Hz, 1H), 2.01 (ddt, J = 13.0, 9.8, 4.0 Hz, 1H), 1.75 - 1.66 (m, 1H), 1.66 - 1.55 (m, 1H), 1.51 - 1.42 (m, 1H).
I-O-11	428.2	0.59	^{1}H NMR (500 MHz, DMSO-d6) δ 2.2-2.36 (4H, m), 3.25 masked signal, 4.39 (1H, m), 4.73-4.78 (4H, m), 5.18 (1H, m), 6.81 (2H, br s), 7.71 (1H, m), 8.55 (1H, m), 8.78 (1H, m), 9.56 (1H, m), 9.66 (1H, s) and 10.18 (1H, br s) ppm
I-O-12	386.1	0.59	----------
I-O-13	429.2	0.78	^{1}H NMR (500 MHz, DMSO-d6) δ 1.40-1.76 (4H, m), 2.07 (2H, m), 2.21 (2H, m), 2.63 (1H, m), 3.65 (3H, s), 4.91 (1H, m), 6.76 (2H, br s), 7.73 (1H, m), 8.50 (1H, m), 8.92 (1H, s), 9.52 (1H, m), 9.62 (1H, m) and 10.34 (1H, s) ppm
I-O-14	317.1	0.60	----------
I-O-15	359.1	1.86*	----------
I-O-16	395.0	0.55	^{1}H NMR (500 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.67 (s, 1H), 9.57 - 9.43 (m, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.52 (dd, J = 6.1, 2.5 Hz, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.69 - 7.59 (m, 2H), 6.77 (s, 2H), 6.09 (d, J = 5.7 Hz, 1H), 4.82 (dd, J = 13.3, 5.3 Hz, 1H), 4.62 (dd, J = 13.4, 1.1 Hz, 1H), 3.94 (dd, J = 18.2, 6.2 Hz, 1H), 3.53 (d, J = 18.2 Hz, 1H).
I-O-17	442.2	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 1.67 (2H, m), 1.85-2.00 (4H, m), 2.12 (2H, m), 2.84 (4H, m), 3.09 (3H, s), 5.22 (1H, m), 6.80 (2H, br s), 7.75 (1H, m), 8.56 (1H, m), 9.11 (1H, m), 9.52 (1H, m), 9.69 (1H, s) and 10.09 (1H, s) ppm
I-O-18	429.2	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.84 (4H, m), 1.91-2.03 (4H, m), 2.57 masked signal, 3.58 (3H, s), 4.92 (1H, s), 6.54 (1H, s), 6.78 (2H, br s), 7.26 (1H, m), 8.21 (1H, m), 8.68 (1H, m), 9.51 (2H, m) and 9.81 (1H, s) ppm

I-O-19	497.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 1.68 (2H, m), 1.85-1.98 (4H, m), 2.12 (2H, m), 2.84 (3H, s), 2.91 (1H, m), 4.42 masked signal, 5.24 (1H, m), 6.81 (2H, br s), 7.72 (1H, m), 8.57 (1H, m), 9.03 (1H, m), 9.53 (1H, m), 9.70 (1H, s) and 10.05 (1H, s) ppm
I-O-20	352.1	0.69	^{1}H NMR (500 MHz, Methanol-d4) δ 1.2 (3H,t), 1.2-2.0 (2H,m), 3.8 (1H,t), 4.45 (3H,s), 7.7 (1H,d), 8.4-8.6 (3H,m), 8.7 (1H,s), 8.9 (1H,s), 9.7 (1H,s),
I-O-21	338.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7 (3H,d), 4.3 (3H,s), 4.55 (1H,q), 6.68-6.8 (2H,m), 7.2 (0.5H,d), 7.5 (0.5H,d), 7.7 (1H,d), 8.15 (1H,d), 8.8 (1H,s), 9.2 (1H,s), 9.7 (1H,s), 10.5 (1H,s).
I-O-22	419.0	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 10.07 (d, J = 2.7 Hz, 1H), 9.70 (s, 1H), 9.13 (dd, J = 1.6, 0.9 Hz, 1H), 8.61 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 6.81 (s, 2H), 5.33 (d, J = 5.4 Hz, 1H), 4.13 (s, 2H), 4.03 - 3.93 (m, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.39 (m, 3H), 3.31 - 3.22 (m, 1H), 2.65 (m, 1H), 2.44 (m, 1H), 2.14 - 1.90 (m, 3H).
I-O-23	407.2	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 1.9, 0.8 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.22 (d, J = 5.6 Hz, 1H), 6.74 (s, 2H), 4.68 (dq, J = 8.5, 4.6, 4.2 Hz, 1H), 4.20 - 4.10 (m, 2H), 2.81 - 2.66 (m, 2H), 2.35 - 2.24 (m, 2H), 2.21 (s, 3H), 2.12 - 2.00 (m, 2H), 1.89 - 1.76 (m, 2H).
I-O-24	381.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.60 (s, 1H), 9.12 (d, J = 2.0 Hz, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 6.1 Hz, 1H), 7.58 (d, J = 5.7 Hz, 1H), 6.79 (s, 2H), 4.80 (d, J = 4.6 Hz, 2H), 4.14 (s, 2H), 3.77 - 3.70 (m, 2H), 2.94 (s, 6H).
I-O-25	386.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.76 (d, J = 0.8 Hz, 1H), 9.08 (dd, J = 1.9, 0.8 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.42 (dd, J = 6.3, 0.8 Hz, 1H), 7.67 - 7.54 (m, 2H), 7.49 - 7.37 (m, 3H), 7.12 (d, J = 6.3 Hz, 1H), 6.79 (s, 2H), 4.07 (s, 2H).
I-O-26	324.1	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.62 (s, 1H), 9.09 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 6.7 Hz, 1H), 7.67 (d, J = 6.5 Hz, 1H), 6.76 (s, 2H), 4.27 (s, 3H), 4.14 (s, 2H).
I-O-27	358.0	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.27 (s, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 7.29 (s, 1H), 6.71 (s, 2H), 4.12 (s, 2H), 4.08 (s, 3H).

I-O-28	338.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.63 (s, 1H), 9.11 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 6.4 Hz, 1H), 7.64 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.51 (q, J = 7.0 Hz, 2H), 4.14 (s, 2H), 1.63 (t, J = 7.0 Hz, 3H).
I-O-29	368.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.10 (dt, J = 1.5, 0.7 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.57 (dd, J = 6.4, 1.0 Hz, 1H), 7.68 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 4.72 - 4.53 (m, 2H), 4.22 - 4.11 (m, 2H), 4.02 - 3.86 (m, 2H), 3.42 (s, 3H).
I-O-30	394.2	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.68 (d, J = 1.0 Hz, 1H), 9.11 (dt, J = 1.6, 0.7 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.58 (dd, J = 6.6, 1.1 Hz, 1H), 7.83 (d, J = 6.7 Hz, 1H), 6.78 (s, 2H), 5.23 (tt, J = 7.9, 3.9 Hz, 1H), 4.15 (s, 2H), 4.02 (ddd, J = 11.4, 5.9, 3.9 Hz, 2H), 3.66 (ddd, J = 11.5, 8.3, 3.1 Hz, 2H), 2.23 - 2.10 (m, 2H), 1.88 (dtd, J = 12.2, 8.1, 3.8 Hz, 2H).
I-O-31	380.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.63 (d, J = 1.0 Hz, 1H), 9.08 (dt, J = 1.6, 0.8 Hz, 1H), 8.60 - 8.53 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.75 (s, 2H), 5.56 (ddd, J = 5.7, 3.7, 1.8 Hz, 1H), 4.16 (d, J = 0.8 Hz, 2H), 4.13 - 3.98 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.50 - 2.40 (m, 1H), 2.29 - 2.18 (m, 1H).
I-O-32	364.1	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.65 (d, J = 1.0 Hz, 1H), 9.11 (dd, J = 1.9, 0.8 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.59 - 8.48 (m, 1H), 7.60 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.34 (d, J = 7.2 Hz, 2H), 4.14 (s, 2H), 1.50 (pt, J = 7.5, 4.7 Hz, 1H), 0.86 - 0.74 (m, 2H), 0.58 - 0.46 (m, 2H).
I-O-33	354.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.10 (dd, J = 1.9, 0.8 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 6.4 Hz, 1H), 7.67 (d, J = 6.4 Hz, 1H), 6.76 (s, 2H), 5.07 (s, 1H), 4.50 (t, J = 4.8 Hz, 2H), 4.15 (s, 2H), 4.00 (t, J = 4.7 Hz, 2H).
I-O-34	392.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.72 (d, J = 0.7 Hz, 1H), 9.09 (dt, J = 2.0, 0.7 Hz, 1H), 8.58 (dd, J = 6.2, 0.8 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 6.3 Hz, 1H), 6.77 (s, 2H), 5.27 (q, J = 8.4 Hz, 2H), 4.22 - 4.14 (m, 2H).
I-O-35	352.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.69 - 10.33 (m, 1H), 9.64 (d, J = 5.6 Hz, 1H), 9.23 - 9.02 (m, 1H), 8.80 - 8.64 (m, 1H), 8.55 (t, J = 6.5 Hz, 1H), 7.72 (t, J = 5.7 Hz, 1H), 6.76 (s, 2H), 5.19 (hept, J = 6.6 Hz, 1H), 4.29 - 4.03 (m, 2H), 1.67 - 1.44 (m, 6H).

I-O-36	364.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.11 (dt, J = 1.6, 0.7 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 6.4, 1.0 Hz, 1H), 7.46 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 5.29 - 5.13 (m, 1H), 4.14 (s, 2H), 2.73 - 2.59 (m, 2H), 2.40 - 2.27 (m, 2H), 2.03 - 1.91 (m, 1H), 1.80 (dtt, J = 10.9, 9.8, 8.3 Hz, 1H).
I-O-37	380.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.64 (d, J = 0.9 Hz, 1H), 9.10 (dd, J = 1.9, 0.8 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.58 - 8.52 (m, 1H), 7.66 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 5.57 (ddd, J = 5.6, 3.5, 1.7 Hz, 1H), 4.16 (d, J = 0.9 Hz, 2H), 4.13 - 4.00 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.49 - 2.40 (m, 1H), 2.32 - 2.19 (m, 1H).
I-O-38	366.0	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.67 (d, J = 0.8 Hz, 1H), 9.11 (dt, J = 1.9, 0.7 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 6.3, 0.9 Hz, 1H), 7.32 (d, J = 6.3 Hz, 1H), 6.77 (s, 2H), 5.75 (tt, J = 5.8, 4.4 Hz, 1H), 5.14 (ddd, J = 7.8, 5.9, 1.1 Hz, 2H), 4.80 (ddd, J = 7.8, 4.4, 1.0 Hz, 2H), 4.16 - 4.11 (m, 2H).
I-O-39	392.2	0.79	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.67 (d, J = 1.0 Hz, 1H), 9.12 (dt, J = 2.0, 0.7 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.55 (dd, J = 6.6, 1.1 Hz, 1H), 7.77 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.03 (tt, J = 8.0, 3.6 Hz, 1H), 4.20 - 4.12 (m, 2H), 2.15 - 2.01 (m, 2H), 1.96 - 1.83 (m, 2H), 1.83 - 1.69 (m, 2H), 1.66 - 1.38 (m, 4H).
I-O-40	368.1	0.52	^{1}H NMR (500 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.09 (dd, J = 1.9, 0.9 Hz, 1H), 8.69 - 8.47 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.52 (t, J = 5.8 Hz, 2H), 4.15 (d, J = 0.8 Hz, 2H), 3.81 (q, J = 7.0, 6.5 Hz, 2H), 2.14 (p, J = 6.0 Hz, 2H).
I-O-41	394.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.69 (d, J = 1.0 Hz, 1H), 9.10 (dt, J = 1.6, 0.7 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.55 (dd, J = 6.5, 1.1 Hz, 1H), 7.76 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.03 (h, J = 3.7, 3.2 Hz, 1H), 4.16 (d, J = 0.7 Hz, 2H), 3.97 - 3.85 (m, 2H), 3.83 - 3.74 (m, 1H), 3.69 (ddd, J = 11.3, 8.1, 3.1 Hz, 1H), 2.16 (tt, J = 9.2, 4.7 Hz, 1H), 2.11 - 1.92 (m, 2H), 1.73 - 1.59 (m, 1H).
I-O-42	380.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.09 (dd, J = 2.0, 0.8 Hz, 1H), 8.59 - 8.55 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.75 (s, 2H), 5.57 (ddd, J = 5.9, 3.8, 1.7 Hz, 1H), 4.16 (d, J = 0.9 Hz, 2H), 4.13 - 3.99 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.50 - 2.41 (m, 1H), 2.27 - 2.21 (m, 1H).

I-O-43	378.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.11 (dt, J = 1.9, 0.7 Hz, 1H), 8.63 - 8.49 (m, 2H), 7.68 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.39 (dq, J = 5.8, 3.7, 2.9 Hz, 1H), 4.20 - 4.12 (m, 2H), 2.20 - 2.07 (m, 2H), 2.07 - 1.95 (m, 2H), 1.96 - 1.84 (m, 2H), 1.83 - 1.66 (m, 2H).
I-O-44	405.0	0.5	^{1}H NMR (500 MHz, DMSO-d6) δ 9.95 (s, 1H), 9.69 (d, J = 1.0 Hz, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 8.77 - 8.69 (m, 1H), 8.58 (dd, J = 6.5, 1.1 Hz, 1H), 7.77 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 5.34 - 5.26 (m, 1H), 3.10 (td, J = 13.7, 12.2, 3.0 Hz, 2H), 3.01 - 2.90 (m, 2H), 2.55 (m, 2H), 2.14 (dd, J = 15.1, 4.3 Hz, 2H).
I-O-45	421.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.68 (d, J = 0.9 Hz, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.83 (dd, J = 2.5, 0.7 Hz, 1H), 8.58 (dd, J = 6.5, 1.0 Hz, 1H), 7.76 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 5.34 - 5.27 (m, 1H), 3.50 (ddd, J = 14.4, 10.8, 3.7 Hz, 2H), 3.39 - 3.32 (m, 2H), 2.50 - 2.34 (m, 4H).
I-O-46	436.1	0.8	^{1}H NMR (500MHz, Methanol-d4) δ 2.10 (6H, m), 2.27 (3H, s), 2.90 (2H, m), 4.75 (1H, m), 8.28 (1H, s), 8.75 (1H, d), 9.02 (1H, m) and 9.61 (1H, s) ppm
I-O-47	420.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.48 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.77 (s, 2H), 4.37 - 4.31 (m, 2H), 3.95 - 3.89 (m, 2H), 3.60 (t, J = 6.0 Hz, 2H), 2.36 (t, J = 6.0 Hz, 2H), 2.07 (s, 6H).
I-O-48	376.1	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.48 (s, 1H), 9.42 (d, J = 2.3 Hz, 1H), 8.62 - 8.56 (m, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.19 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.30 (t, J = 5.6 Hz, 2H), 2.84 (t, J = 5.6 Hz, 2H), 2.26 (s, 6H).
I-O-49	402.1	0.73	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72 (3H, m), 2.09 (1H, m), 2.28 (1H, m), 2.39 (3H, s), 2.79 (1H, m), 2.97 (1H, m), 4.00 (1H, m), 4.25 (1H, m), 6.79 (2H, br s), 7.18 (1H, m), 8.19 (1H, m), 8.54 (1H, m), 9.42 (1H, d), 9.47 (1H, s) and 9.81 (1H, s) ppm
I-O-50	402.2	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72 (3H, m), 2.11 (1H, m), 2.27 (1H, m), 2.39 (3H, s), 2.78 (1H, m), 2.97 (1H, m), 4.00 (1H, m), 4.25 (1H, m), 6.79 (2H, br s), 7.19 (1H, m), 8.20 (1H, m), 8.54 (1H, m), 9.42 (1H, m), 9.47 (1H, s) and 9.81 (1H, s) ppm

I-O-51	402.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 9.98 (s, 1H), 9.53 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.69 (s, 1H), 2.92 (s, 1H), 2.59 - 2.47 (m, 1H), 2.35 - 2.12 (m, 2H), 2.33 (s, 3H), 2.07 (d, J = 5.5 Hz, 1H), 1.91 (s, 1H), 1.73 - 1.51 (m, 2H).
I-O-52	390.1	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.51 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 4.22 (t, J = 5.9 Hz, 2H), 2.16 (s, 6H), 2.06 (p, J = 6.6 Hz, 2H).
I-O-53	365.1	0.59	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.61 (s, 1H), 9.47 (d, J = 2.2 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.52 (d, J = 6.4 Hz, 1H), 7.60 (d, J = 6.4 Hz, 1H), 6.81 (s, 2H), 4.47 (t, J = 5.9 Hz, 2H), 3.77 (s, 2H), 2.12 (p, J = 6.2 Hz, 2H).
I-O-54	375.0	0.66	^{1}H NMR (500 MHz, Methanol-d4) δ 10.29 (s, 1H), 9.61 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 6.5 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 5.47 (t, J = 4.9 Hz, 1H), 4.20 (dt, J = 11.0, 1.0 Hz, 1H), 4.08 - 4.00 (m, 2H), 3.93 (td, J = 8.5, 4.2 Hz, 1H), 2.47 - 2.36 (m, 1H), 2.27 - 2.18 (m, 1H).
I-O-55	363.0	0.67	^{1}H NMR (500 MHz, Methanol-d4) δ 10.44 (s, 1H), 9.70 (d, J = 1.2 Hz, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 6.7, 1.2 Hz, 1H), 7.59 (d, J = 6.7 Hz, 1H), 4.60 - 4.55 (m, 2H), 3.96 - 3.90 (m, 2H), 3.39 (s, 3H).
I-O-56	333.0	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.49 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.19 (d, J =5.4 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.77 (s, 2H), 4.25 (q, J = 6.9 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H).
I-O-57	319.1	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 4.28 (3H, s), 6.81 (2H, br s), 7.68 (1H, d), 8.60 (1H, d), 8.81 (1H, d), 9.47 (1H, d), 9.61 (1H, s) and 10.34 (1H, s) ppm
I-O-58	375.0	0.66	^{1}H NMR (500 MHz, Methanol-d4) δ 10.31 (s, 1H), 9.62 (s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.39 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 6.6 Hz, 1H), 7.57 (d, J = 6.6 Hz, 1H), 5.51 - 5.45 (m, 1H), 4.20 (d, J = 10.9 Hz, 1H), 4.08 - 4.00 (m, 2H), 3.93 (td, J = 8.5, 4.2 Hz, 1H), 2.47 - 2.36 (m, 1H), 2.29 - 2.18 (m, 1H).
I-O-59	387.0	0.78	^{1}H NMR (500 MHz, Methanol-d4) δ 10.41 (s, 1H), 9.79 (d, J = 1.1 Hz, 1H), 8.94 (dd, J = 2.1, 0.4 Hz, 1H), 8.42 (dd, J = 6.6, 1.1 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.61 (d, J = 6.6 Hz, 1H), 5.10 - 5.01 (m, 2H)

I-O-60	418.1	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 9.91 (s, 1H), 9.47 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 4.35 (t, J = 5.9 Hz, 2H), 3.53 (t, J = 4.6 Hz, 4H), 2.90 (t, J = 5.8 Hz, 2H), 2.52 - 2.50 (masked signal, 4H).
I-O-61	389.0	0.68	^{1}H NMR (500 MHz, Methanol-d4) δ 10.28 (s, 1H), 9.75 (d, J = 1.2 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.35 (dd, J = 6.7, 1.3 Hz, 1H), 7.66 (d, J = 6.8 Hz, 1H), 5.15 (dt, J = 7.9, 4.0 Hz, 1H), 4.05 (ddd, J = 10.8, 6.1, 3.9 Hz, 2H), 3.66 (ddd, J = 11.6, 8.2, 3.3 Hz, 2H), 2.22 - 2.14 (m, 2H), 1.92 (ddt, J = 13.2, 8.5, 4.0 Hz, 2H).
I-O-62	414.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (s, 1H), 9.41 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.80 (s, 2H), 4.75 - 4.66 (m, 1H), 3.38 (d, J = 4.0 Hz, 0H), 2.92 - 2.82 (m, 1H), 2.82 - 2.64 (m, 4H), 2.21 (dd, J = 4.9, 1.8 Hz, 1H), 1.97 (ddd, J = 14.8, 11.1, 3.5 Hz, 1H), 1.76 - 1.66 (m, 1H), 1.66 - 1.55 (m, 1H), 1.48 - 1.39 (m, 1H).
I-O-63	388.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.51 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.11 - 5.07 (m, 1H), 2.93 (dd, J = 10.7, 6.0 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.45 - 2.40 (m, 2H), 2.32 (s, 3H), 2.02 - 1.96 (m, 1H).
I-O-64	402.0	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.52 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 6.79 (s, 2H), 4.66 (dq, J = 8.3, 4.1 Hz, 1H), 2.71 (q, J = 5.5 Hz, 2H), 2.26 (t, J = 10.3 Hz, 2H), 2.20 (s, 3H), 2.12 - 2.01(m, 2H), 1.82 (dtd, J = 12.6, 8.8, 3.6 Hz, 2H).
I-O-65	389.0	0.73	^{1}H NMR (500 MHz, Methanol-d4) δ 10.47 (s, 1H), 9.74 (d, J = 1.2 Hz, 1H), 8.91 (d, J = 2.2 Hz, 1H), 8.47 (d, J = 2.2 Hz, 1H), 8.37 - 8.32 (m, 1H), 7.59 (dd, J = 6.8, 2.1 Hz, 1H), 4.95 - 4.88 (m, 1H), 4.00 (dd, J = 12.6, 3.8 Hz, 1H), 3.89 (dd, J = 12.5, 2.3 Hz, 1H), 3.82 (dt, J = 11.1, 4.0 Hz, 1H), 3.64 (ddd, J = 11.3, 9.4, 2.8 Hz, 1H), 2.10 (dt, J = 9.1, 4.3 Hz, 2H), 2.06 - 1.99 (m, 1H), 1.59 (dddd, J = 12.8, 7.6, 4.6, 2.7 Hz, 1H).
I-O-66	349.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.50 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.76 (s, 2H), 4.92 (t, J = 5.1 Hz, 1H), 4.24 (t, J = 4.8 Hz, 2H), 3.94 (q, J = 4.9 Hz, 2H).

I-O-67	446.2	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.53 (s, 1H), 9.43 (s, 1H), 8.56 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.22 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.71 - 4.56 (m, 1H), 3.44 (dd, J = 6.5, 4.8 Hz, 1H), 3.21 (s, 3H), 3.11 (dd, J = 12.8, 2.5 Hz, 1H), 2.76 - 2.46 (m, 4H), 2.37 (d, J = 5.6 Hz, 1H), 2.30 - 2.20 (m, 1H), 2.13 (d, J = 11.0 Hz, 1H), 1.86 (d, J = 8.5 Hz, 1H), 1.71 - 1.57 (m, 1H), 1.57 - 1.45 (m, 1H).
I-O-68	410.0	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.71 (s, 1H), 9.46 (d, J = 2.2 Hz, 1H), 9.30 (s, 1H), 8.76 (d, J = 2.2 Hz, 1H), 7.40 (s, 1H), 6.81 (s, 1H), 4.74 - 4.61 (m, 2H), 3.69 (s, 2H), 2.92 (s, 6H).
I-O-69	388.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.51 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.11 - 5.07 (m, 1H), 2.93 (dd, J = 10.7, 6.0 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.45 - 2.40 (m, 2H), 2.32 (s, 3H), 2.02 - 1.96 (m, 1H).
I-O-70	382.0	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.73 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 8.71 (dd, J = 2.9, 0.6 Hz, 1H), 8.66 - 8.55 (m, 2H), 8.41 (d, J = 6.0 Hz, 1H), 7.84 (ddd, J = 8.4, 2.9, 1.3 Hz, 1H), 7.61 (ddd, J = 8.4, 4.8, 0.6 Hz, 1H), 7.20 (d, J = 6.0 Hz, 1H), 6.82 (s, 2H).
I-O-71	444.1	0.84	^{1}H NMR (500 MHz, DMSO-d6) δ 10.01 (s, 1H), 9.70 (br s, 1H), 9.68 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H), 7.72 (s, 1H), 6.85 (s, 2H), 4.84 - 4.69 (m, 2H), 3.71 (s, 2H), 2.92 (s, 6H).
I-O-72	400.0	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.63 (s, 1H), 9.49 (dt, J = 2.8, 1.4 Hz, 1H), 8.77 (s, 2H), 8.72 (dd, J = 2.1, 0.7 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 7.38 (s, 1H), 6.83 (s, 2H), 5.06 (t, J = 6.3 Hz, 1H), 4.09 (d, J = 3.1 Hz, 4H), 2.99 (dd, J = 13.8, 6.7 Hz, 2H), 2.55 (d, J = 5.6 Hz, 2H).
I-O-73	360.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.57 (s, 1H), 9.46 (d, J = 2.2 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 6.99 (d, J = 5.5 Hz, 1H), 6.80 (s, 2H), 5.32 (tt, J = 6.5, 4.5 Hz, 1H), 4.64 - 4.56 (m, 2H), 4.22 - 4.15 (m, 2H).
I-O-74	388.2	0.62	^{1}H NMR (500 MHz, Methanol-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.56 (dd, J = 6.7, 1.2 Hz, 1H), 7.84 (d, J = 6.7 Hz, 1H), 5.37 (dt, J = 7.8, 4.0 Hz, 1H), 3.69 (d, J = 4.1 Hz, 2H), 3.44 - 3.36 (m, 2H), 2.49 (ddq, J = 13.6, 8.9, 4.5 Hz, 1H), 2.35 (ddt, J = 25.5, 11.3, 5.0 Hz, 2H), 2.22 - 2.06 (m, 1H).

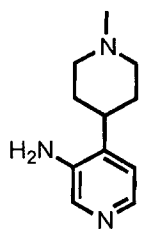
I-O-75	388.1	0.65	^{1}H NMR (500 MHz, Methanol-d4) δ 9.78 (d, J = 1.2 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.42 (dd, J = 6.7, 1.3 Hz, 1H), 7.69 (d, J = 6.7 Hz, 1H), 5.24 (td, J = 5.1, 2.7 Hz, 1H), 3.63 - 3.50 (m, 2H), 3.37 - 3.28 (m, 1H), 3.24 - 3.18 (m, 1H), 2.40 (dd, J = 9.5, 4.7 Hz, 1H), 2.29 - 2.14 (m, 2H), 2.01 (dd, J = 10.3, 4.2 Hz, 1H).
I-O-76	374.2	0.56	^{1}H NMR (500 MHz, Methanol-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.57 (dd, J = 6.7, 1.2 Hz, 1H), 7.82 (d, J = 6.8 Hz, 1H), 5.79 (q, J = 4.4, 3.5 Hz, 1H), 3.91 (dd, J = 13.8, 4.7 Hz, 1H), 3.87 - 3.69 (m, 3H), 2.75 - 2.64 (m, 2H).
I-O-77	374.0	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.01 (s, 1H), 9.51 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.17 - 5.10 (m, 1H), 3.30 - 3.18 (m, 2H), 3.12 - 2.99 (m, 2H), 2.90 (ddd, J = 10.8, 8.0, 4.4 Hz, 1H), 2.16 - 2.05 (m, 1H), 1.99 - 1.90 (m, 1H).
I-O-78	400.0	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.50 (s, 1H), 9.42 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 5.4 Hz, 1H), 6.99 (d, J = 5.4 Hz, 1H), 6.77 (s, 2H), 4.64 (p, J = 6.9 Hz, 1H), 3.33 (m, 2H), 2.93 (ddd, J = 9.9, 6.7, 3.3 Hz, 2H), 2.32 (t, J = 7.1 Hz, 2H), 2.24 (ddd, J = 10.0, 7.2, 3.5 Hz, 2H).
I-O-79	400.0	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (s, 1H), 9.45 (dd, J = 2.2, 0.6 Hz, 1H), 9.02 (s, 2H), 8.71 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.4 Hz, 1H), 6.92 (d, J = 5.5 Hz, 1H), 6.80 (d, J = 3.6 Hz, 2H), 5.04 (tt, J = 6.7, 4.7 Hz, 1H), 3.83 (t, J = 8.2 Hz, 2H), 3.27 (dd, J = 14.7, 6.8 Hz, 2H), 2.66 - 2.56 (m, 4H).
I-O-80	388.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 9.98 (s, 1H), 9.52 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.77 (tt, J = 7.9, 3.5 Hz, 1H), 3.11 - 3.03 (m, 2H), 2.65 (ddd, J = 12.4, 9.0, 3.1 Hz, 2H), 1.98 (ddt, J = 12.9, 6.5, 3.6 Hz, 2H), 1.65 (dtt, J = 12.4, 9.2, 3.4 Hz, 2H).
I-O-81	388.2	0.62	^{1}H NMR (500 MHz, Methanol-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.55 (dd, J = 6.7, 1.2 Hz, 1H), 7.83 (d, J = 6.7 Hz, 1H), 5.42 - 5.31 (m, 1H), 3.69 (d, J = 4.1 Hz, 2H), 3.48 - 3.35 (m, 2H), 2.49 (ddq, J = 13.5, 8.8, 4.5 Hz, 1H), 2.43 - 2.25 (m, 2H), 2.21 - 2.08 (m, 1H).

I-O-82	365.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.66 (s, 1H), 9.33 (s, 1H), 9.20 - 9.01 (m, 2H), 8.76 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 7.31 (d, J = 5.9 Hz, 1H), 6.79 (s, 2H), 5.56 - 5.38 (m, 1H), 4.66 (p, J = 6.5, 6.1 Hz, 2H), 4.25 (dd, J = 13.6, 6.9 Hz, 2H), 4.14 (s, 2H).
I-O-83	353.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.60 (s, 1H), 9.11 (dd, J = 1.9, 0.9 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 6.1 Hz, 1H), 8.15 (s, 3H), 7.59 (d, J = 6.1 Hz, 1H), 6.77 (s, 2H), 4.61 (t, J = 4.9 Hz, 2H), 4.12 (s, 2H), 3.49 (q, J = 5.2, 4.6 Hz, 2H).
I-O-84	393.1	0.52	^{1}H NMR (500 MHz, DMSO-d6) δ 10.09 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 1.5, 0.7 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.74 (s, 2H), 4.77 (tt, J = 7.7, 3.5 Hz, 1H), 4.14 (s, 2H), 3.13 - 3.02 (m, 2H), 2.74 - 2.62 (m, 2H), 2.06 - 1.95 (m, 2H), 1.74 - 1.61 (m, 2H).
I-O-85	372.2	0.60	----------
I-O-86	377.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 10.08 (s, 1H), 9.52 (s, 1H), 9.04 (dd, J = 2.0, 0.9 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 6.72 (s, 2H), 5.12 (ddt, J = 6.7, 4.6, 2.0 Hz, 1H), 4.14 (s, 2H), 3.20 (dd, J = 12.6, 5.1 Hz, 1H), 3.12 - 3.01 (m, 2H), 2.90 (ddd, J = 10.9, 8.1, 4.5 Hz, 1H), 2.12 (dtd, J = 14.0, 8.0, 6.2 Hz, 1H), 1.97 (dqd, J = 13.4, 4.3, 2.0 Hz, 1H).
I-O-87	379.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.53 (s, 1H), 9.04 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 5.4 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 6.72 (s, 2H), 5.18 - 5.07 (m, 1H), 4.15 (s, 2H), 3.28 - 3.17 (m, 1H), 3.15 - 3.02 (m, 2H), 2.99 - 2.86 (m, 1H), 2.21 - 2.07 (m, 1H), 2.02 - 1.93 (m, 1H).
I-O-88	345.0	1.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.74 (9H,s), 6.79 (2H, s), 7.82-7.83 (1H, d), 8.45-8.46 (1H, d), 8.74-8.75 (1H, d), 9.53-9.54 (1H, dd), 9.68-9.69 (1H, d), 10.29 (1H, s).
I-O-89	404.1	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.99-2.15 (2H, m), 2.27-2.37 (2H, m), 2-76-2.79 (3H, m), 3.09-3.30 (2H, m), 3.46-3.57 (2H, m), 4.74 (1H, m), 6.78 (2H, br s), 8.36 (1H, d), 8.83-8.88 (1H, m), 9.45-9.54 (2H, m), 9.77 (1H, m) and 10.09 (1H, s) ppm rotamers observed.
I-O-90	332.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.47 (s, 1H), 9.91 (s, 1H), 9.50 (dd, J = 4.8, 2.6 Hz, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.74 (s, 1H), 6.69 (s, 2H), 6.50 (s, 1H), 4.12 (s, 3H), 2.94 (d, J = 4.7 Hz, 3H).

I-O-91	446.1	2.06*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85 (2H, m), 1.92-2.08 (4H, m), 2.67 (2H, m), 4.40 (2H, m), 4.49 (2H, m), 4.61 (1H, m), 6.77 (2H, br s), 8.30 (1H, m), 8.82 (1H, m), 9.47 (1H, s), 9.52 (1H, m) and 10.03 (1H, s) ppm Oxetane CH not observed.
I-O-92	345.0	1.76*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.68 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 8.96 - 8.85 (m, 1H), 8.48 (s, 1H), 7.25 (s, 1H), 6.78 (s, 2H), 5.71 (tt, J = 5.9, 4.5 Hz, 1H), 5.10 (ddd, J = 7.8, 5.9, 1.1 Hz, 2H), 4.79 (ddd, J = 7.9, 4.5, 1.0 Hz, 2H).

Retention times measured using HPLC Method B, described in the Experimental Methods and Materials section, above., are designated by (*). For all other compounds, the retention time was measured using the HPLC Method A.

Preparation C-1: 4-(1-methylpiperidin-4-yl)pyridin-3-amine



Step 1: 4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-3-nitro-pyridine

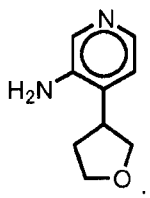
[00488] To a solution of 4-chloro-3-nitro-pyridine (350 mg, 2.208 mmol) in Toluene (7.00 mL), Ethanol (1.75 mL) and sodium carbonate solution (aq) (2.21 mL of 1 M, 2.21mmol) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (985.3 mg, 4.416 mmol), $Pd_2(dba)_3$ (60.66 mg, 0.07 mmol) and triphenyl phosphine (115.8 mg, 102.3 µL, 0.44 mmol). The mixture was stirred at 75°C (reflux) for 18 hours. The reaction mixture was evaporated to dryness and the residue was partitioned between water (30 mL) and DCM (2x30 mL). The combined organics were washed with water (30 mL) and brine (30 mL), dried and evaporated to dryness to afford a dark brown oil which was purified by column chromatography on silica gel eluting with petroleum ether (A): ethyl acetate (B) (20-100% (B), 24 g, 30.0 CV, 35 mL/min) then ethyl acetate (A): methanol (B) (0-10% (B)) to afford 4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-3-nitro-pyridine as a red oil (305 mg, 63%). MS (ES+) 220.1.

Step 2: 4-(1-methylpiperidin-4-yl)pyridin-3-amine

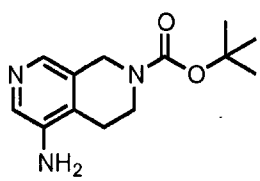
[00489] To a solution of 4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-3-nitro-pyridine (300 mg, 1.37 mmol) in Methanol (3.00 mL) was added Pd on C, (10%, wet, Degussa) (29.12 mg, 0.274 mmol) and the mixture was stirred at ambient temperature under an atmosphere of hydrogen, for 18 hours. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to afford 4-(1-methylpiperidin-4-yl)pyridin-3-amine. MS (ES+) 192.1.

[00490] The following aminopyridine were synthesized according to **Preparation C-1**:

4-(tetrahydrofuran-3-yl)pyridin-3-amine:



Preparation C-2: *tert*-butyl 5-amino-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate



Step 1: 7-tert-butoxycarbonyl-6,8-dihydro-5H-2,7-naphthyridine-4-carboxylic acid

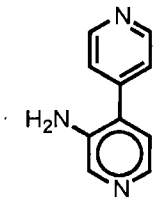
[00491] To a solution of 5,6,7,8-tetrahydro-2,7-naphthyridine-4-carboxylic acid (Hydrochloric Acid (2)) (1 g, 3.982 mmol) in a mixture of $NaHCO_3$ (1.673 g, 19.91 mmol) in water (20.00 mL) and dioxane (20.00 mL), was added Boc_2O (869.1 mg, 914.8 µL, 3.982 mmol), and the mixture was stirred overnight at RT. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and water mixture and the pH of the aqueous phase was adjusted to pH4 using a sodium bisulfate solution. The organic and aqueous layers were separated, the organic layer washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield 7-tert-butoxycarbonyl-6,8-dihydro-5H-2,7-naphthyridine-4-carboxylic acid (440 mg, 40%). MS (ES+) 279.2.

Step 2: tert-butyl 5-amino-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate

00492] To a solution of 7-tert-butoxycarbonyl-6,8-dihydro-5H-2,7-naphthyridine-4-

carboxylic acid (440 mg, 1.581 mmol) in NMP (6 mL) was added TEA (207.9 mg, 286.4 µL, 2.055 mmol) followed by diphenylphosphoryl azide (478.6 mg, 374.8 µL, 1.739 mmol) at rt under nitrogen. The reaction was heated to 90°C for 2 hours. At RT, the reaction mixture was partitioned between an aqueous saturated solution of $NaHCO_3$ and EtOAc. Combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 1-15% MeOH:DCM to yield *tert*-butyl 5-amino-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate. (397mg, 100.7%). MS (2ES+) 501.2.

Preparation C-3: [4,4'-bipyridin]-3-amine



[00493] 4-chloro-3-nitro-pyridine (100 mg, 0.6307 mmol), 4-pyridylboronic acid (77.52 mg, 0.6307 mmol), palladium; triphenylphosphane (36.45 mg, 0.03154 mmol), K_3PO_4 (946.0 µL of 2 M, 1.892 mmol) in dioxane (3 mL) was heated at 130°C for 30 min in a microwave. The mixture was loaded on a SCX column, washed with MeOH. The product was eluted with a 2M NH_3 in MeOH. The filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) , Pd/C 10% (42.04 mg, 0.3950 mmol) was added and the mixture was hydrogenated (H_2 balloon) overnight. The catalyst was filtered off and the filtrate was concentrated *in vacuo* yielding [4,4'-bipyridin]-3-amine that was used in next step without further purification. MS (ES+) 172.1.

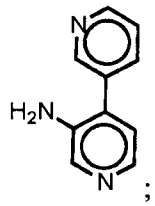
Preparation C-4 : 3'-methyl-[4,4'-bipyridin]-3-amine

[00494] [3-(tert-butoxycarbonylamino)-4-pyridyl]boronic acid (100 mg, 0.4201 mmol), palladium; triphenylphosphane (48.55 mg, 0.04201 mmol), 4-bromo-3-methyl-pyridine (113.9 mg, 0.5461 mmol), K_3PO_4 (630.0 µL of 2 M, 1.260 mmol) , in dioxane (4.000 mL) was heated at 130°C for 30min in a MW. The reaction mixture was partitioned between water and DCM. Combined organic extract was dried and concentrated *in vacuo*. The residue was dissolved in DCM (10mL) and TFA (2mL) was added. After 1h, the reaction mixture

was concentrated *in vacuo*. The residue was loaded on a SCX colum, washed with MeOH. The product was eluted with a 2M NH_3 in MeOH., filtrate was concentrated *in vacuo* yielding 3'-methyl-[4,4'-bipyridin]-3-amine that was used in next reaction w/o further purification (90mg). MS (ES+) 172.1.

[00495] The following amino pyridine were prepared using procedures similar to **Preparation C-3** or **Preparation C-4**:

[3,4'-bipyridin]-3'-amine:



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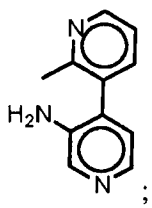
2-methyl-[3,4'-bipyridin]-3'-amine:



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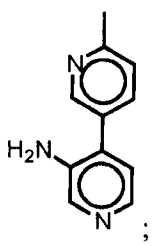
6-methyl-[3,4'-bipyridin]-3'-amine:



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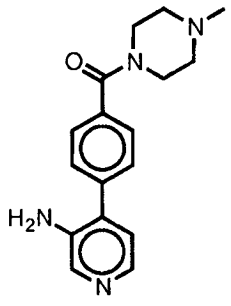
(4-(3-aminopyridin-4-yl)phenyl)(4-methylpiperazin-1-yl)methanone:



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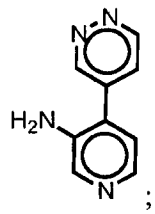
4-(pyridazin-4-yl)pyridin-3-amine:



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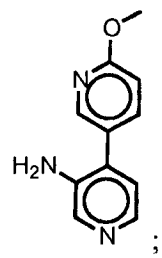
6-methoxy-[3,4'-bipyridin]-3'-amine:



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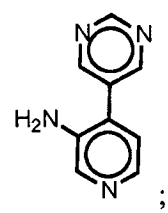
4-(pyrimidin-5-yl)pyridin-3-amine:



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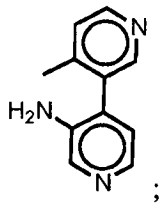
4-methyl-[3,4'-bipyridin]-3'-amine:



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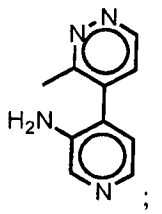
4-(3-methylpyridazin-4-yl)pyridin-3-amine:



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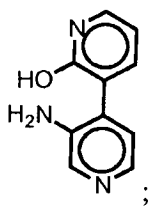
3'-amino-[3,4'-bipyridin]-2-ol:



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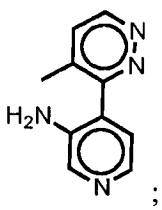
4-(4-methylpyridazin-3-yl)pyridin-3-amine:



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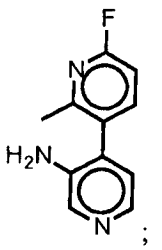
6-fluoro-2-methyl-[3,4'-bipyridin]-3'-amine:



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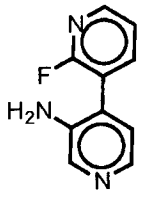
2-fluoro-[3,4'-bipyridin]-3'-amine:



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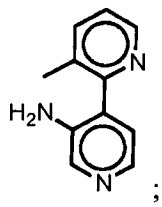
3-methyl-[2,4'-bipyridin]-3'-amine:



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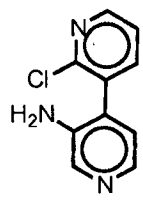
2-chloro-[3,4'-bipyridin]-3'-amine:



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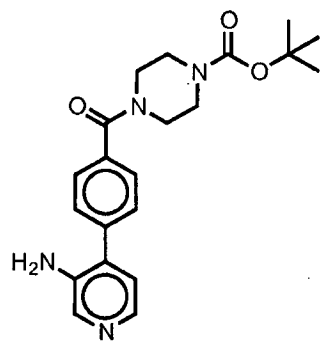
tert-butyl 4-(4-(3-aminopyridin-4-yl)benzoyl)piperazine-1-carboxylate:



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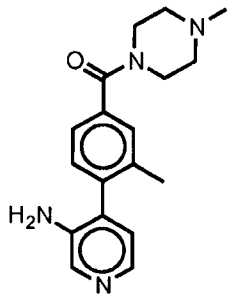
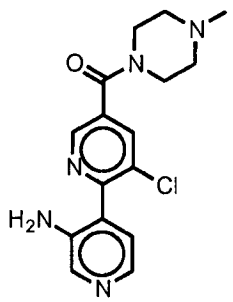
(4-(3-aminopyridin-4-yl)-3-methylphenyl)(4-methylpiperazin-1-yl)methanone:



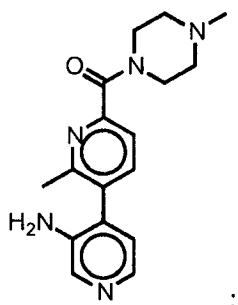
;

(3'-amino-3-chloro-[2,4'-bipyridin]-5-yl)(4-methylpiperazin-1-yl)methanone:



;

(3'-amino-2-methyl-[3,4'-bipyridin]-6-yl)(4-methylpiperazin-1-yl)methanone:



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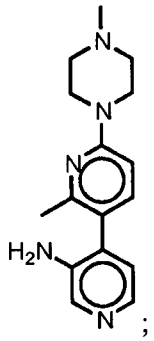
2-methyl-6-(4-methylpiperazin-1-yl)-[3,4'-bipyridin]-3'-amine:



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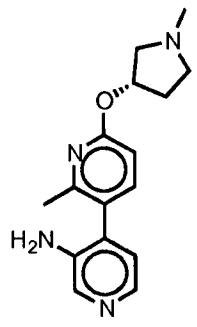
(*S*)-2-methyl-6-((1-methylpyrrolidin-3-yl)oxy)-[3,4'-bipyridin]-3'-amine:



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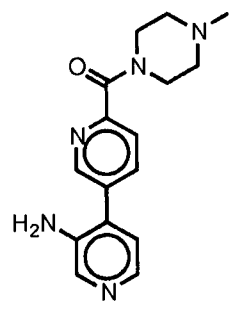
(3'-amino-[3,4'-bipyridin]-6-yl)(4-methylpiperazin-1-yl)methanone:



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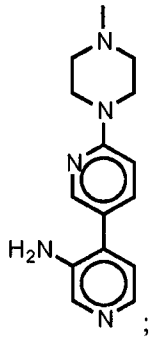
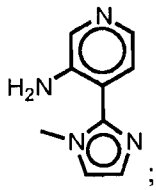
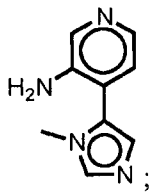
6-(4-methylpiperazin-1-yl)-[3,4'-bipyridin]-3'-amine:



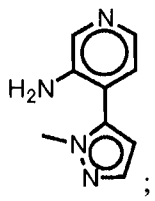
4-(1-methyl-1*H*-imidazol-2-yl)pyridin-3-amine:



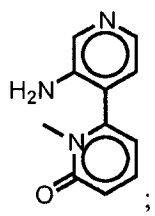
4-(1-methyl-1*H*-imidazol-5-yl)pyridin-3-amine:



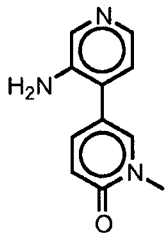
4-(1-methyl-1*H*-pyrazol-5-yl)pyridin-3-amine:



3'-amino-1-methyl-[2,4'-bipyridin]-6(1*H*)-one:



3'-amino-1-methyl-[3,4'-bipyridin]-6(1*H*)-one:



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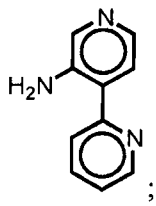
[2,4'-bipyridin]-3'-amine:



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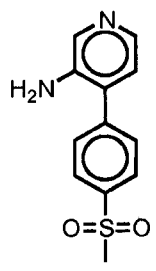
4-(4-(methylsulfonyl)phenyl)pyridin-3-amine:



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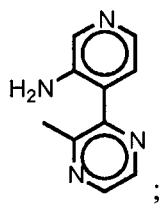
4-(3-methylpyrazin-2-yl)pyridin-3-amine:



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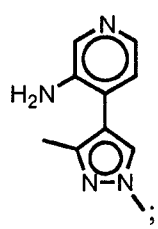
4-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-amine:



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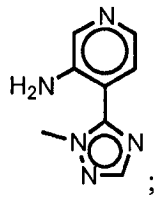
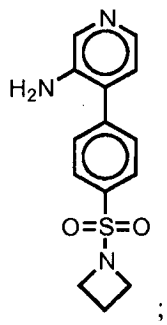
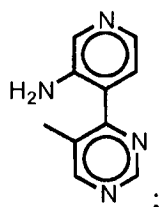
4-(1-methyl-1*H*-1,2,4-triazol-5-yl)pyridin-3-amine:



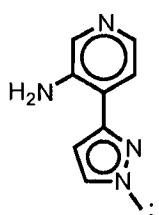
4-(4-(azetidin-1-ylsulfonyl)phenyl)pyridin-3-amine:



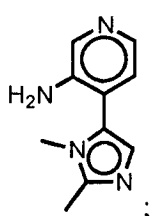
4-(5-methylpyrimidin-4-yl)pyridin-3-amine:



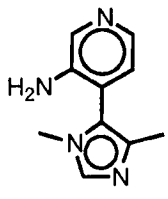
4-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-amine:



4-(1,2-dimethyl-1*H*-imidazol-5-yl)pyridin-3-amine:



4-(1,4-dimethyl-1*H*-imidazol-5-yl)pyridin-3-amine:



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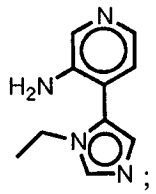
4-(1-ethyl-1*H*-imidazol-5-yl)pyridin-3-amine:



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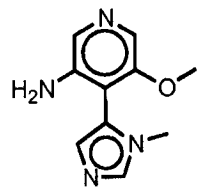
5-methoxy-4-(1-methyl-1*H*-imidazol-5-yl)pyridin-3-amine:



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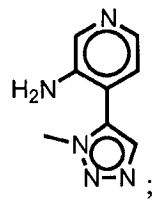
4-(1-methyl-1*H*-1,2,3-triazol-5-yl)pyridin-3-amine:



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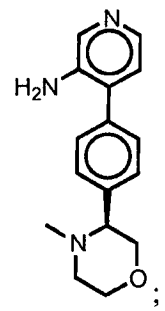
(*S*)-4-(4-(4-methylmorpholin-3-yl)phenyl)pyridin-3-amine:



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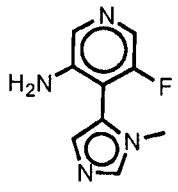
5-fluoro-4-(1-methyl-1*H*-imidazol-5-yl)pyridin-3-amine:



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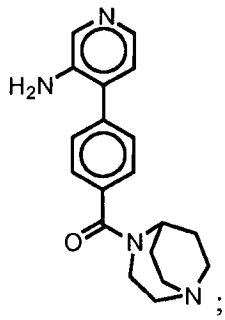
(4-(3-aminopyridin-4-yl)phenyl)(1,4-diazabicyclo[3.2.2]nonan-4-yl)methanone:



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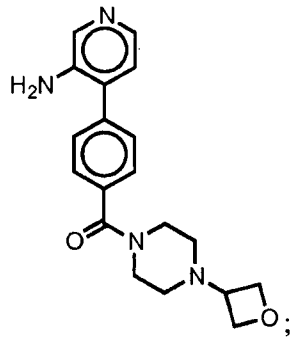
(4-(3-aminopyridin-4-yl)phenyl)(4-(oxetan-3-yl)piperazin-1-yl)methanone:



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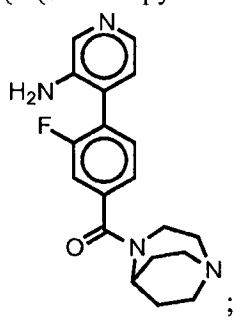
(4-(3-aminopyridin-4-yl)-3-fluorophenyl)(1,4-diazabicyclo[3.2.2]nonan-4-yl)methanone:



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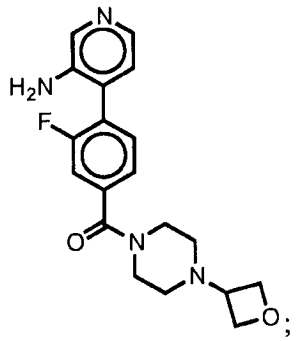
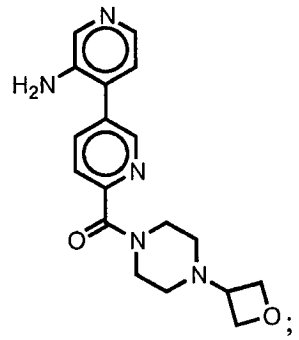
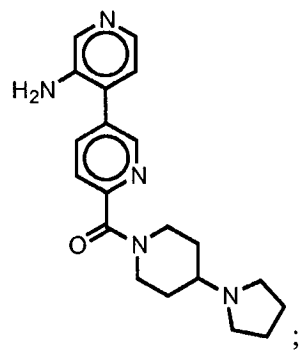
(4-(3-aminopyridin-4-yl)-3-fluorophenyl)(4-(oxetan-3-yl)piperazin-1-yl)methanone:



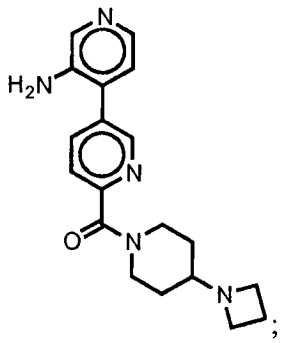
(3'-amino-[3,4'-bipyridin]-6-yl)(4-(oxetan-3-yl)piperazin-1-yl)methanone:



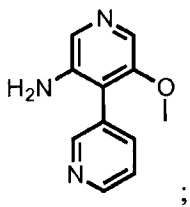
(3'-amino-[3,4'-bipyridin]-6-yl)(4-(pyrrolidin-1-yl)piperidin-1-yl)methanone:



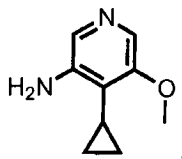
(3'-amino-[3,4'-bipyridin]-6-yl)(4-(azetidin-1-yl)piperidin-1-yl)methanone:



5'-methoxy-[3,4'-bipyridin]-3'-amine:

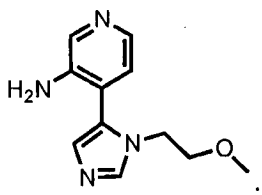


4-cyclopropyl-5-methoxypyridin-3-amine:

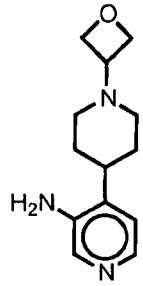


; and

4-(1-(2-methoxyethyl)-1*H*-imidazol-5-yl)pyridin-3-amine:



Preparation C-5: 4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine



Step 1: tert-butyl 3'-nitro-5,6-dihydro-[4,4'-bipyridine]-1(2H)-carboxylate

[00496] 4-chloro-3-nitro-pyridine (1 g, 6.307 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (2.145 g, 6.938 mmol) and $PdCl_2(PPh_3)_2$ (221.4 mg, 0.3154 mmol) in DME (20.00 mL) were degassed using 3x vacuum/nitrogen cycles. Na_2CO_3 (9.460 mL of 2 M, 18.92 mmol) was added followed by further degassing and the reaction heated at 80°C for 18 hours. The reaction was cooled to ambient temperature and diluted with EtOAc/water. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x1), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO Companion, 120 g column, eluting with 0 to 70% EtOAc/Petroleum Ether, dry loaded) to give *tert*-butyl 3'-nitro-5,6-dihydro-[4,4'-bipyridine]-1(2*H*)-carboxylate as a pale yellow solid (884 mg, 46% Yield). MS (ES Na+) 328.1.

Step 2: 3'-nitro-1,2,3,6-tetrahydro-4,4'-bipyridine

[00497] TFA (2 mL, 25.96 mmol) was added to a stirred solution of tert-butyl 4-(3-nitro-4-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (883 mg, 2.892 mmol) in DCM (10 mL) and the reaction stirred at ambient temperature for 15 hours. The solvent was removed *in vacuo* and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 25 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures and concentrated *in vacuo* to give 3'-nitro-1,2,3,6-tetrahydro-4,4'-bipyridine as an orange oil (523 mg, 88% Yield). MS (ES+) 206.1.

Step 3: 3'-nitro-1-(oxetan-3-yl)-1,2,3,6-tetrahydro-4,4'-bipyridine

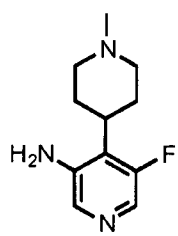
[00498] Sodium triacetoxyborohydride (Sodium Ion (1)) (1.189 g, 5.608 mmol) was added

in portions to a stirred solution of 3-nitro-4-(1,2,3,6-tetrahydropyridin-4-yl)pyridine (523 mg, 2.549 mmol) and 3-oxetanone (312.2 mg, 277.8 µL, 4.333 mmol) in THF (10 mL) at 0°C under an atmosphere of nitrogen. The reaction was allowed to warm to ambient temperature and was stirred for 16 hours. MeOH (2 mL) was added dropwise and the mixture stirred at ambient temperature for 30 minutes. The mixture was concentrated *in vacuo* and the residue was partitioned between water and EtAOc. The pH of the aqueous layer was adjusted to pH 7-8 by the addition of NH_4OH and the layers separated. The aqueous layer was extracted with EtOAc (x 3) and the combined organic extracts washed with brine (x 1), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 3'-nitro-1-(oxetan-3-yl)-1,2,3,6-tetrahydro-4,4'-bipyridine as a red oil (615 mg, 92% Yield). MS (ES+) 262.1.

Step 4: 4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine

[00499] Pd on C, wet, Degussa (240 mg, 0.2255 mmol) was added to a stirred solution of 3-nitro-4-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]pyridine (614 mg, 2.350 mmol) in EtOAc (20 mL) / EtOH (20 mL). The reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 15 hours. The catalyst was removed by filtration through a pad of celite and the filtrate concentrated *in vacuo* to give the 4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine as a pale yellow solid (518 mg, 95% Yield). MS (ES+) 234.2.

Preparation C-6 : 5-fluoro-4-(1-methylpiperidin-4-yl)pyridin-3-amine



Step 1: 3'-chloro-5'-fluoro-1-methyl-1,2,3,6-tetrahydro-4,4'-bipyridine

[00500] 3-chloro-5-fluoro-4-iodo-pyridine (500 mg, 1.942 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (476.6 mg, 2.136 mmol) and $Pd(PPh_3)_2Cl_2$ (68.15 mg, 0.09710 mmol) in DME (10.00 mL) were degassed using 3 x

vacuum/nitrogen cycles. Na_2CO_3 (2.913 mL of 2 M, 5.826 mmol) was added followed by further degassing and the reaction heated at 80 °C for 18 hours. The reaction was cooled to ambient temperature and diluted with EtOAc/water. The layers were separated and the aqueous layer extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x1), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was passed through a 10 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures and concentrated *in vacuo* . The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% MeOH/DCM + 1% NH_4OH, loaded in DCM) to give 3'-chloro-5'-fluoro-1-methyl-1,2,3,6-tetrahydro-4,4'-bipyridine as a red solid (378 mg, 86% Yield). MS (ES+) 227.1.

Step 2: tert-butyl (5-fluoro-1'-methyl-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-yl)carbamate

[00501] 3-chloro-5-fluoro-4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyridine (377 mg, 1.663 mmol), tert-butyl carbamate (974.1 mg, 8.315 mmol), sodium tert-butoxide (815.1 mg, 8.481 mmol), BrettPhos pre-catalyst (66.25 mg, 0.08315 mmol) and BrettPhos (44.63 mg, 0.08315 mmol) were placed in a sealable tube an degassed by vacuum/nitrogen cycles (x 5). Dry dioxane (10 mL) was added and the resulting mixture was placed into a pre-heated block at 100°C and stirred at this temperature for 16 hours. Further portions of BrettPhos pre-catalyst (66.25 mg, 0.08315 mmol) and BrettPhos (44.63 mg, 0.08315 mmol) were added and the reaction heated at 100°C for 8 hours . The reaction mixture was cooled to ambient temperature and quenched with saturated NH_4Cl. The mixture was passed through a pre-wetted (EtOAc) celite cartridge (2.5 g). The cartridge was washed with EtOAc/saturated NH_4Cl and the layers of the filtrate separated. The aqueous layer was extracted with EtOAc (x 3) and the combined organic extracts were washed with brine (x 1), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% MeOH/DCM, loaded in DCM) to give *tert*-butyl (5-fluoro-1'-methyl-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-yl)carbamate. MS (ES+) 308.2.

Step 3: 5-fluoro-1'-methyl-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-amine

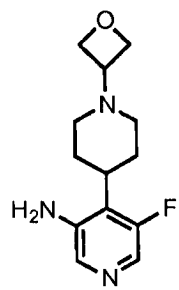
[00502] TFA (2 mL, 25.96 mmol) was added to a stirred solution of tert-butyl N-[5-fluoro-4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]carbamate (483 mg, 1.571 mmol) in

DCM (10 mL) and the reaction stirred at ambient temperature for 6 hours. The solvent was removed *in vacuo* and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 10 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures and concentrated *in vacuo.* The residue was purified by column chromatography (ISCO Companion, 40 g column, eluting with 0 to 10% MeOH/DCM + 1% NH_4OH, loaded in DCM) to give 5-fluoro-1'-methyl-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-amine as an off-white solid (61 mg, 19% Yield over 2 steps). MS (ES+) 208.1.

Step 4: 5-fluoro-4-(1-methylpiperidin-4-yl)pyridin-3-amine

[00503] Pd on C, wet, Degussa (25 mg, 0.1175 mmol) was added to a stirred solution of 5-fluoro-4-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyridin-3-amine (61 mg, 0.2943 mmol) in EtOAc (5 mL) / EtOH (5 mL). The reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 15 hours. A further portion of Pd on C, wet, Degussa (25 mg, 0.1175 mmol) was added and the reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 24 hours. The catalyst was removed by filtration through a pad of celite and the filtrate concentrated *in vacuo* to give 5-fluoro-4-(1-methylpiperidin-4-yl)pyridin-3-amine as an off-white solid (58 mg, 95% Yield). MS (ES+) 210.1.

Preparation C-7 : 5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine



Step 1: tert-butyl 3'-chloro-5'-fluoro-5,6-dihydro-[4,4'-bipyridine]-1(2H)-carboxylate

[00504] 3-chloro-5-fluoro-4-iodo-pyridine (750 mg, 2.913 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (990.7 mg, 3.204 mmol) and $Pd(PPh_3)_2Cl_2$ (102.2 mg, 0.1456 mmol) in DME (15 mL) were degassed using 3 x vacuum/nitrogen cycles. Na_2CO_3 (4.370 mL of 2 M, 8.739 mmol) was added

followed by further degassing and the reaction heated at 90°C for 2 hours. The reaction was cooled to ambient temperature and diluted with EtOAc/water. The layers were separated and the aqueous layer extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x1), dried ($MgSO_4$), filtered and concentrated *in vacuo* . The residue was purified by column chromatography (ISCO Companion, 80 g column, eluting with 0 to 20% EtOAc/Petroleum Ether, loaded in DCM) to give *tert*-butyl 3'-chloro-5'-fluoro-5,6-dihydro-[4,4'-bipyridine]-1(2*H*)-carboxylate as an off-white solid (708 mg, 78% Yield). MS (ES+) 313.1.

Step 2: 3'-chloro-5'-fluoro-1,2,3,6-tetrahydro-4,4'-bipyridine

[00505] TFA (2 mL, 25.96 mmol) was added to a stirred solution of tert-butyl 4-(3-chloro-5-fluoro-4-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (708 mg, 2.264 mmol) in DCM (10 mL) and the reaction stirred at ambient temperature for 2 hours. The solvent was removed *in vacuo* and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 10 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures and concentrated *in vacuo* to give 3'-chloro-5'-fluoro-1,2,3,6-tetrahydro-4,4'-bipyridine as an off-white solid (468 mg , 97% Yield). MS (ES+) 213.1.

Step 3: 3'-chloro-5'-fluoro-1-(oxetan-3-yl)-1,2,3,6-tetrahydro-4,4'-bipyridine

[00506] Sodium triacetoxyborohydride (Sodium Ion (1)) (1.026 g, 4.842 mmol) was added in portions to a stirred solution of 3-chloro-5-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)pyridine (468 mg, 2.201 mmol) and 3-oxetanone (269.7 mg, 239.9 µL, 3.742 mmol) in THF (10 mL) at 0°C under an atmosphere of nitrogen. The reaction was allowed to warm to ambient temperature over 16 hours. MeOH (2 mL) was added dropwise and the mixture stirred at ambient temperature for 30 minutes. The mixture was concentrated *in vacuo* and partitioned between water and EtAOc. The pH of the aqueous layer was adjusted to p H 7-8 by the additon of NH_4OH and the layers separated. The aqueous layer was extracted with EtOAc (x 3) and the combined organic extracts washed with brine (x 1), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 3'-chloro-5'-fluoro-1-(oxetan-3-yl)-1,2,3,6-tetrahydro-4,4'-bipyridine as a white solid (573 mg, 97% Yield). MS (ES+) 269.1.

Step 4: tert-butyl (5-fluoro-1'-(oxetan-3-yl)-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-

yl)carbamate

[00507] 3-chloro-5-fluoro-4-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]pyridine (572 mg, 2.129 mmol) , tert-butyl carbamate (1.246 g, 10.64 mmol) , sodium tert-butoxide (1.044 g, 10.86 mmol) , BrettPhos pre-catalyst (84.78 mg, 0.1064 mmol) and BrettPhos (57.11 mg, 0.1064 mmol) were placed in a sealable tube and degassed by vacuum/nitrogen cycles (x5). Dry dioxane (10 mL) was added and the resulting mixture was placed into a pre-heated block at 100°C and stirred at this temperature for 16 hours. The reaction mixture was cooled to ambient temperature and quenched with saturated NH_4Cl. The mixture was passed through a pre-wetted (EtOAc) celite cartridge (2.5 g). The cartridge was washed with EtOAc/saturated NH_4Cl and the layers of the filtrate separated. The aqueous layer was extracted with EtOAc (x 3) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* . The residue was purified by column chromatography (ISCO Companion, 80 g column, eluting with 0 to 100% EtOAc/Petroleum Ether, loaded in DCM) to give *tert*-butyl (5-fluoro-1'-(oxetan-3-yl)-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-yl)carbamate as a pale yellow solid (180 mg, 24% Yield). Also isolate 197 mg of a mixture of SM and product. MS (ES+) 350.2.

Step 5: tert-butyl (5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-yl)carbamate

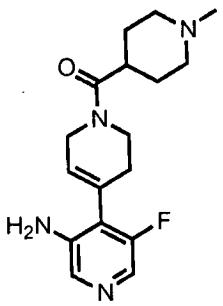
[00508] Pd on C, wet, Degussa (70 mg, 0.06578 mmol) was added to a stirred solution of tert-butyl N-[5-fluoro-4-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-3-pyridyl]carbamate (180 mg, 0.5152 mmol) in EtOH (5 mL) / EtOAc (5 mL). The reaction was placed under an atmosphere of hydrogen and stirred at ambient temperature for 46 hours. The catalyst was removed by filtration through a pad of celite and the filtrate concentrated *in vacuo* to give *tert*-butyl (5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-yl)carbamate as an off-white solid (175 mg, 97% Yield). MS (ES+) 352.2.

Step 6: 5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine

[00509] TFA (1 mL, 12.98 mmol) was added to a stirred solution of tert-butyl N-[5-fluoro-4-[1-(oxetan-3-yl)-4-piperidyl]-3-pyridyl]carbamate (174 mg, 0.4951 mmol) in DCM (5 mL) and the reaction stirred at ambient temperature for 4 hours. The solvent was removed *in vacuo* and the residue azeotroped with DCM (x 2) and ether (x 2). The residue was passed through a 5 g SCX-2 cartridge and washed with MeOH/DCM mixtures. The product was

eluted by washing the cartridge with 2M NH_3 in MeOH/DCM mixtures and concentrated *in vacuo* to give 5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-amine as a yellow oil (109 mg, 88% Yield). MS (ES+) 252.1.

Preparation C-8 : (3'-amino-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2*H*)-yl)(1-methylpiperidin-4-yl)methanone



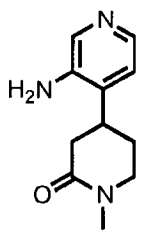
Step 1: (3'-chloro-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2H)-yl)(1-methylpiperidin-4-yl)methanone

[00510] To a solution of 3-chloro-5-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)pyridine (540 mg, 2.539 mmol) (prepared according to methods similar to the ones depicted in *step 1* and *step 2* of **Preparation C-7**) in NMP (5 mL) was added TBTU (1.223 g, 3.809 mmol), 1-methylpiperidine-4-carboxylic acid (Hydrochloric Acid (1)) (547.4 mg, 3.047 mmol) and DIPEA (656.3 mg, 884.5 µL, 5.078 mmol) and the reaction was stirred at ambient temperature for 2 hours. The reaction mixture was adsorbed onto a pre-wetted (methanol, 20 mL) SCX-2 cartridge (10 g) and flushed with DCM/methanol (1:1, 2 x 20 mL) and then the basic components eluted with 2 M ammonia in methanol (2x20 mL). The basic eluent was evaporated to dryness to afford a pale orange oil (744 mg). The residue was triturated in DCM (2 mL) and a white solid was filtered off. The filtrate was purified by column chromatography on silica gel eluting with DCM (A): DCM/Methanol/NH_4OH (90:10:1, (B)) (0-100% (B), 40 g, 20.0 CV, 40 mL/min) to afford (3'-chloro-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2H)-yl)(1-methylpiperidin-4-yl)methanone as a pale orange oil (410 mg, 48%). MS (ES+) 338.5.

Step 2: (3'-amino-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2H)-yl)(1-methylpiperidin-4-yl)methanone

[00511] [4-(3-chloro-5-fluoro-4-pyridyl)-3,6-dihydro-2H-pyridin-1-yl]-(1-methyl-4-piperidyl)methanone (400 mg, 1.184 mmol), tert-butyl carbamate (693.5 mg, 5.920 mmol) , BrettPhos (63.55 mg, 0.1184 mmol), BrettPhos pre-catalyst (94.34 mg, 0.1184 mmol) and sodium tert-butoxide (580.3 mg, 6.038 mmol) were added to a Schlenk tube under a nitrogen atmosphere. The solid mixture was degassed by vacuum/nitrogen cycles (x5) then was added anhydrous Toluene (8.000 mL) and the resulting mixture was placed into a pre-heated block at 100°C and was stirred for 4 hours. The reaction mixture was cooled to ambient temperature, quenched with saturated NH_4Cl solution and partitioned between DCM/MeOH (9:1, 2x50 mL) and water (50 mL). The combined organics were washed with brine (50 mL), dried and concentrated *in vacuo* to afford a pale orange oil (456 mg). The residue was purified by column chromatography on silica gel eluting with DCM (A): DCM/MeOH/NH_4OH (90:10:1, (B)) (0-100% (B), 40 g, 20.0 CV, 40 mL/min) to afford (3'-amino-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2H)-yl)(1-methylpiperidin-4-yl)methanone (200 mg). It was dissolved in DCM (2.000 mL) and TFA (1.0 mL) was added and the mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated in vacuo and the residue was loaded onto a pre-wetted (DCM/methanol, (1:1) 10 mL) SCX-2 cartridge (5 g) and flushed with DCM/methanol (1:1, 25 mL) and then the basic components was eluted with 2 M ammonia in methanol (20 mL). The basic eluent was evaporated to dryness to afford a pale yellow oil (325 mg) that was purified by column chromatography on silica gel eluting with DCM (A): DCM/Methanol/NH_4OH (90:10:1, (B)) (50-100% (B), 2 4 g, 20.0 CV, 35 mL/min) to afford (3'-amino-5'-fluoro-5,6-dihydro-[4,4'-bipyridin]-1(2H)-yl)(1-methylpiperidin-4-yl)methanone as a colourless oil (55 mg, 12%). MS (ES+) 319.2.

Preparation C-9: 4-(3-aminopyridin-4-yl)-1-methylpiperidin-2-one



Step 1: tert-butyl (1'-methyl-2'-oxo-1',2'-dihydro-[4,4'-bipyridin]-3-yl)carbamate

[00512] To a suspension of [3-(tert-butoxycarbonylamino)-4-pyridyl]boronic acid (200 mg, 0.8402 mmol), 4-bromo-1-methyl-pyridin-2-one (158.0 mg, 0.8402 mmol) and $Pd(PPh_3)_4$ (48.55 mg, 0.04201 mmol) in Dioxane (2 mL) was added Na_2CO_3 (840.0 µL of 2

M, 1.680 mmol) and was heated at 80°C overnight. The reaction mixture was cooled to ambient temperature and filtered through a prewetted (methanol, 5 mL) Celite cartridge (2.5 g) and washed with methanol (35 mL). The filtrate was concentrated in vacuo to afford a pale brown oil (500 mg). The residue was partitioned between DCM (2x30 mL) and saturated sodium bicarbonate solution (30 mL). The combined organics were dried (phase sep cartridge) and concentrated in vacuo to afford an orange oil (280 mg). The residue was purified by column chromatography on ISCO Companion eluting with DCM (A): DCM/Methanol/NH_4OH (90:10:1, (B)) (0-100% (B), 12 g, 16.0 CV, 30 mL/min) to afford tert-butyl (1'-methyl-2'-oxo-1',2'-dihydro-[4,4'-bipyridin]-3-yl)carbamate as a pale yellow oil (121 mg, 48%). MS (ES+) 302.1.

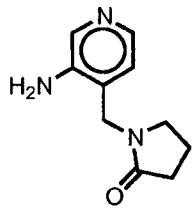
Step 2: tert-butyl (4-(1-methyl-2-oxopiperidin-4-yl)pyridin-3-yl)carbamate

[00513] A 0.05 M solution of tert-butyl N-[4-(1-methyl-2-oxo-4-pyridyl)-3-pyridyl]carbamate (120 mg, 0.3982 mmol) in Ethanol (8 mL) was passed through a Pd/C CatCart in the H-cube at a flow rate of 0.5 mL/min at 50 C and 50 bar. The procedure was repeated 3 more time. The product solution was concentrated in vacuo to afford tert-butyl (4-(1-methyl-2-oxopiperidin-4-yl)pyridin-3-yl)carbamate as a colourless oil (74 mg, 61%). MS (ES+) 306.1.

Step 3: 4-(3-aminopyridin-4-yl)-1-methylpiperidin-2-one

[00514] TFA (0.75 mL, 9.735 mmol) was added to a solution of tert-butyl N-[4-(1-methyl-2-oxo-4-piperidyl)-3-pyridyl]carbamate (74 mg, 0.2423 mmol) in DCM (2 mL) and was stirred at ambient temperature for 2 hours. The reaction mixture was adsorbed onto a pre-wetted (methanol/DCM (1:1), 2 mL) SCX-2 cartridge (2 g) and flushed with DCM/methanol (1:1, 20 mL) and then the basic components eluted with 2 M ammonia in methanol (20 mL). The basic eluent was evaporated to dryness to afford 4-(3-aminopyridin-4-yl)-1-methylpiperidin-2-one as a pale yellow oil (50 mg, 97%). MS (ES+) 206.1.

Preparation C-10: 1-((3-aminopyridin-4-yl)methyl)pyrrolidin-2-one



Step 1: 1-((3-bromopyridin-4-yl)methyl)pyrrolidin-2-one

[00515] Solution A: Sodium hydride (141.5 mg, 3.537 mmol) was added to a solution of pyrrolidin-2-one (316.1 mg, 282.2 μL, 3.714 mmol) in THF (5 mL) and the solution was stirred for 30 mins.

[00516] Solution B: To a solution of (3-bromo-4-pyridyl)methanol (665 mg, 3.537 mmol) in DCM (20 mL) at 0°C was added triethylamine (0.467 mL, 3.351 mmol) and methanesulfonyl chloride (0.287 mL, 3.708 mmol) and the solution allowed to warm to room temperature and stirred for 1h.

[00517] Solution B was added to Solution A and the mixture was stirred for 2h. The reaction mixture was partitioned between water and EtOAc. Combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo (at RT) to give a oil that was purified by chromatography on silica (eluting with 2-4% MeOH in EtOAc) to give 1-((3-bromopyridin-4-yl)methyl)pyrrolidin-2-one as a yellow oil. MS (ES+) 211.0.

Step 2: 1-((3-aminopyridin-4-yl)methyl)pyrrolidin-2-one

[00518] Prepared according to a procedure similar to *Step 3* of **Preparation N-14**. MS (ES+) 192.0.

[00519] The following amides were formed using a procedure similar to **Example 1** or **Example 3a**:

2-amino-6-fluoro-*N*-(4-(1-methylpiperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-1**);

2-amino-6-chloro-*N*-(4-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-2**);

2-amino-6-(cyanomethyl)-*N*-(4-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-

carboxamide (**Compound I-C-3**);

2-amino-6-fluoro-*N*-(4-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-4**);

2-amino-6-fluoro-*N*-(4-phenylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-5**);

2-amino-6-(cyanomethyl)-*N*-(4-phenylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-6**);

2-amino-6-fluoro-*N*-(5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-7**);

2-amino-6-fluoro-*N*-(4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-10**);

2-amino-6-chloro-*N*-(4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-11**);

2-amino-6-fluoro-*N*-(5-fluoro-1'-(oxetan-3-yl)-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-12**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide(**Compound I-C-13**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(1-methylpiperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-14**);

N-([3,4'-bipyridin]-3'-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-15**);

2-amino-6-fluoro-*N*-(6-(4-methylpiperazine-1-carbonyl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-19**);

2-amino-6-fluoro-*N*-(2-methyl-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-20**)

2-amino-6-fluoro-*N*-(6-(4-methylpiperazin-1-yl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-

a]pyrimidine-3-carboxamide (**Compound I-C-21**);

2-amino-6-fluoro-*N*-(6-methyl-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-22**);

2-amino-6-(2-cyanopropan-2-yl)-*N*-(4-(1-methylpiperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-23**);

N-([4,4'-bipyridin]-3-yl)-2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-24**);

2-amino-6-fluoro-*N*-(4-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-25**);

2-amino-6-fluoro-*N*-(4-(pyridazin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-26**);

2-amino-6-fluoro-*N*-(6-methoxy-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-27**);

2-amino-6-fluoro-*N*-(4-(pyrimidin-5-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-28**);

2-amino-6-fluoro-*N*-(3'-methyl-[4,4'-bipyridin]-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide **I-C-29**);

2-amino-6-fluoro-*N*-(4-methyl-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-30**);

2-amino-6-fluoro-*N*-(4-(3-methylpyridazin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-31**);

2-amino-6-fluoro-*N*-(2-hydroxy-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-32**);

2-amino-6-fluoro-*N*-(4-(4-methylpyridazin-3-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-33**);

2-amino-6-fluoro-*N*-(6-fluoro-2-methyl-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-34**);

2-amino-6-fluoro-*N*-(2-fluoro-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-35**);

2-amino-6-fluoro-*N*-(3-methyl-[2,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-36**);

2-amino-*N*-(2-chloro-[3,4'-bipyridin]-3'-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-37**);

2-amino-6-fluoro-*N*-(5-fluoro-1'-(1-methylpiperidine-4-carbonyl)-1',2',3',6'-tetrahydro-[4,4'-bipyridin]-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-38**);

2-amino-6-fluoro-*N*-(2-methyl-6-(4-methylpiperazine-1-carbonyl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-39**);

2-amino-6-fluoro-*N*-(2-methyl-6-(4-methylpiperazin-1-yl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-40**);

(*R*)-2-amino-6-fluoro-*N*-(2-methyl-6-((1-methylpyrrolidin-3-yl)oxy)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-41**);

2-amino-*N*-(4-cyclopropylpyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-42**);

2-amino-6-fluoro-*N*-(5-fluoro-4-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-43**);

2-amino-6-fluoro-*N*-(4-(4-(piperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-44**);

2-amino-6-fluoro-*N*-(4-(2-methyl-4-(4-methylpiperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-45**);

2-amino-*N*-(3-chloro-5-(4-methylpiperazine-1-carbonyl)-[2,4'-bipyridin]-3'-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-46**); and

2-amino-*N*-(4-(1-(cyclopropylsulfonyl)piperidin-4-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-47**);

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonane-4-carbonyl)phenyl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-48**);

2-amino-6-fluoro-N-(4-(4-(4-(oxetan-3-yl)piperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-49**);

N-(4-(4-(1,4-diazabicyclo[3.2.2]nonane-4-carbonyl)-2-fluorophenyl)pyridin-3-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-50**);

2-amino-6-fluoro-N-(4-(2-fluoro-4-(4-(oxetan-3-yl)piperazine-1-carbonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-51**);

2-amino-6-fluoro-N-(6-(4-(oxetan-3-yl)piperazine-1-carbonyl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-52**);

2-amino-6-fluoro-N-(6-(4-(pyrrolidin-1-yl)piperidine-1-carbonyl)-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-53**);

2-amino-N-(6-(4-(azetidin-1-yl)piperidine-1-carbonyl)-[3,4'-bipyridin]-3'-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-54**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-imidazol-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-55**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-imidazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-56**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-57**);

2-amino-6-fluoro-N-(1-methyl-6-oxo-1,6-dihydro-[2,4'-bipyridin]-3'-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-58**);

2-amino-6-fluoro-N-(1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-59**);

N-([2,4'-bipyridin]-3'-yl)-2-amino-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-60**);

2-amino-6-fluoro-N-(4-(4-(methylsulfonyl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-61**);

2-amino-6-fluoro-N-(4-(3-methylpyrazin-2-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-62**);

2-amino-N-(4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-63**);

2-amino-N-(4-(4-(azetidin-1-ylsulfonyl)phenyl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-64**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-1,2,4-triazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-65**);

(S)-2-amino-6-fluoro-N-(4-(4-(4-methylmorpholin-3-yl)phenyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-66**);

2-amino-6-fluoro-N-(4-(5-methylpyrimidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-67**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-68**);

2-amino-6-fluoro-N-(4-(1-methyl-1H-1,2,3-triazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-72**);

2-amino-6-fluoro-N-(4-(1-methyl-2-oxopiperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-73**);

2-amino-6-fluoro-N-(4-(tetrahydrofuran-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-75**);

2-amino-6-fluoro-N-(4-((2-oxopyrrolidin-1-yl)methyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-76**);

2-amino-N-(4-(1,2-dimethyl-1H-imidazol-5-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-77**);

2-amino-N-(4-(1,4-dimethyl-1H-imidazol-5-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-78**);

2-amino-6-fluoro-N-(5-fluoro-4-(1-methyl-1H-imidazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-79**);

2-amino-N-(4-(1-ethyl-1H-imidazol-5-yl)pyridin-3-yl)-6-fluoropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-80**);

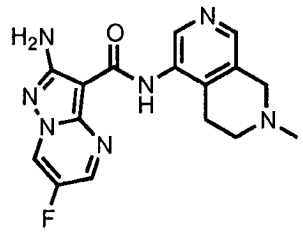
2-amino-6-fluoro-N-(5-methoxy-4-(1-methyl-1H-imidazol-5-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound I-C-81**);

2-amino-6-fluoro-*N*-(5'-methoxy-[3,4'-bipyridin]-3'-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-82**);

2-amino-6-fluoro-*N*-(4-(1-(2-methoxyethyl)-1*H*-imidazol-5-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-83**); and

2-amino-*N*-(4-cyclopropyl-5-methoxypyridin-3-yl)-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-84**).

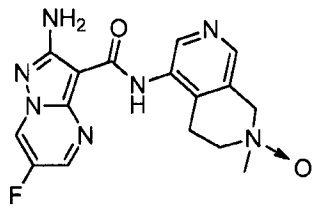
Example 15: 2-amino-6-fluoro-*N*-(7-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-C-8)



[00520] *tert*-butyl 5-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate was dissolved in MeOH (8 mL). Acetic acid (91.88 mg, 87.01 μL, 1.530 mmol), formaldehyde (37% solution in water, 99.33 mg, 91.13 μL, 1.224 mmol) and $NaBH(OAc)_3$ (324.3 mg, 1.530 mmol) was sequentially added and the

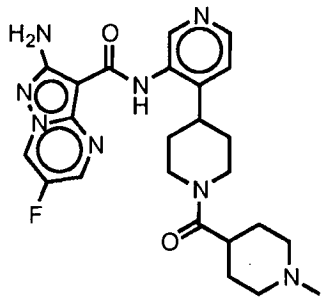
mixture was stirred for 1 hour at RT. The reaction mixture was partitioned between an aqueous saturated solution of $NaHCO_3$ and DCM. The insoluble was filtered off and the combined organic extract was dried and concentrated *in vacuo*. The insoluble and the residue were combined and purified by fractionlynx to yield 2-amino-6-fluoro-*N*-(7-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. MS (ES+) 342.2.

Example 16: 5-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-2-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine 2-oxide (Compound I-C-9)



[00521] To 2-amino-6-fluoro-*N*-(7-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (12 mg, 0.03516 mmol) in DCM (2 mL) was added mCPBA (5.764 mg, 0.03340 mmol) and the mixture was stirred at RT for 2h before the solvent was removed *in vacuo*. The residue was purified by FractionLynx to yield 5-(2-amino-6-fluoropyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-2-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine 2-oxide. MS (ES+) 358.2.

Example 17: 2-amino-6-fluoro-*N*-(4-(1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (Compound I-C-16)



Step 1: 2-amino-6-fluoro-N-(4-(piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00522] To a solution of tert-butyl 4-[3-[(2-amino-6-fluoro-pyrazolo[1,5-a]pyrimidine-3-carbonyl)amino]-4-pyridyl]piperidine-1-carboxylate (555 mg, 1.218 mmol) (prepared using a procedure similar to **example 2**) in MeOH (2.135 mL) and DCM (2.135 mL) was added TFA (6.2 g, 4.2 mL, 54 mmol) and the resulting solution stirred at rt for 96h. The reaction mixture was concentrated *in vacuo* and taken up in methanol and DCM and passed through an 25 g SCX cartridge flushing with methanol (3 column volumes) followed by 2M ammonia in methanol (3 column volumes) to elute the product. The filtrate was concentrated *in vacuo* to leave 2-amino-6-fluoro-*N*-(4-(piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a yellow solid that was used directly in the next step without further purification. MS (ES+) 356.1.

Step 2: 2-amino-6-fluoro-N-(4-(1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[00523] TBTU (154.5 mg, 0.4812 mmol) and DIPEA (82.92 mg, 111.8 µL, 0.6416 mmol) were added to a solution of 2-amino-6-fluoro-N-[4-(4-piperidyl)-3-pyridyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (114 mg, 0.3208 mmol) and 1-methylpiperidine-4-carboxylic acid (Hydrochloric Acid (1)) (69.16 mg, 0.3850 mmol) in NMP (2.280 mL) and the resulting solution stirred at RT for 2 h. Passed through an SCX cartridge flushing the desired product with 2M ammonia in methanol and the filtrate concentrated *in vacuo*. The residue was purified by fractionlynx HPLC and the product fractions combined and freeze dried to leave 2-amino-6-fluoro-*N*-(4-(1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl)pyridin-3-

yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a yellow crystalline solid. MS (ES+) 481.3.

[00524] The following compounds were formed using a procedure similar to **Example 17**:

2-amino-6-fluoro-*N*-(4-(1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-17**); and

2-amino-6-fluoro-*N*-(4-(1-(quinuclidine-4-carbonyl)piperidin-4-yl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (**Compound I-C-18**).

Example 18: 2-amino-6-fluoro-N-(1-methyl-1H-pyrrolo[2,3-c]pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound I-C-74)

[00525] NaH (3.958 mg, 0.09894 mmol) was added to a suspension of 2-amino-6-fluoro-N-(1H-pyrrolo[2,3-c]pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (28 mg, 0.08995 mmol) (synthesized according to a procedure similar to **Example 1** or **Example 3a**) and MeI (11.49 mg, 5.039 μL, 0.08096 mmol) in DMF (3 mL) under N_2. The suspension was stirred at RT for 5h before water (2 drops) was added. The crude mixture was purified by fractionlynx HPLC. Clean fractions were liophilized to yield 2-amino-6-fluoro-N-(1-methyl-1H-pyrrolo[2,3-c]pyridin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (5mg, 16%). MS (ES+) 326.1.

Compound Analytical Data

Cmpd No.	LCMS ES +	LCMS (Rt min)	HNMR
I-C-1	370.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 9.24 (s, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.29 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 5.1 Hz, 1H), 6.71 (s, 2H), 2.93 (dt, J = 12.0, 2.9 Hz, 2H), 2.81 (tq, J = 7.4, 3.8, 3.4 Hz, 1H), 2.23 (s, 3H), 2.04 (td, J = 11.7, 2.6 Hz, 2H), 1.82 - 1.66 (m, 4H).
I-C-2	303.1	0.94	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.51 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H), 7.74 (d, J = 5.3 Hz, 1H), 6.80 (s, 2H), 2.57 (s, 3H).
I-C-3	308.1	0.58	----------

I-C-4	287.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 9.89 (s, 1H), 9.57 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 8.91 (dd, J = 2.6, 0.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 7.91 - 7.73 (m, 1H), 6.77 (s, 2H), 2.61 (s, 3H).
I-C-5	349.0	2.48*	^{1}H NMR (500 MHz, CDCl3) δ7.53-7.55 (2H, m), 7.67-7.73 (3H, m), 7.87 (1H, s), 8.45-8.46 (1H, d), 7.61-8.62 (1H, d), 9.96 91H, s), 10.28 (1H, s).
I-C-6	370.0	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.64 (s, 1H), 8.97 - 8.93 (m, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.62 - 7.55 (m, 3H), 7.54 - 7.50 (m, 2H), 7.33 (dd, J = 4.8, 0.7 Hz, 1H), 6.68 (s, 2H), 4.06 (s, 2H).
I-C-7	328.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 (s, 1H), 9.53 (dd, J = 4.8, 2.6 Hz, 1H), 9.24 (s, 1H), 9.16 (s, 2H), 8.85 (dd, J = 2.6, 0.5 Hz, 1H), 8.30 (s, 1H), 6.73 (s, 2H), 4.49 - 4.34 (m, 2H), 3.57 - 3.49 (m, 2H), 3.04 (t, J = 6.2 Hz, 2H).
I-C-8	342.2	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.59 - 9.47 (m, 2H), 9.24 (s, 1H), 8.83 (dd, J = 2.6, 0.5 Hz, 1H), 8.26 (s, 1H), 6.73 (s, 2H), 4.74 - 4.58 (m, 1H), 4.45 - 4.32 (m, 1H), 3.91 - 3.71 (m, 1H), 3.51 - 3.37 (m, 1H), 3.24 - 3.12 (m, 1H), 3.12 - 3.03 (m, 1H), 3.00 (s, 3H).
I-C-9	358.2	0.38	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.24 (s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.10 (s, 1H), 6.75 - 6.67 (m, 3H), 4.77 (d, J = 14.9 Hz, 1H), 4.36 (d, J = 14.9 Hz, 1H), 3.73 (td, J = 11.5, 5.1 Hz, 1H), 3.61 - 3.49 (m, 1H), 3.25 - 3.15 (m, 1H), 3.02 - 2.90 (m, 1H). Methyl singlet hidden under water peak.
I-C-10	412.2	1.78*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.62 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 8.94 (d, J = 2.5 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.44 (d, J = 5.1 Hz, 1H), 6.75 (s, 2H), 4.89 - 4.71 (m, 4H), 4.51 (s, 1H), 3.59 (d, J = 11.8 Hz, 2H), 3.37 - 3.09 (m, 1H), 3.08 - 2.84 (m, 2H), 2.17 (d, J = 14.0 Hz, 2H), 1.97 (q, J = 13.2 Hz, 2H).
I-C-11	428.1	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.53 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 9.27 (s, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 6.1 Hz, 1H), 6.78 (s, 2H), 4.79 (p, J = 8.0 Hz, 4H), 4.51 (s, 1H), 3.59 (s, 2H), 3.27 - 3.15 (m, 1H), 2.98 (d, J = 15.4 Hz, 2H), 2.16 (d, J = 14.0 Hz, 2H), 1.95 (q, J = 10.6, 8.2 Hz, 2H).
I-C-12	428.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 - 9.52 (m, 2H), 9.45 (s, 1H), 8.93 (d, J = 2.5 Hz, 1H), 8.39 (s, 1H), 6.78 (s, 1H), 6.16 (s, 2H), 4.79 (s, 4H), 4.40 - 3.35 (very broad m, 7H).

I-C-13	430.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.03 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 6.71 (s, 2H), 4.55 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.52 - 3.43 (m, 1H), 3.09 - 2.91 (m, 1H), 2.86 (d, J = 10.9 Hz, 2H), 2.11 (q, J = 13.0, 12.4 Hz, 2H), 1.85 (t, J = 11.5 Hz, 2H), 1.77 (d, J = 12.3 Hz, 2H).
I-C-14	388.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.41 (s, 1H), 8.91 (d, J = 2.6 Hz, 1H), 8.86 (s, 1H), 8.40 (d, J = 2.3 Hz, 1H), 6.71 (s, 2H), 3.56 (d, J = 13.0 Hz, 2H), 3.16 (t, J = 12.2 Hz, 1H), 3.03 (q, J = 12.0, 11.5 Hz, 2H), 2.82 (d, J = 4.6 Hz, 3H), 2.26 (q, J = 13.8, 12.8 Hz, 2H), 2.08 (d, J = 13.7 Hz, 2H).
I-C-15	350.0	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 6.8 (2H, br s), 7.68-7.69 (1H, d), 7.75-7.77 (1H, dd), 8.14-8.16 (1H, dd), 8.21-8.22 (1H, d), 8.56-8.57 (1H, dd), 8.82-8.83 (1H, d), 8.87-8.88 1H, d), 9.41-9.42 (1H, d), 9.67 (1H, s), 9.77 (1H, s).
I-C-16	481.3	1.80*	^{1}H NMR (DMSO-d6, 500 MHz) δ 1.42-1.65 (6H, m), 1.91 (2H, m), 2.10 (1H, m), 2.29 (3H, br s), 2.64-2.71 (2H, m), 2.89 (2H, m), 3.12-3.21 (3H, m), 4.09 (1H, m), 4.63 (1H, m), 6.72 (2H, br s), 7.34 (1H, d, J = 5 Hz), 8.29 (1H, d, J = 5 Hz), 8.93 (1H, m), 9.28 (1H, s), 9.51 (1H, dd) and 9.62 (1H, s) ppm.
I-C-17	482.2	1.85*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.67-1.75 (2H, m), 1.87 (2H, m), 2.85 (3H, s), 3.01-3.22 (7H, m), 3.41 (2H, m), 3.69 (2H, m), 3.86 (2H, m), 6.77 (2H, br s), 7.65 (1H, d, J = 5 Hz), 8.47 (1H, d), 8.95 (1H, d), 9.49 (1H, s), 9.55 (1H, m), 9.83 (1H, s) and 9.95 (1H, br s) ppm.
I-C-18	493.2	1.69*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.50-1.59 (2H, m), 1.73 (6H, m), 1.87 (2H, m), 2.76 (6H, m), 2.93 (2H, m), 3.15 (1H, m), 4.61 (2H, m), 6.72 (2H, br s), 7.34 (1H, d), 8.29 (1H, d), 8.93 (1H, d), 9.26 (1H, s), 9.50 (1H, dd) and 9.62 (1H, s) ppm.
I-C-19	476.0	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.70 (s, 1H), 9.53 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.75 (dd, J = 2.2, 0.9 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.36 - 8.32 (m, 1H), 8.22 (dd, J = 8.0, 2.2 Hz, 1H), 7.90 (dd, J = 8.0, 0.9 Hz, 1H), 7.48 (dd, J = 4.9, 0.7 Hz, 1H), 6.70 (m, 2H), 4.68 (m, 1H), 4.07 (m, 1H), 3.59 (m, 1H), 3.44 (m, 2H), 3.16 (m, 3H), 2.87 (s, 3H).
I-C-20	364.0	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 0H), 9.42 (dd, J = 4.8, 2.5 Hz, 0H), 9.35 (s, 0H), 8.86 (dd, J = 5.2, 1.6 Hz, 0H), 8.57 (d, J = 5.1 Hz, 0H), 8.07 (d, J = 2.5 Hz, 0H), 7.99 (d, J = 7.5 Hz, 0H), 7.68 (dd, J = 7.7, 5.2 Hz, 0H), 7.63 (d, J = 5.1 Hz, 0H), 2.35 (s, 1H).

I-C-21	448.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.90 (s, 1H), 9.67 (s, 1H), 9.47 (dd, *J* = 4.8, 2.5 Hz, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 8.42 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.30 (d, *J* = 2.5 Hz, 1H), 7.94 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.69 (d, *J* = 5.4 Hz, 1H), 7.21 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.60 (s, 2H), 3.59 (s, 2H), 3.28 (s, 2H), 3.13 (s, 2H), 2.89 (s, 3H).
I-C-22	364.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.68 (s, 1H), 9.44 (dd, J = 4.8, 2.5 Hz, 1H), 8.81 (dd, J = 2.4, 0.9 Hz, 1H), 8.58 (d, J = 5.2 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 8.21 (dd, J = 8.1, 2.3 Hz, 1H), 7.76 - 7.72 (m, 1H), 7.69 (dd, J = 5.2, 0.6 Hz, 1H), 2.72 (s, 3H).
I-C-23	419.1	2.01*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.86 (6H, s), 1.90 - 2.00 (2H, br m), 2.07 (2H, d), 2.79 (3H,s), 3.0-3.1 (1H,m), 3.52 (2H,br s), 6.63 (2H,s), 7.32 (1H,s), 8.40 (1H,d), 8.81 (1H,d), 9.09 (2H,d), 9.51 (1H,s).
I-C-24	350.0	1.80*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.58 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.91 - 8.86 (m, 2H), 8.54 (d, J = 5.1 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.77 - 7.72 (m, 2H), 7.59 (d, J = 5.0 Hz, 1H).
I-C-25	475.0	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.80 (s, 1H), 9.66 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.75 - 7.69 (m, 2H), 7.68 - 7.63 (m, 2H), 7.56 (d, J = 5.0 Hz, 1H), 6.72 (s, 2H), 4.65 (s, 2H), 3.0 to 4.0 (m, 6H), 2.86 (s, 3H).
I-C-26	351.0	1.47*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.49 (s, 1H), 9.49 (s, 1H), 9.48 (dd, J = 5.3, 1.3 Hz, 1H), 9.44 (dd, J = 2.4, 1.2 Hz, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.50 (d, J = 4.9 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 5.3, 2.4 Hz, 1H), 7.52 (dd, J = 5.0, 0.7 Hz, 1H), 6.66 (s, 1H).
I-C-27	380.0	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (s, 1H), 9.69 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.55 (d, J = 5.3 Hz, 1H), 8.41 (dd, J = 2.6, 0.8 Hz, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 8.6, 2.5 Hz, 1H), 7.69 (dd, J = 5.2, 0.6 Hz, 1H), 7.12 (dd, J = 8.6, 0.8 Hz, 1H), 3.99 (s, 3H).
I-C-28	351.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 9.40 (s, 1H), 9.05 (s, 2H), 8.26 (d, J = 2.5 Hz, 1H), 7.53 (d, J = 4.7 Hz, 1H), 6.68 (s, 2H).
I-C-29	364.0	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.22 (s, 1H), 8.80 (s, 1H), 8.71 (d, J = 5.0 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.50 - 7.44 (m, 2H), 6.70 (bs, 1h), 2.12 (s, 3H).
I-C-30	364.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (d, J = 0.7 Hz, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.29 (s, 1H), 8.79 (d, J = 5.3 Hz, 1H), 8.59 (s, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.11 (d, J = 2.5 Hz, 1H), 7.75 - 7.68 (m, 1H), 7.54 (dd, J = 5.1, 0.7 Hz, 1H), 6.71 (s, 2H), 2.19 (d, J = 0.7 Hz, 3H).

I-C-31	365.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (d, J = 0.6 Hz, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.38 (d, J = 5.0 Hz, 1H), 9.21 (s, 1H), 8.53 (d, J = 5.0 Hz, 1H), 2.45 (s, 3H).
I-C-32	366.0	1.53*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.15 (s, 1H), 9.61 (s, 1H), 9.52 (s, 1H), 9.43 (dd, J = 4.8, 2.6 Hz, 1H), 8.46 (s, 1H), 8.42 (d, J = 5.0 Hz, 1H), 7.78 - 7.60 (m, 2H), 7.45 (d, J = 5.1 Hz, 1H), 6.70 (s, 2H), 6.43 (t, J = 6.6 Hz, 1H).
I-C-33	365.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.59 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 9.37 (d, J = 5.3 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.87 (dd, J = 5.1, 1.0 Hz, 1H), 7.71 - 7.62 (m, 1H), 2.21 (d, J = 0.8 Hz, 3H).
I-C-34	382.0	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.44 (dd, J = 4.8, 2.5 Hz, 1H), 9.35 (s, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 7.98 (t, J = 8.2 Hz, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.33 - 7.26 (m, 1H), 2.23 (s, 3H).
I-C-35	368.0	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.47 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.55 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.19 (ddd, J = 9.6, 7.4, 2.0 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.65 (ddd, J = 7.1, 4.9, 1.9 Hz, 1H), 7.59 (d, J = 5.0 Hz, 1H).
I-C-36	364.0	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 9.78 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.77 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.95 (ddd, J = 7.8, 1.6, 0.8 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.60 (dd, J = 7.8, 4.8 Hz, 1H), 2.22 (s, 3H).
I-C-37	384.0	2.08*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 9.34 (s, 1H), 8.74 (dd, J = 4.8, 1.9 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.07 - 8.00 (m, 2H), 7.72 (dd, J = 7.5, 4.8 Hz, 1H), 7.55 (d, J = 5.0 Hz, 1H).
I-C-38	497.2	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.58 (s, 1H), 9.46 (s, 1H), 9.32 (dd, J = 4.7, 2.5 Hz, 1H), 8.61 (s, 1H), 8.31 (s, 1H), 6.08 (dt, J = 3.3, 1.9 Hz, 1H), 4.29 (q, J = 2.9 Hz, 2H), 3.82 (t, J = 5.6 Hz, 2H), 3.49 (s, 1H), 3.01 (s, 3H), 2.80 (s, 3H), 2.44 (d, J = 6.3 Hz, 3H), 1.90 (s, 4H).
I-C-39	490.0	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.86 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 9.31 (s, 1H), 8.51 (s, 1H), 8.29 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 6.72 (s, 2H), 4.70 (s, 1H), 4.02 (s, 1H), 3.33 (d, J = 118.2 Hz, 5H), 2.87 (s, 3H), 2.28 (s, 3H).
I-C-40	462.0	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.47 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.27 (dd, J = 4.8, 0.7 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.70 (s, 2H), 3.63 (d, J = 33.6 Hz, 4H), 2.47 (s, 4H), 2.28 (s, 3H), 2.08 (s, 3H).

I-C-41	463.0	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 4.8, 0.7 Hz, 1H), 6.85 (dd, J = 8.4, 0.8 Hz, 1H), 6.71 (s, 2H), 2.86 (dd, J = 10.5, 6.1 Hz, 1H), 2.73 (td, J = 8.2, 5.7 Hz, 1H), 2.69 - 2.62 (m, 1H), 2.41 (td, J = 7.9, 6.1 Hz, 1H), 2.37 - 2.31 (m, 0H), 2.29 (s, 3H), 2.15 (s, 3H), 1.93 - 1.83 (m, 1H).
I-C-42	313.0	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.61 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.51 - 8.40 (m, 1H), 7.58 (d, J = 5.6 Hz, 1H), 6.77 (s, 2H), 2.18 (tt, J = 8.4, 5.2 Hz, 1H), 1.39 - 1.33 (m, 2H), 1.01 - 0.94 (m, 2H).
I-C-43	493.0	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.39 (s, 1H), 9.22 (dd, J = 4.7, 2.5 Hz, 1H), 8.42 (s, 1H), 8.35 (dd, J = 2.5, 0.6 Hz, 1H), 7.69 - 7.54 (m, 4H), 6.49 (s, 2H), 3.66 (s, 4H), 2.74 (s, 4H), 2.48 (s, 3H).
I-C-44	461.0	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.54 (s, 1H), 9.37 (dd, J = 4.8, 2.5 Hz, 1H), 8.41 - 8.38 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.57 - 7.53 (m, 2H), 7.37 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 3.62 (s, 2H), 2.73 (d, J = 55.4 Hz, 4H).
I-C-45	489.0	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.34 (dd, J = 4.8, 2.5 Hz, 1H), 9.27 (s, 1H), 8.39 (s, 1H), 8.39 (d, J = 1.9 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.41 (dd, J = 7.7, 1.6 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.30 (dd, J = 4.7, 0.7 Hz, 1H), 6.68 (s, 2H), 3.73 (bs, 2H), 3.42 (bs, 2H), 2.45 - 2.30 (m, 4H), 2.08 (s, 3H).
I-C-46	510.0	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (d, J = 0.7 Hz, 1H), 9.61 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.53 (dd, J = 2.6, 0.6 Hz, 1H), 8.50 (d, J = 4.9 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 7.53 (dd, J = 5.0, 0.7 Hz, 1H), 6.71 (s, 2H), 2.86 (s, 3H).
I-C-47	460.1	2.13*	^{1}H NMR (500 MHz, methanol-d4) δ 1.09-1.15 (4H, m), 1.99 (2H, m), 2.15-2.17 (2H, m), 2.64-2.69 (1H, m), 3.17-3.19 (2H, m), 3.31-3.34 (1H, masked), 4.03-4.06 (2H, m), 7.94-7.95 (1H, d), 8.50-8.51 (1H, d), 8.78 (1H, dd), 9.13-9.14 (1H, dd), 9.74 (1H, s).
I-C-48	501.0	2.01*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.77 (s, 1H), 9.61 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 (d, J = 4.9 Hz, 1H), 8.41 (s, 1H), 7.71 (d, J = 7.7 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 5.0 Hz, 1H), 6.72 (bs, 2H), 4.85 (s, 1H), 4.09 (s, 1H), 3.77 (t, J = 5.6 Hz, 1H), 3.58 (s, 1H), 3.45 (s, 2H), 3.33 (s, 1H), 2.20 (d, J = 69.6 Hz, 4H), 1.96 (s, 1H).

I-C-49	517.0	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (s, 1H), 9.53 (s, 1H), 9.38 (dd, J = 4.8, 2.5 Hz, 1H), 8.44 - 8.32 (m, 2H), 7.64 - 7.59 (m, 2H), 7.59 - 7.53 (m, 2H), 7.37 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 4.56 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.73 (s, 2H), 3.47 (t, J = 6.2 Hz, 1H), 3.40 (d, J = 5.8 Hz, 2H), 2.38 (d, J = 6.0 Hz, 2H), 2.27 (s, 2H).
I-C-50	519.0	2.08*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.42 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 – 8.38 (m, 2H), 7.63 – 7.54 (m, 2H), 7.45 (dd, J = 7.8, 1.5 Hz, 1H), 7.42 (dd, J = 4.8, 0.7 Hz, 1H), 6.70 (s, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 3.73 (s, 2H), 3.49 (m, 2H), 3.39 (m, 2H), 2.46 – 2.35 (m, 3H), 2.29 (m, 2H).
I-C-51	535.0	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.42 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 - 8.39 (m, 2H), 7.62 - 7.55 (m, 2H), 7.48 - 7.40 (m, 2H), 6.70 (s, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.73 (s, 2H), 3.49 (s, 1H), 3.39 (s, 2H), 2.40 (s, 2H), 2.29 (s, 2H).
I-C-52	518.0	1.7*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.49 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.71 (dd, J = 2.1, 0.8 Hz, 1H), 8.44 (d, J = 4.9 Hz, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.13 (dd, J = 8.0, 2.2 Hz, 1H), 7.80 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (d, J = 4.9 Hz, 1H), 6.69 (s, 2H), 4.56 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 3.76 (s, 2H), 3.58 - 3.40 (m, 3H), 2.42 (s, 2H), 2.29 (s, 2H).
I-C-53	530.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.50 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.70 (dd, J = 2.2, 0.9 Hz, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.41 - 8.40 (m, 1H), 8.12 (dd, J = 8.0, 2.2 Hz, 1H), 7.78 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 4.37 (d, J = 12.1 Hz, 1H), 3.64 (d, J = 12.6 Hz, 1H), 3.18 - 3.03 (m, 2H), 2.56 (s, 4H), 2.37 (s, 1H), 1.98 (d, J = 12.1 Hz, 1H), 1.80 (d, J = 10.1 Hz, 1H), 1.71 (d, J = 6.2 Hz, 4H), 1.47 (td, J = 20.6, 17.0, 10.5 Hz, 2H).
I-C-54	516.2	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 11.57 (s, 1H), 10.33 (s, 1H), 9.68 (s, 1H), 9.43 (dd, J = 4.8, 2.6 Hz, 1H), 8.96 (dd, J = 2.2, 0.9 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.09 (dd, J = 8.1, 2.2 Hz, 1H), 8.04 (dd, J = 8.1, 0.9 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 6.73 (s, 2H), 4.60 (s, 1H), 4.16 (s, 2H), 4.06 (s, 2H), 3.69 (s, 1H), 3.55 - 3.38 (m, 1H), 3.17 (d, J = 7.9 Hz, 1H), 2.90 (s, 1H), 2.45 (dt, J = 11.6, 9.3 Hz, 1H), 2.24 (ddd, J = 12.4, 7.8, 4.6 Hz, 1H), 2.07 (d, J = 11.5 Hz, 1H), 1.89 (s, 1H), 1.37 (s, 2H).
I-C-55	353.0	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.72 (d, J = 0.6 Hz, 1H), 9.40 (dd, J = 4.9, 2.6 Hz, 1H), 8.67 (d, J = 2.6 Hz, 1H), 8.42 (d, J = 4.9 Hz, 1H), 7.59 (dd, J = 5.0, 0.7 Hz, 1H), 7.48 (d, J = 1.2 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 6.71 (s, 2H), 3.72 (s, 3H).

I-C-56	353.0	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 - 9.70 (m, 1H), 9.35 - 9.28 (m, 1H), 8.52 (d, J = 4.9 Hz, 1H), 8.50 (dd, J = 2.5, 0.5 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 7.60 (dd, J = 5.0, 0.7 Hz, 1H), 3.69 (d, J = 0.6 Hz, 3H).
I-C-57	353.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.65 (3H, s), 6.55 (1H, d), 6.71 (2H, br s), 7.44 (1H, m), 7.75 (1H, m), 8.35 (1H, m), 8.42 (1H, m), 9.41 (1H, m), 9.56 (1H, s) and 9.77 (1H, s) ppm.
I-C-58	380.0	1.67*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.16 (3H, s), 6.34 (1H, m), 6.70 (1H, m), 7.53 (1H, m), 7.59-7.62 (1H, m), 8.24 (1H, m), 8.49 (1H, d), 9.39 (1H, s), 9.45 (1H, m) and 9.79 (1H, s) ppm.
I-C-59	380.1	1.52*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.47 (3H, s), 6.57 (1H, m), 6.72 (2H, br s), 7.36 (1H, m), 7.58 (1H, m), 8.06 (1H, m), 8.26 (1H, m), 8.36 (1H, m), 9.44 (1H, m) and 9.52 (1H, s) ppm.
I-C-60	350.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 6.73 (2H, br s), 7.54 (1H, m), 7.72 (1H, m), 7.96 (1H, m), 8.04 (1H, m), 8.42 (1H, m), 8.89 (1H, m), 9.40 (1H, m), 9.58 (1H, s) and 11.85 (1H, s) ppm.
I-C-61	427.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.37 (3H, s), 6.70 (2H, br s), 7.40 (1H, m), 7.81 (2H, m), 8.14-8.17 (2H, m), 8.43 (1H, m), 9.39 (1H, m), 9.47 (1H, s) and 9.64 (1H, s) ppm.
I-C-62	365.0	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.92 (s, 1H), 9.83 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.88 (dd, J = 2.5, 0.8 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 5.4 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 5.3 Hz, 1H), 6.67 (s, 2H), 2.46 (d, J = 0.7 Hz, 3H).
I-C-63	367.8	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.06 (3H, s), 3.88 (3H, s), 6.72 (2H, br s), 7.27 (1H, m), 7.91 (1H, s), 8.30 (1H, m), 8.37 (1H, m), 9.42 (1H, m) and 9.59 (2H, m) ppm.
I-C-64	468.0	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.08 (2H, m), 3.78 (4H, m), 6.69 (2H, br s),7.44 (1H, m), 7.82 (2H, m), 8.01 (2H, m), 8.21 (1H, m), 8.44 (1H, m), 9.40 (1H, m), 9.48 (1H, s) and 9.57 (1H, s) ppm.
I-C-65	354.0	1.51*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.82 (d, J = 0.7 Hz, 1H), 9.43 (dd, J = 4.9, 2.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H), 7.84 - 7.79 (m, 1H), 6.75 (s, 1H), 3.91 (s, 3H).
I-C-66	448.1	2.26*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.59 (s, 1H), 9.52 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.37 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 2.5 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 4.8, 0.7 Hz, 1H), 6.70 (s, 2H), 3.90 - 3.80 (m, 1H), 3.72 - 3.62 (m, 2H), 3.17 (dd, J = 10.2, 3.3 Hz, 1H), 2.85 (dt, J = 11.8, 1.9 Hz, 1H), 2.32 (td, J = 11.7, 3.4 Hz, 1H), 1.98 (d, J = 11.0 Hz, 3H).

I-C-67	365.1	1.69*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.76 (s, 1H), 9.46 - 9.39 (m, 2H), 9.00 (d, J = 0.9 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.41 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 5.2 Hz, 1H), 6.68 (s, 2H), 2.23 (t, J = 0.7 Hz, 3H).
I-C-68	353.1	1.93*	1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 9.49 - 9.36 (m, 2H), 8.86 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 5.1 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.74 (s, 2H), 3.92 (s, 3H).
I-C-69	398.0	1.76*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s,1H), 9.53-9.55 (m, 2H), 8.99 (dd, 1H), 8.50 (d, 1H), 7.71-7.73 (d, 1H), 6.80 3(s, 2H), 4.63-4.66 (m, 1H),4.03-4.05 (m, 1H), 3.25-3.28 (m, 2H), 2.70-2.75 (m, 1H), 2.06 (s, 3H), 1.85-1.95 (m, 2H), 1.75-1.80 (m, 1H), 1.55-1.60 (m, 1H).
I-C-70	424.0	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s,1H), 9.53-9.55 (m, 2H), 9.00 (dd, 1H), 8.50 (dd, 1H), 7.73-7.74 (d, 1H), 6.80 3(s, 2H), 4.65-4.70 (m, 1H), 4.50-4.55 (m, 1H), 3.25-3.33 (m, 2H), 2.85-2.88 (m, 1H), 1.85- 2.06 (m, 3H), 1.55-1.80 (m, 2H), 0.71-0.77 (m, 4H).
I-C-71	449.0	2.07*	----------
I-C-72	354.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (d, J = 0.7 Hz, 1H), 9.48 (s, 1H), 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.06 (s, 1H), 7.56 (dd, J = 4.9, 0.7 Hz, 1H), 6.71 (s, 2H), 3.91 (s, 3H).
I-C-73	384.1	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.34 (s, 1H), 8.69 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 5.4 Hz, 1H), 7.58 (d, J = 5.2 Hz, 1H), 6.73 (s, 2H), 3.38 (dt, J = 12.4, 4.5 Hz, 2H), 2.91 (s, 3H), 2.70 - 2.62 (m, 1H), 2.49 - 2.45 (m, 1H), 2.15 - 2.08 (m, 2H).
I-C-74	326.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.02 (s, 1H), 9.51-9.52 (dd, 1H), 9.11 (s, 1H), 9.00 (dd, 1H), 8.70 (s, 1H), 7.70 (s, 1H), 6.74-6.75 (m, 3H), 3.97 (s, 3H).
I-C-75	343.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.87 (s, 1H), 9.53 (dd, 1H), 9.39 (s, 1H), 8.91 (dd, 1H), 8.48 (d, 1H), 7.68 (d, 1H), 6.74 (s, 2H), 4.09 (dd, 1H), 3.97 - 3.88 (m, 3H), 3.81 -3.76 (m, 1H), 2.61 - 2.53 (m, 1H), 2.04 - 1.97 (m, 1H).
I-C-76	370.0	1.53*	run in D6-DMSO
I-C-77	367.1	1.68*	^{1}H NMR (500 MHz, DMSO) δ 15.03 (s, 1H), 9.76 (d, J = 0.7 Hz, 1H), 9.52 - 9.46 (m, 2H), 8.55 (d, J = 2.5 Hz, 1H), 8.51 (d, J = 4.8 Hz, 1H), 8.02 (s, 1H), 7.52 (dd, J = 4.9, 0.7 Hz, 1H), 6.75 (s, 2H), 3.49 (s, 3H), 2.72 (s, 3H).
I-C-78	367.1	1.71*	^{1}H NMR (500 MHz, DMSO) δ? 9.80 (d, J = 0.7 Hz, 1H), 9.56 (s, 1H), 9.42 (dd, J = 4.8, 2.6 Hz, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.91 (s, 1H), 7.39 (dd, J = 4.8, 0.7 Hz, 1H), 6.71 (s, 2H), 3.40 (s, 3H), 1.97 (s, 3H).
I-C-79	371.0	1.84*	^{1}H NMR (500 MHz, DMSO-d6) 9.70 (s, 2H), 09.44 (dd, 1H), 8.47 (s, 1H), 8.32 (d, 1H), 8.08 (dd, 1H), 7.26 (d, 1H), 6.79 - 6.64 (m, 2H), 3.47 (s, 3H).

I-C-80	367.1	1.76*	^{1}H NMR (500 MHz, DMSO-d6) 9.76 (s, 1H), 9.59 (s, 1H), 9.41-9.43 (m, 1H), 8.40 (d, 1H), 8.33 (d, 1H), 8.07 (d, 1H), 7.40 (m, 1H), 7.13 (d, 1H), 6.71 (s, 2H), 3.79-3.83 (qd, 2H), 1.09-1.12 (t, 3H).
I-C-81	383.1	1.7*	^{1}H NMR (500 MHz, Methanol-d4) 3.90 (d, 1H), 9.08 (s, 1H), 8.91 (d, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.78 (s, 1H), 3.91 (s, 3H), 3.65 (s, 3H).
I-C-82	380.1	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.49 (s, 1H0, 9.39-9.40 (d, 1H), 9.32 (s, 1H), 8.87-8.89 (d, 1H), 8.69 (dd, 1H), 8.41 (s, 1H), 8.08 (d, 1H0, 8.02-8.05 (m, 1H0, 7.78-7.80 (m, 1H0, 6.80 (br s, 2H), 3.89 (s, 3H).
I-C-83	397.1	1.69*	^{1}H NMR (500 MHz, CDCl3) δ 9.95 (s, 1H), 9.60 (s, 1H), 8.53 (m, 1H0, 8.47-8.48 (m, 1H), 8.43-8.44 (m, 1H), 8.38 (m, 1H), 7.93 (s, 1H), 7.20-7.30 (masked, 2H),5.73 (s, 2H), 3.91-3.93 (t, 2H), 3.40-3.42 (t, 2H), 3.14 (s, 3H).
I-C-84	343.1	2.3*	----------

Retention times measured using HPLC Method B, described in the Experimental Methods and Materials section, above., are designated by (*). For all other compounds, the retention time was measured using the HPLC Method A.

Example 19: Cellular ATR Inhibition Assay:

[00526] Compounds can be screened for their ability to inhibit intracellular ATR using an immunofluorescence microscopy assay to detect phosphorylation of the ATR substrate histone H2AX in hydroxyurea treated cells. HT29 cells are plated at 14,000 cells per well in 96-well black imaging plates (BD 353219) in McCoy's 5A media (Sigma M8403) supplemented with 10% foetal bovine serum (JRH Biosciences 12003), Penicillin/Streptomycin solution diluted 1:100 (Sigma P7539), and 2mM L-glumtamine (Sigma G7513), and allowed to adhere overnight at 37°C in 5% CO_2. Compounds are then added to the cell media from a final concentration of 25μM in 3-fold serial dilutions and the cells are incubated at 37°C in 5% CO_2. After 15min, hydroxyurea (Sigma H8627) is added to a final concentration of 2mM.

[00527] After 45min of treatment with hydroxyurea, the cells are washed in PBS, fixed for 10min in 4% formaldehyde diluted in PBS (Polysciences Inc 18814), washed in 0.2% Tween-20 in PBS (wash buffer), and permeabilised for 10min in 0.5% Triton X-100 in PBS, all at room temperature. The cells are then washed once in wash buffer and blocked for 30 min at room temperature in 10% goat serum (Sigma G9023) diluted in wash buffer (block buffer). To detect H2AX phosphorylation levels, the cells are then incubated for 1h at room temperature in primary antibody (mouse monoclonal anti-phosphorylated histone H2AX Ser139 antibody; Upstate 05-636) diluted 1:250 in block buffer. The cells are then washed

five times in wash buffer before incubation for 1h at room temperature in the dark in a mixture of secondary antibody (goat anti-mouse Alexa Fluor 488 conjugated antibody; Invitrogen A11029) and Hoechst stain (Invitrogen H3570); diluted 1:500 and 1:5000, respectively, in wash buffer. The cells are then washed five times in wash buffer and finally 100ul PBS is added to each well before imaging.

[00528] Cells are imaged for Alexa Fluor 488 and Hoechst intensity using the BD Pathway 855 Bioimager and Attovision software (BD Biosciences, Version 1.6/855) to quantify phosphorylated H2AX Ser139 and DNA staining, respectively. The percentage of phosphorylated H2AX-positive nuclei in a montage of 9 images at 20x magnification is then calculated for each well using BD Image Data Explorer software (BD Biosciences Version 2.2.15). Phosphorylated H2AX-positive nuclei are defined as Hoechst-positive regions of interest containing Alexa Fluor 488 intensity at 1.75-fold the average Alexa Fluor 488 intensity in cells not treated with hydroxyurea. The percentage of H2AX positive nuclei is finally plotted against concentration for each compound and IC50s for intracellular ATR inhibition are determined using Prism software (GraphPad Prism version 3.0cx for Macintosh, GraphPad Software, San Diego California, USA).

[00529] The compounds described herein can also be tested according to other methods known in the art (see Sarkaria et al, "Inhibition of ATM and ATR Kinase Activities by the Radiosensitizing Agent, Caffeine: *Cancer Research* 59: 4375-5382 (1999); Hickson et al, "Identification and Characterization of a Novel and Specific Inhibitor of the Ataxia-Telangiectasia Mutated Kinase ATM" *Cancer Research* 64: 9152-9159 (2004); Kim et al, "Substrate Specificities and Identification of Putative Substrates of ATM Kinase Family Members" *The Journal of Biological Chemistry*, 274(53): 37538-37543 (1999); and Chiang et al, "Determination of the catalytic activities of mTOR and other members of the phosphoinositide-3-kinase-related kinase family" *Methods Mol. Biol.* 281:125-41 (2004)).

Example 20: ATR Inhibition Assay:

[00530] Compounds were screened for their ability to inhibit ATR kinase using a radioactive-phosphate incorporation assay. Assays were carried out in a mixture of 50mM Tris/HCl (pH 7.5), 10mM $MgCl_2$ and 1mM DTT. Final substrate concentrations were 10μM [γ-33P]ATP (3mCi 33P ATP/mmol ATP, Perkin Elmer) and 800 μM target peptide (ASELPASQPQPFSAKKK).

[00531] Assays were carried out at 25°C in the presence of 5 nM full-length ATR. An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP and the test compound of interest. 13.5 μL of the stock solution was placed in a 96 well plate followed by addition of 2 μL of DMSO stock containing serial dilutions of the test compound (typically starting from a final concentration of 15 μM with 3-fold serial dilutions) in duplicate (final DMSO concentration 7%). The plate was pre-incubated for 10 minutes at 25°C and the reaction initiated by addition of 15 μL [γ-33P]ATP (final concentration 10 μM).

[00532] The reaction was stopped after 24 hours by the addition of 30μL 0.1M phosphoric acid containing 2mM ATP. A multiscreen phosphocellulose filter 96-well plate (Millipore, Cat no. MAPHN0B50) was pretreated with 100μL 0.2M phosphoric acid prior to the addition of 45μL of the stopped assay mixture. The plate was washed with 5 x 200μL 0.2M phosphoric acid. After drying, 100 μL Optiphase 'SuperMix' liquid scintillation cocktail (Perkin Elmer) was added to the well prior to scintillation counting (1450 Microbeta Liquid Scintillation Counter, Wallac).

[00533] After removing mean background values for all of the data points, Ki(app) data were calculated from non-linear regression analysis of the initial rate data using the Prism software package (GraphPad Prism version 3.0cx for Macintosh, GraphPad Software, San Diego California, USA).

[00534] Table 5, below, shows the ATR Inhibition Ki values of compounds of the disclosure. Compounds with a Ki value of < 0.01 μM are marked with "+++." Compounds with a Ki value > 0.01 μM but < 1 μM are marked with "++." Compounds with a Ki value > 1 μM but < 5 μM are marked with "+."

Table 5

Cmpd. #	ATR Ki
I-N-1	++
I-N-2	++
I-N-3	++
I-N-4	++
I-N-5	++
I-N-6	----
I-N-7	++

Cmpd. #	ATR Ki
I-N-8	+
I-N-9	+
I-N-10	++
I-N-11	++
I-N-12	++
I-N-13	++
I-N-14	++

Cmpd. #	ATR Ki
I-N-15	++
I-N-16	++
I-N-17	++
I-N-18	++
I-N-19	++
I-N-20	++
I-N-21	++

I-N-22	++
I-N-23	++
I-N-24	++
I-N-25	++
I-N-26	++
I-N-27	++
I-N-28	++
I-N-29	++
I-N-30	++
I-N-31	+
I-N-32	++
I-N-33	++
I-N-34	+
I-N-35	+
I-N-36	+
I-N-37	+
I-N-38	++
I-N-39	++
I-N-40	++
I-N-41	++
I-N-42	++
I-N-43	++
I-N-44	++
I-N-45	++
I-N-46	++
I-N-47	++
I-N-48	++
I-N-49	++
I-N-50	++
I-N-51	++
I-N-52	+
I-N-53	++

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I-N-70	++
I-N-71	++
I-N-72	++
I-N-73	++
I-N-74	++
I-N-75	++
I-N-76	+
I-N-77	++
I-N-78	++
I-N-79	++
I-N-80	++
I-N-81	++
I-N-82	+++
I-N-83	+++
I-N-84	+++
I-N-85	++

I-N-86	++
I-N-87	++
I-N-88	++
I-N-89	++
I-N-90	++
I-N-91	+++
I-N-92	+
I-N-93	++
I-N-94	++
I-N-95	++
I-N-96	-----
I-N-97	++
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I-N-104	++
I-N-105	++
I-N-106	++
I-N-107	++
I-N-108	++
I-N-109	++
I-N-110	-----
I-N-111	+
I-N-112	+
I-N-113	+
I-N-114	-----
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I-N-278	++
I-N-279	++
I-N-280	++
I-N-281	++
I-N-282	++
I-N-283	++
I-N-284	++
I-N-285	++
I-N-286	++
I-N-287	++
I-N-288	++
I-N-289	+
I-N-290	++
I-O-1	++
I-O-2	+++
I-O-3	++
I-O-4	++
I-O-5	++
I-O-6	++
I-O-7	++
I-O-8	++
I-O-9	++
I-O-10	++
I-O-11	++
I-O-12	++
I-O-13	++
I-O-14	++
I-O-15	++
I-O-16	++

Cmpd. #	ATR Ki
I-O-17	++
I-O-18	++
I-O-19	++
I-O-20	++
I-O-21	++
I-O-22	++
I-O-23	++
I-O-24	+++
I-O-25	+++
I-O-26	+++
I-O-27	+++
I-O-28	+++
I-O-29	+++
I-O-30	+++
I-O-31	+++
I-O-32	+++
I-O-33	+++
I-O-34	+++
I-O-35	+++
I-O-36	+++
I-O-37	+++
I-O-38	+++
I-O-39	+++
I-O-40	+++
I-O-41	+++
I-O-42	+++
I-O-43	+++
I-O-44	++
I-O-45	++

Cmpd. #	ATR Ki
I-O-46	+
I-O-47	++
I-O-48	++
I-O-49	++
I-O-50	++
I-O-51	++
I-O-52	+
I-O-53	++
I-O-54	++
I-O-55	++
I-O-56	++
I-O-57	++
I-O-58	++
I-O-59	++
I-O-60	++
I-O-61	++
I-O-62	++
I-O-63	++
I-O-64	++
I-O-65	++
I-O-66	++
I-O-67	++
I-O-68	++
I-O-69	++
I-O-70	++
I-O-71	++
I-O-72	++
I-O-73	++
I-O-74	++

Cmpd. #	ATR Ki
I-O-75	++
I-O-76	++
I-O-77	++
I-O-78	++
I-O-79	-----
I-O-80	++
I-O-81	++
I-O-82	+++
I-O-83	+++
I-O-84	+++
I-O-85	++
I-O-86	+++
I-O-87	++
I-O-88	++
I-O-89	++
I-O-90	++
I-O-91	++
I-O-92	++
I-C-1	+
I-C-2	+
I-C-3	++
I-C-4	++
I-C-5	++
I-C-6	++
I-C-7	++
I-C-8	++
I-C-9	++
I-C-10	++
I-C-11	++

Cmpd. #	ATR Ki
I-C-12	++
I-C-13	+
I-C-14	+
I-C-15	++
I-C-16	++
I-C-17	++
I-C-18	++
I-C-19	++
I-C-20	++
I-C-21	++
I-C-22	++
I-C-23	+
I-C-24	++
I-C-25	++
I-C-26	++
I-C-27	++
I-C-28	++
I-C-29	++
I-C-30	++
I-C-31	++
I-C-32	++
I-C-33	++
I-C-34	++
I-C-35	++
I-C-36	++
I-C-37	+
I-C-38	++
I-C-39	++
I-C-40	++

Cmpd. #	ATR Ki
I-C-41	++
I-C-42	++
I-C-43	++
I-C-44	++
I-C-45	++
I-C-46	++
I-C-47	++
I-C-48	++
I-C-49	++
I-C-50	++
I-C-51	++
I-C-52	++
I-C-53	++
I-C-54	++
I-C-55	++
I-C-56	++
I-C-57	++
I-C-58	++
I-C-59	++
I-C-60	++
I-C-61	++
I-C-62	++
I-C-63	++
I-C-64	++
I-C-65	++
I-C-66	++
I-C-67	++
I-C-68	++
I-C-69	++

Cmpd. #	ATR Ki
I-C-70	++
I-C-71	++
I-C-72	++
I-C-73	++
I-C-74	++
I-C-75	++
I-C-76	+
I-C-77	++
I-C-78	++
I-C-79	++
I-C-80	++
I-C-81	+++
I-C-82	++
I-C-83	++
I-C-84	++
I-G-1	++
I-G-2	++
I-G-3	++
I-G-4	++
I-G-5	++
I-G-6	++
I-G-7	++
I-G-8	++
I-G-9	++
I-G-10	++
I-G-11	++
I-G-12	++
I-G-13	++
I-G-14	+++

Cmpd. #	ATR Ki
I-G-15	++
I-G-16	++
I-G-17	+
I-G-18	++
I-G-19	++
I-G-20	++
I-G-21	++
I-G-22	++
I-G-23	++
I-G-24	++
I-G-25	++
I-G-26	++
I-G-27	++
I-C-28	++
I-G-29	++
I-G-30	++
I-G-31	++
I-G-32	++
I-G-33	++
I-G-34	++
I-G-35	++
I-G-36	++
I-G-37	++
I-G-38	++
I-G-40	++
I-G-41	+
I-G-42	++
I-G-43	++
I-G-44	++

Cmpd. #	ATR Ki
I-G-45	++
I-G-46	+
I-G-47	++
I-G-48	++
I-G-49	++
I-G-50	++
I-G-51	++
I-G-52	++
I-G-53	++
I-G-54	++
I-G-55	++
I-G-56	++
I-G-57	++
I-G-58	++
I-G-59	++
I-G-60	++
I-G-61	++
I-G-62	++
I-G-63	++
I-G-64	++
I-G-65	++
I-G-66	++
I-G-67	+++
I-G-68	+++
I-G-69	++
I-G-70	++
I-G-71	++
I-G-72	++
I-G-73	++

Cmpd. #	ATR Ki
I-G-74	++
I-G-75	++
I-G-76	++
I-G-77	++
I-G-78	++
I-G-79	++
I-G-80	++
I-G-81	++
I-G-82	++
I-G-83	++
I-G-84	++
I-G-85	++
I-G-86	++
I-G-87	++
I-G-88	++
I-G-89	++
I-G-90	++
I-G-91	++
I-G-92	++
I-G-93	++
I-G-94	++
I-G-95	++
I-G-96	++
I-G-98	++
I-G-99	++

Example 21: Cisplatin Sensitization Assay

[00535] Compounds can be screened for their ability to sensitize HCT116 colorectal cancer cells to Cisplatin using a 96h cell viability (MTS) assay. HCT116 cells, which possess a defect in ATM signaling to Cisplatin (see, Kim et al.; *Oncogene* 21:3864 (2002); see also, Takemura et al.; *JBC* 281:30814 (2006)) are plated at 470 cells per well in 96-well polystyrene plates (Costar 3596) in 150µl of McCoy's 5A media (Sigma M8403) supplemented with 10% foetal bovine serum (JRH Biosciences 12003), Penicillin/Streptomycin solution diluted 1:100 (Sigma P7539), and 2mM L-glumtamine (Sigma G7513), and allowed to adhere overnight at 37°C in 5% CO_2. Compounds and Cisplatin are then both added simultaneously to the cell media in 2-fold serial dilutions from a top final concentration of 10µM as a full matrix of concentrations in a final cell volume of 200µl, and the cells are then incubated at 37°C in 5% CO_2. After 96h, 40µl of MTS reagent (Promega G358a) is added to each well and the cells are incubated for 1h at 37°C in 5% CO_2. Finally, absorbance is measured at 490nm using a SpectraMax Plus 384 reader (Molecular Devices) and the concentration of compound required to reduce the IC_{50} of Cisplatin alone by at least 3-fold (to 1 decimal place) can be reported.

[00536] Table 6, below, shows the Cisplatin sensitization values of compounds of the disclosure. Compounds with a Cisplatin sensitization value of < 0.02 µM are marked with "+++." Compounds with a Cisplatin sensitization value > 0.02 µM but < 0.2 µM are marked with "++." Compounds with a Cisplatin sensitization value > 0.2 µM but < 5 µM are marked with "+."

Table 6

Cmpd. #	Cisplatin Sensitization Assay
I-N-1	++
I-N-2	+++
I-N-3	+++
I-N-4	+++
I-N-5	++
I-N-6	----
I-N-7	++
I-N-8	+
I-N-9	+
I-N-10	++
I-N-11	++
I-N-12	+++
I-N-13	+++
I-N-14	+++
I-N-15	+++
I-N-16	+++
I-N-17	+++
I-N-18	++
I-N-19	+++
I-N-20	+++
I-N-21	+++

I-N-22	-----
I-N-23	+++
I-N-24	+++
I-N-25	-----
I-N-26	+
I-N-27	++
I-N-28	+++
I-N-29	++
I-N-30	++
I-N-31	+
I-N-32	++
I-N-33	+
I-N-34	++
I-N-35	+
I-N-36	++
I-N-37	++
I-N-38	++
I-N-39	++
I-N-40	++
I-N-41	+++
I-N-42	-----
I-N-43	++
I-N-44	++
I-N-45	++
I-N-46	+++
I-N-47	++
I-N-48	++
I-N-49	+++
I-N-50	+
I-N-51	-----
I-N-52	++
I-N-53	++

I-N-54	+++
I-N-55	++
I-N-56	++
I-N-57	+++
I-N-58	++
I-N-59	++
I-N-60	+++
I-N-61	+++
I-N-62	++
I-N-63	++
I-N-64	+++
I-N-65	+
I-N-66	+++
I-N-67	+++
I-N-68	+++
I-N-69	+++
I-N-70	++
I-N-71	+++
I-N-72	+++
I-N-73	+++
I-N-74	+++
I-N-75	+++
I-N-76	+++
I-N-77	+
I-N-78	-----
I-N-79	++
I-N-80	++
I-N-81	+++
I-N-82	++
I-N-83	++
I-N-84	+++
I-N-85	++

I-N-86	+++
I-N-87	++
I-N-88	++
I-N-89	++
I-N-90	+
I-N-91	++
I-N-92	+
I-N-93	----
I-N-94	+++
I-N-95	++
I-N-96	-----
I-N-97	+++
I-N-98	+++
I-N-99	+++
I-N-100	++
I-N-101	++
I-N-102	++
I-N-103	+++
I-N-104	+++
I-N-105	+++
I-N-106	+++
I-N-107	+++
I-N-108	+++
I-N-109	+++
I-N-110	----
I-N-111	++
I-N-112	+
I-N-113	+
I-N-114	-----
I-N-115	+++
I-N-116	++
I-N-117	+++

I-N-118	+++
I-N-119	++
I-N-120	+++
I-N-121	+++
I-N-122	++
I-N-123	++
I-N-124	+++
I-N-125	+++
I-N-126	+++
I-N-127	+++
I-N-128	+++
I-N-129	-----
I-N-130	++
I-N-131	+++
I-N-132	+++
I-N-133	++
I-N-134	+
I-N-135	+++
I-N-136	++
I-N-137	++
I-N-138	++
I-N-139	+++
I-N-140	+++
I-N-141	+++
I-N-142	++
I-N-143	++
I-N-144	+++
I-N-145	-----
I-N-146	+++
I-N-147	+++
I-N-148	+++
I-N-149	+++

I-N-150	+++
I-N-151	+
I-N-152	+++
I-N-153	++
I-N-154	+++
I-N-155	+++
I-N-156	+++
I-N-157	++
I-N-158	+++
I-N-159	+++
I-N-160	+++
I-N-161	+
I-N-162	++
I-N-163	+++
I-N-164	+++
I-N-165	+++
I-N-166	+++
I-N-167	+++
I-N-168	+
I-N-169	+++
I-N-170	+++
I-N-171	+++
I-N-172	+++
I-N-173	+++
I-N-174	+++
I-N-175	+++
I-N-176	+++
I-N-177	+++
I-N-178	+++
I-N-179	+++
I-N-180	-----
I-N-181	+++

I-N-182	++
I-N-183	+++
I-N-184	++
I-N-185	++
I-N-186	+++
I-N-187	+++
I-N-188	+++
I-N-189	+++
I-N-190	+++
I-N-191	+
I-N-192	+++
I-N-193	+++
I-N-194	+++
I-N-195	+++
I-N-196	+++
I-N-197	+++
I-N-198	++
I-N-199	+++
I-N-200	+++
I-N-201	+++
I-N-202	+++
I-N-203	+++
I-N-204	-----
I-N-205	++
I-N-206	+++
I-N-207	-----
I-N-208	+++
I-N-209	+++
I-N-210	+++
I-N-211	++
I-N-212	+++
I-N-213	+++

I-N-214	++
I-N-215	+++
I-N-216	+++
I-N-217	++
I-N-218	+
I-N-219	+++
I-N-220	++
I-N-221	++
I-N-222	++
I-N-223	++
I-N-224	+
I-N-225	++
I-N-226	+++
I-N-227	+++
I-N-228	+++
I-N-229	+++
I-N-230	+++
I-N-231	+++
I-N-232	++
I-N-233	++
I-N-234	+
I-N-235	++
I-N-236	+++
I-N-237	+
I-N-238	++
I-N-239	+++
I-N-240	++
I-N-241	+++
I-N-242	+
I-N-243	+++
I-N-244	+++
I-N-245	++

I-N-246	++
I-N-247	+++
I-N-248	++
I-N-249	+++
I-N-250	++
I-N-251	+++
I-N-252	+++
I-N-253	+++
I-N-254	+++
I-N-255	++
I-N-256	++
I-N-257	+++
I-N-258	++
I-N-259	+
I-N-260	+++
I-N-261	+++
I-N-262	+++
I-N-263	+
I-N-264	+
I-N-265	++
I-N-266	+++
I-N-267	+++
I-N-268	+++
I-N-269	++
I-N-270	+++
I-N-271	+++
I-N-272	+++
I-N-273	+++
I-N-274	+++
I-N-275	+++
I-N-276	+++
I-N-277	+++

I-N-278	+++
I-N-279	+++
I-N-280	+++
I-N-281	+++
I-N-282	+++
I-N-283	++
I-N-284	+++
I-N-285	++
I-N-286	++
I-N-287	+++
I-N-288	+++
I-N-289	++
I-N-290	++
I-O-1	+++
I-O-2	++
I-O-3	++
I-O-4	++
I-O-5	+++
I-O-6	+++
I-O-7	++
I-O-8	+
I-O-9	++
I-O-10	+++
I-O-11	+++
I-O-12	+++
I-O-13	+++
I-O-14	+++
I-O-15	+++
I-O-16	+++
I-O-17	+++
I-O-18	-----
I-O-19	+++

Cmpd. #	Cisplatin Sensitization Assay
I-O-20	++
I-O-21	++
I-O-22	-----
I-O-23	+++
I-O-24	++
I-O-25	+++
I-O-26	++
I-O-27	++
I-O-28	+++
I-O-29	+++
I-O-30	+++
I-O-31	+++
I-O-32	+++
I-O-33	++
I-O-34	++
I-O-35	+++
I-O-36	+++
I-O-37	+++
I-O-38	+++
I-O-39	+++
I-O-40	++
I-O-41	+++
I-O-42	+++
I-O-43	+++
I-O-44	++
I-O-45	+++
I-O-46	+

Cmpd. #	Cisplatin Sensitization Assay
I-O-47	+
I-O-48	++
I-O-49	+
I-O-50	+
I-O-51	----
I-O-52	+
I-O-53	+++
I-O-54	+++
I-O-55	++
I-O-56	+++
I-O-57	+++
I-O-58	+++
I-O-59	+++
I-O-60	++
I-O-61	+++
I-O-62	+++
I-O-63	++
I-O-64	+++
I-O-65	+++
I-O-66	+
I-O-67	++
I-O-68	++
I-O-69	++
I-O-70	+++
I-O-71	+
I-O-72	+
I-O-73	+

Cmpd. #	Cisplatin Sensitization Assay
I-O-74	++
I-O-75	++
I-O-76	++
I-O-77	++
I-O-78	+
I-O-79	++
I-O-80	+++
I-O-81	++
I-O-82	++
I-O-83	+++
I-O-84	++
I-O-85	+++
I-O-86	++
I-O-87	++
I-O-88	+++
I-O-89	++
I-O-90	+
I-O-91	++
I-O-92	+++
I-C-1	++
I-C-2	++
I-C-3	-----
I-C-4	++
I-C-5	+++
I-C-6	+++
I-C-7	++
I-C-8	+

Cmpd. #	Cisplatin Sensitization Assay
I-C-9	+
I-C-10	+++
I-C-11	+++
I-C-12	+++
I-C-13	++
I-C-14	+
I-C-15	++
I-C-16	+
I-C-17	++
I-C-18	+
I-C-19	++
I-C-20	+++
I-C-21	+++
I-C-22	++
I-C-23	+
I-C-24	+++
I-C-25	+++
I-C-26	++
I-C-27	++
I-C-28	-----
I-C-29	+++
I-C-30	+++
I-C-31	+++
I-C-32	-----
I-C-33	+
I-C-34	+++
I-C-35	+++

Cmpd. #	Cisplatin Sensitization Assay
I-C-36	+++
I-C-37	+++
I-C-38	++
I-C-39	+++
I-C-40	+++
I-C-41	+++
I-C-42	++
I-C-43	+++
I-C-44	+++
I-C-45	+++
I-C-46	+
I-C-47	+++
I-C-48	+++
I-C-49	+++
I-C-50	+++
I-C-51	++
I-C-52	++
I-C-53	+++
I-C-54	+++
I-C-55	+
I-C-56	+++
I-C-57	+++
I-C-58	+++
I-C-59	++
I-C-60	++
I-C-61	+++
I-C-62	++

Cmpd. #	Cisplatin Sensitization Assay
I-C-63	+++
I-C-64	+++
I-C-65	++
I-C-66	+++
I-C-67	++
I-C-68	+
I-C-69	+++
I-C-70	+++
I-C-71	+++
I-C-72	+++
I-C-73	++
I-C-74	+
I-C-75	++
I-C-76	+
I-C-77	+++
I-C-78	++
I-C-79	+++
I-C-80	+++
I-C-81	+++
I-C-82	+++
I-C-83	++
I-C-84	++
I-G-1	+++
I-G-2	+++
I-G-3	+++
I-G-4	+++
I-G-5	+++

Cmpd. #	Cisplatin Sensitization Assay
I-G-6	+++
I-G-7	+++
I-G-8	+++
I-G-9	+++
I-G-10	+++
I-G-11	+++
I-G-12	+++
I-G-13	+++
I-G-14	+++
I-G-15	+++
I-G-16	+++
I-G-17	+
I-G-18	+++
I-G-19	++
I-G-20	+
I-G-21	+++
I-G-22	+++
I-G-23	+++
I-G-24	+++
I-G-25	+++
I-G-26	++
I-G-27	++
I-G-28	+++
I-G-29	+++
I-G-30	+++
I-G-31	+++
I-G-32	+++

Cmpd. #	Cisplatin Sensitization Assay
I-G-33	+++
I-G-34	+++
I-G-35	+++
I-G-36	+++
I-G-37	++
I-G-38	+++
I-G-40	+++
I-G-41	+++
I-G-42	+++
I-G-43	+++
I-G-44	+++
I-G-45	+++
I-G-46	+++
I-G-47	+++
I-G-48	+++
I-G-49	+++
I-G-50	+++
I-G-51	+++
I-G-52	+++
I-G-53	+++
I-G-54	+++
I-G-55	+++
I-G-56	+++
I-G-57	+++
I-G-58	+++
I-G-59	+++
I-G-60	+++

Cmpd. #	Cisplatin Sensitization Assay
I-G-61	+++
I-G-62	+++
I-G-63	+++
I-G-64	+++
I-G-65	+++
I-G-66	+++
I-G-67	+++
I-G-68	+++
I-G-69	+++
I-G-70	---
I-G-71	---
I-G-72	+++
I-G-73	+++
I-G-74	+++
I-G-75	+++
I-G-76	+++
I-G-77	+++
I-G-78	+++
I-G-79	+++
I-G-80	+++
I-G-81	+++
I-G-82	+++
I-G-83	+++
I-G-84	+++
I-G-85	+++
I-G-86	+++
I-G-87	+++

Cmpds. #	Cisplatin Sensitization Assay
I-G-88	+++
I-G-89	+
I-G-90	+++
I-G-91	+++
I-G-92	+++
I-G-93	+++
I-G-94	+++
I-G-95	+++

Cmpds. #	Cisplatin Sensitization Assay
I-G-96	+++
I-G-98	+++
I-G-99	+++

Cmpds. #	Cisplatin Sensitization Assay

Example 22: Single Agent HCT116 Activity

[00537] Compounds can be screened for single agent activity against HCT116 colorectal cancer cells using a 96h cell viability (MTS) assay. HCT116 are plated at 470 cells per well in 96-well polystyrene plates (Costar 3596) in 150µl of McCoy's 5A media (Sigma M8403) supplemented with 10% foetal bovine serum (JRH Biosciences 12003), Penicillin/ Streptomycin solution diluted 1:100 (Sigma P7539), and 2mM L-glumtamine (Sigma G7513), and allowed to adhere overnight at 37°C in 5% CO_2. Compounds are then added to the cell media in 2-fold serial dilutions from a top final concentration of 10µM as a full matrix of concentrations in a final cell volume of 200µl, and the cells are then incubated at 37°C in 5% CO_2. After 96h, 40µl of MTS reagent (Promega G358a) is added to each well and the cells are incubated for 1h at 37°C in 5% CO_2. Finally, absorbance is measured at 490nm using a SpectraMax Plus 384 reader (Molecular Devices) and IC50 values can be calculated.

Example 23: ATR-complex Inhibition Assay

[00538] Compounds were screened for their ability to inhibit ATR kinase, in the presence of partner proteins ATRIP, CLK2 and TopBP1, using a radioactive-phosphate incorporation assay. Assays were carried out in a mixture of 50 mM Tris/HCl (pH 7.5), 10 mM $MgCl_2$ and 1 mM DTT. Final substrate concentrations were 10 µM [g-33P]ATP (3.5 µCi 33P ATP/nmol ATP, Perkin Elmer, Massachusetts, USA) and 800 µM target peptide

(ASELPASQPQPFSAKKK, Isca Biochemicals, Cambridgeshire, UK).

[00539] Assays were carried out at 25°C in the presence of 4 nM full-length ATR, 40 nM full-length ATRIP, 40 nM full-length CLK2 and 600 nM TopBP1(A891-S1105). An enzyme stock buffer solution was prepared containing all of the reagents listed above, with the exception of target peptide, ATP and the test compound of interest. This enzyme stock was pre-incubated for 30 minutes at 25°C. 8.5 μL of the enzyme stock solution was placed in a 96-well plate followed by addition of 5μl of target peptide and 2 μL of DMSO stock containing serial dilutions of the test compound (typically starting from a final concentration of 1.5 μM with 2.5-fold serial dilutions) in duplicate (final DMSO concentration 7%). The plate was pre-incubated for 10 minutes at 25°C and the reaction initiated by addition of 15 μL [g-33P]ATP (final concentration 10 μM).

[00540] The reaction was stopped after 20 hours by the addition of 30 μL 0.3 M phosphoric acid containing 2 mM ATP. A phosphocellulose filter 96-well plate (Multiscreen HTS MAPHNOB50, Merck-Millipore, Massachusetts, USA) was pretreated with 100 μL 0.1 M phosphoric acid prior to the addition of 45 μL of the stopped assay mixture. The plate was washed with 5 x 200 μL 0.1 M phosphoric acid. After drying, 50 μL Optiphase 'SuperMix' liquid scintillation cocktail (Perkin Elmer, Massachusetts, USA) was added to the well prior to scintillation counting (Wallac 1450 Microbeta Liquid Scintillation Counter, Perkin Elmer, Massachusetts, USA).

[00541] After removing mean background values for all of the data points, Ki(app) data were calculated from non-linear regression analysis of the initial rate data using the Prism software package (GraphPad Prism version 6.0c for Macintosh, GraphPad Software Inc., San Diego, USA).

[00542] Table 7, below, shows the Cisplatin sensitization values of compounds of the disclosure. Compounds with a Cisplatin sensitization value of < 0.02 μM are marked with "+++." Compounds with a Ki value > 0.02 μM but < 0.2 μM are marked with "++." Compounds with a Ki value > 0.2 μM but < 5 μM are marked with "+."

Table 7

Cmpd. #	ATR Ki
I-N-1	+++
I-N-13	+++

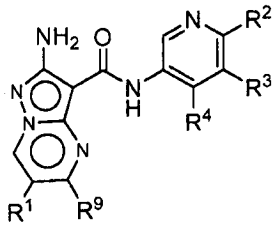
Cmpd. #	ATR Ki
I-N-58	+++
I-N-118	+++
I-N-166	+++
I-N-186	+++
I-N-275	+++
I-C-25	+++
I-C-31	+++
I-C-43	+++
I-C-79	+++
I-G-4	+++
I-G-7	+++
I-G-12	+++
I-G-21	+++
I-G-32	+++

[00543] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds, methods, and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example herein.

CLAIMS

We claim:

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

R^9 is independently selected from H, $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

k is 0 or 1;

M and L are a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$, each M and L^1 is optionally substituted with 0-3 occurrences of J^{LM};

J^{LM} is independently selected from halo, -CN, or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$;

W is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein W is optionally substituted with 0-5 occurrences of J^W;

J^W is independently selected from -CN, halo, $-CF_3$; a C_{1-4}aliphatic wherein up to two methylene units are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n-$; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; 3-4 membered heterocyclyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^Z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; $\rightarrow$O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from-CN; =O; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-;

J^T is independently selected from halo, -CN; →O; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

2. The compound of any one of claims 1, wherein R^9 is H.

3. The compound of any one of claims 1-2, wherein R^9 is M.

4. The compound of claim 3, wherein M is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-.

5. The compound of claim 4, wherein, M is C_{1-4}alkyl, -(C_{1-4}alkyl)O(C_{1-3}aliphatic), -(C_{1-3}alkyl)OH, -O(C_{1-4}alkyl)N(C_{1-2}alkyl)$_2$, -NH(C_{1-4}alkyl), or -(C_{1-4}alkyl)NH(C_{1-4}alkyl).

6. The compound of claim 5, wherein M is C_{1-4}alkyl.

7. The compound of any one of claims 4-6, wherein J^{LM} is halo.

8. The compound of any one of claims 1-2, wherein R^9 is $-(L^1)_k$-W.

9. The compound of claim 8, wherein k is 0.

10. The compound of claim 8, wherein k is 1.

11. The compound of claim 10, wherein L is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-.

12. The compound of claim 11, wherein L is -O-, -O(C1-4aliphatic)-, or -NR(C_{1-3}alkyl)-.

13. The compound of any one of claims 8-12, wherein W is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur.

14. The compound of claim 13, wherein W is a 3-7 membered heterocyclyl.

15. The compound of claim 14, wherein W is independently selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or azetidinyl.

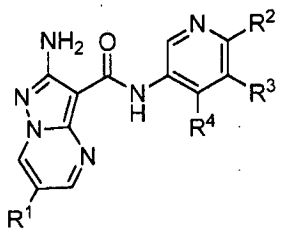
16. The compound of any one of claims 8-12, wherein W is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

17. The compound of any one of claims 8-16, wherein J^W is selected form C_{1-3}alkyl or CF_3.

18. The compound of any one of claims 8-16, wherin two occurrences of J^W on the same atom, together with atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

19. The compound of claim 18, wherein the ring formed by the two occurrences of J^W on the same atom is oxetanyl.

20. Acompound having the formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; →O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from -CN; =O; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-;

J^T is independently selected from halo, -CN; =O; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

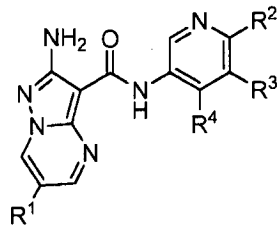
two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

R is independently selected from H or C_{1-4}aliphatic.

n is 0, 1 or 2; and

21. A compound having the formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or $\rightarrow$O;

J^Q is independently selected from –CN; halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from –CN; halo; =O; →O; Q^3; or a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^X is independently selected from -CN; halo; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-;

J^T is independently selected from -CN; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -$S(O)_n$-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

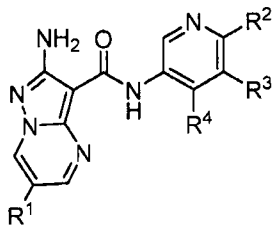
two occurrences of J^T, together with Q^3, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

22. A compound having the formula **I-A**:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^2 is independently selected from H; chloro; NH_2; or a C_{1-2}alkyl optionally substituted with fluoro;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; or -CN;

R^4 is independently selected from Q^1 or a C_{1-10}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -S-; each R^4 is optionally substituted with 0-5 occurrences of J^Q; or

R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring; having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^z is independently selected from C_{1-6}aliphatic, =O, halo, or →O;

J^Q is independently selected from halo; =O; Q^2; or a C_{1-8}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^Q, together with Q^1, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from halo; =O; →O; a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; each J^R is optionally substituted with 0-3 occurrences of J^T; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^R, together with Q^2, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^X is independently selected from halo or a C_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; or

J^T is independently selected from a C_{1-6}aliphatic or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M;

J^M is independently selected from halo or C_{1-6}aliphatic;

n is 1 or 2; and

R is independently selected from H or C_{1-4}aliphatic.

23. The compounds of any one of claims 1-22, wherein R^1 is fluoro.

24. The compounds of any one of claims 1-22, wherein R^1 is $-CH_2CN$, $-C(CH_3)_2CN$ or $-CH(C_{1-2}alkyl)CN$.

25. The compound of any one of claims 1-22, wherein R^1 is chloro.

26. The compound of any one of claims 1-25, wherein R^2 is independently selected from $-CF_3$, -NH(C_{1-2}alkyl), chloro, or H.

27. The compound of claim 26, wherein R^2 is H.

28. The compound of claim 26, wherein R^2 is -chloro.

29. The compound of any one of claims 1-28, wherein R^3 is independently selected from H, chloro, fluoro, CHF_2, -CN, cyclopropyl, or C_{1-4}alkyl.

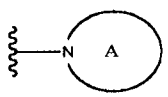
30. The compound of claim 29, wherein R^3 is independently selected from H, chloro, or fluoro.

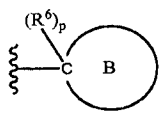
31. The compound of claim 30, wherein R^3 is H.

32. The compound of claim 30, wherein R^3 is chloro.

33. The compound of claim 30, wherein R^3 is fluoro.

34. The compound of any one of claims 1-33, wherein R^4 is independently selected from:

-O-; 

; 

; or $-CH_2-R^7$, wherein:

-O- is substituted with one J^Q;

Ring A is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; or a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

Ring B is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^6 is H;

R^7 is independently selected from H or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -$S(O)_n$-; and

p is 0 or 1.

35. The compound of claim 34, wherein R^4 is -O-.

36. The compound of claim 35, wherein J^Q is independently selected from -(C_{1-4}alkyl), -(C_{1-4}alkyl)N(C_{1-4}alkyl)$_2$, -(C_{1-3}alkyl)O(C_{1-2}alkyl)N(C_{1-3}alkyl)$_2$, (C_{1-4}alkyl)OH, -(C_{1-4}alkyl)NH_2, or -(C_{1-4}alkyl)O(C_{1-4}alkyl).

37. The compound of claim 35, wherein J^Q is Q^2.

38. The compound of claim 37, wherein Q^2 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen.

39. The compound of claim 38, wherein Q^2 is independently selected from a 5-6 membered aryl, a 5-6 membered heteroaryl, a 4-6 membered cycloaliphatic, or a 3-7 membered heterocyclyl.

40. The compound of claim 39, wherein Q^2 is independently selected from a 4-7 membered cycloaliphatic or a 3-7 membered heterocyclyl.

41. The compound of claim 40, wherein Q^2 is a 3-7 membered heterocyclyl.

42. The compound of claim 41, wherein Q^2 is independently selected from pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, and oxetanyl.

43. The compound of claim 42, wherein Q^2 is independently selected from tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, or azetidinyl

44. The compound of claim 43, wherein Q^2 is piperidinyl.

45. The compound of claim 39, wherein Q^2 is a 5-6 membered heteroaryl.

46. The compound of claim 45, wherein Q^2 is independently selected from imidazolyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.

47. The compound of claim 46, wherein Q^2 is pyridinyl.

48. The compound of claim 39, wherein Q^2 is a 4-6 membered cycloaliphatic.

49. The compound of claim 48, wherein Q^2 is independently selected from cyclobutyl or cyclohexyl.

50. The compound of claim 39, wherein Q^2 is phenyl.

51. The compound of claim 37, wherein Q^2 is an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

52. The compound of claim 51, wherein Q^2 is 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole.

53. The compound of any one of claims 36-52, wherein J^R is C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or $-S(O)_n-$.

54. The compound of claim 53, wherein J^R is independently selected from C_{1-4}alkyl, $-N(C_{1-4}alkyl)_2$, -C(O)OH, $-C(O)O(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)_2$, $-(C_{1-4}alkyl)O(C_{1-4}alkyl)$, or -C(O)-.

55. The compound of claim 54, wherein J^R is C_{1-4}alkyl.

56. The compound of any one of claims 36-52, wherein J^R is Q^3.

57. The compound of claim 56, wherein Q^3 is a 3-6 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen.

58. The compound of claim 57, wherein Q^3 is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.

59. The compound of claim 58, wherein Q^3 is independently independently selected from oxetanyl, piperidinyl, azetidinyl, piperazinyl, pyrrolidinyl, morpholinyl.

60. The compound of claim 59, wherein Q^3 is oxetanyl.

61. The compound of claim 57, wherein Q^3 is cyclopropyl.

62. The compound of any one of claims 39-43, wherein J^R is =O or halo.

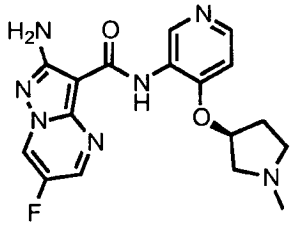
63. The compound of claim 39-43, wherein two occurrences of J^R on the same atom, taken together with the atom to which they are joined, form a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

64. The compound of claim 63, wherein the ring formed by the two occurrences of J^R on the same atom, taken together with the atom to which they are joined, is selected from oxetanyl, cyclobutyl, or azetidinyl.

65. The compound of any one of claims 56-61, wherein J^T is a 4-6 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

66. The compound of claim 65, wherein J^T is piperazinyl.

67. The compound of any one of claims 34-66 independently selected from:



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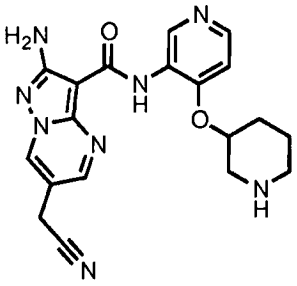

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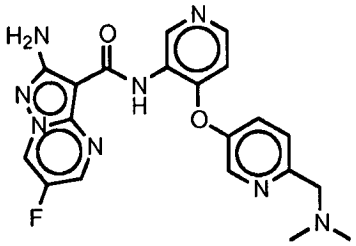

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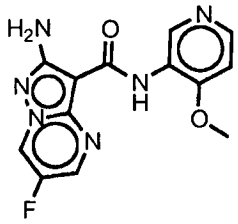

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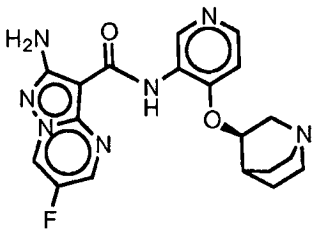

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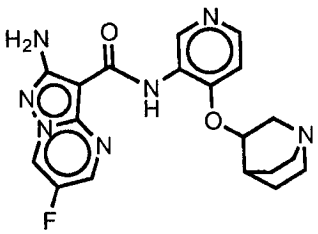

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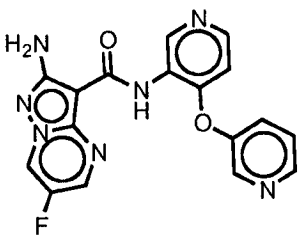

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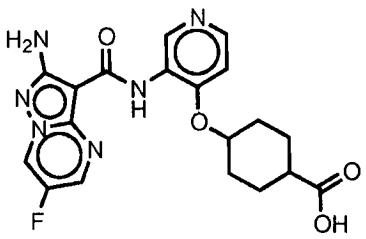

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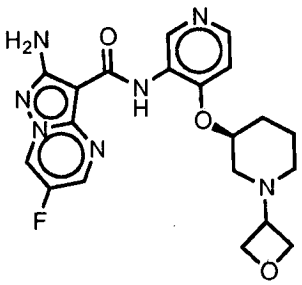

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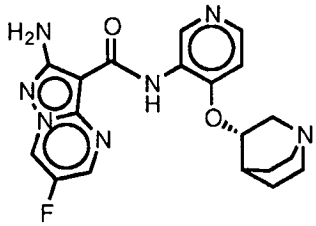

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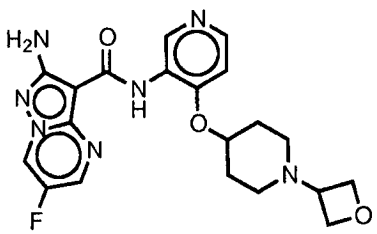

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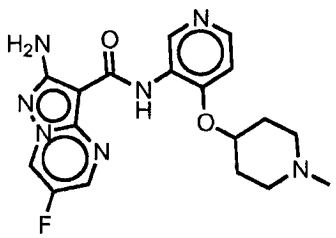

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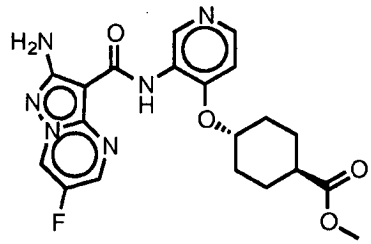

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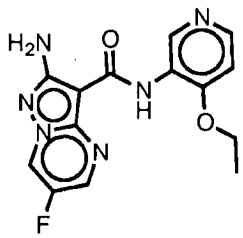

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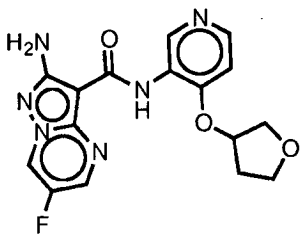

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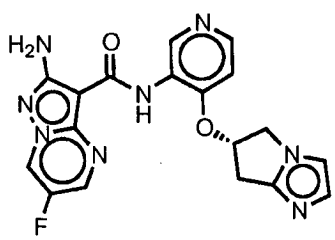

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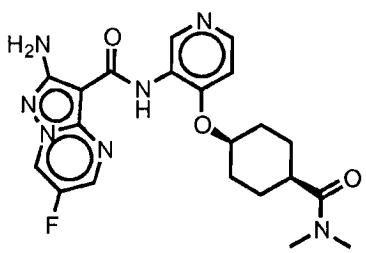

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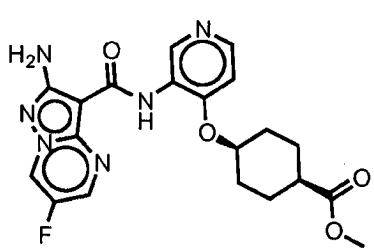

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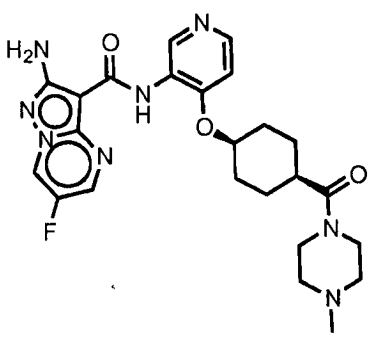

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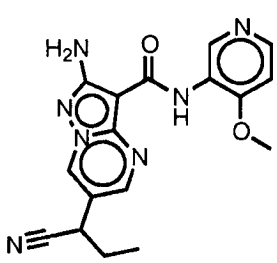

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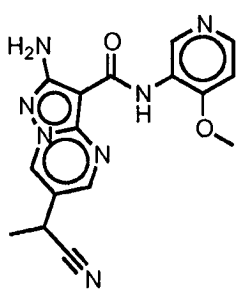

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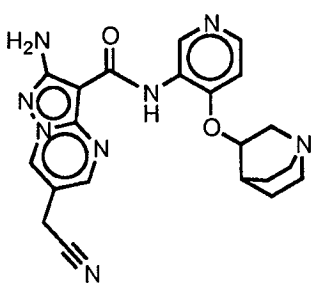

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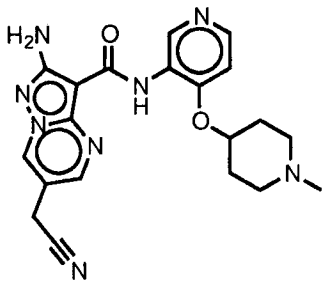

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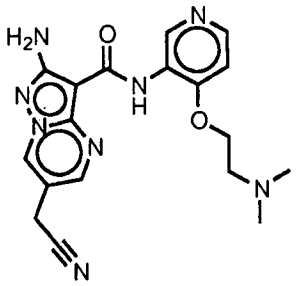

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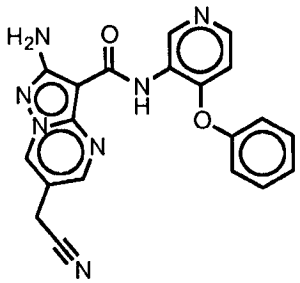

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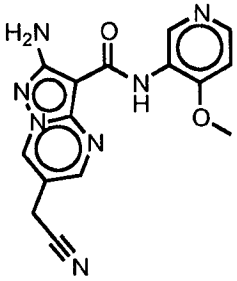

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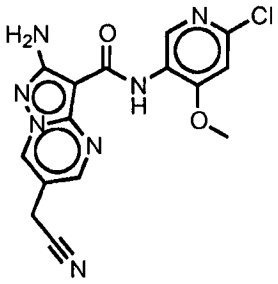

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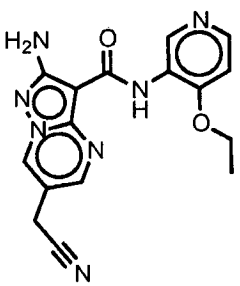

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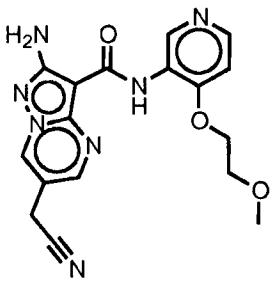

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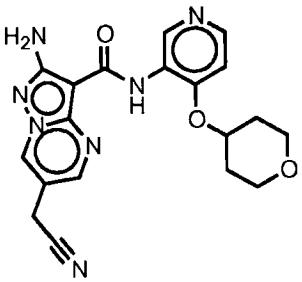

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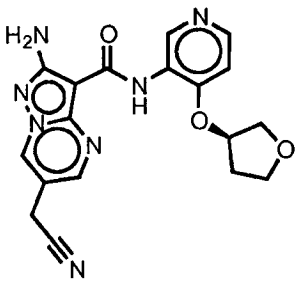

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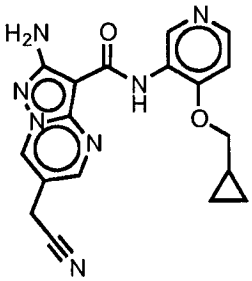

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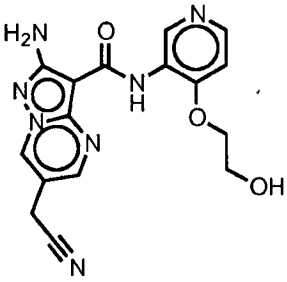

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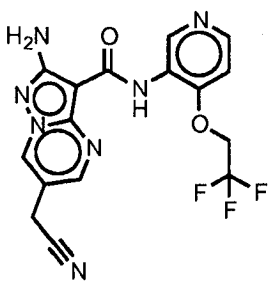
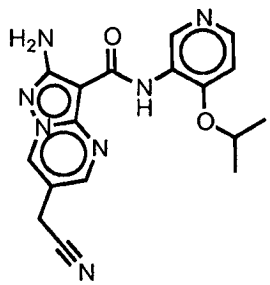
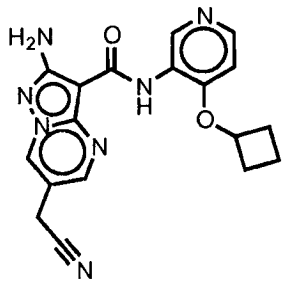


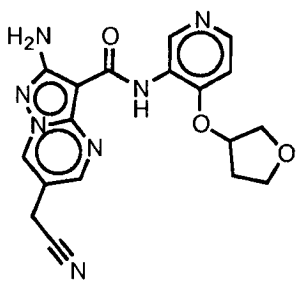
I-O-34



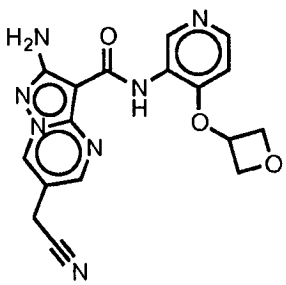
I-O-35



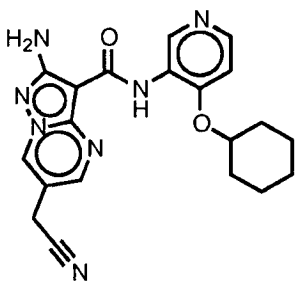
I-O-36



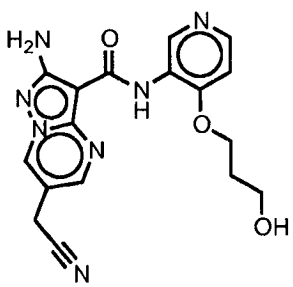
I-O-37



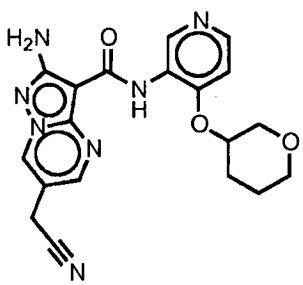
I-O-38



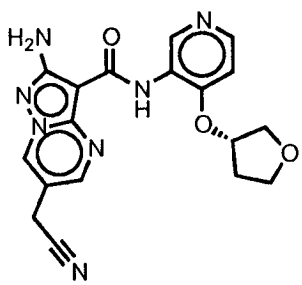
I-O-39



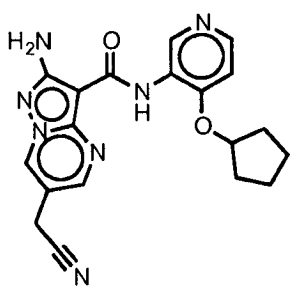
I-O-40

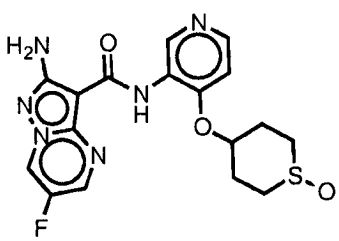


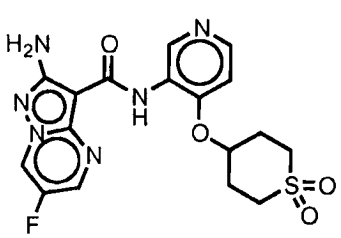
I-O-41



I-O-42







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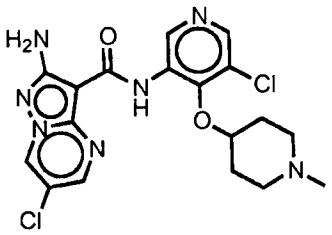
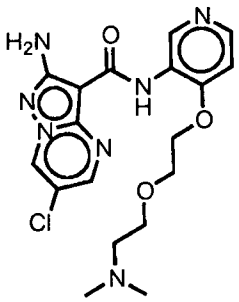


I-O-44



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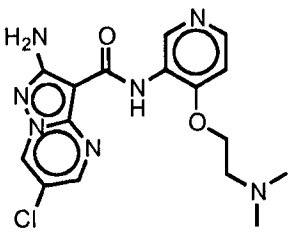
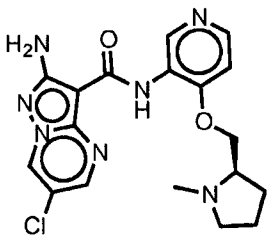
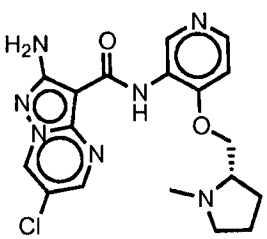


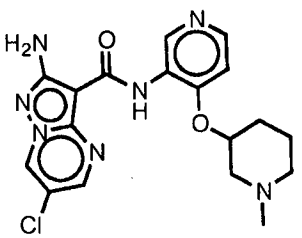
I-O-46



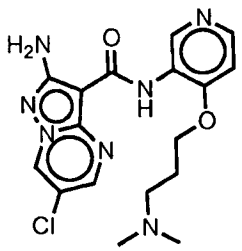
I-O-47



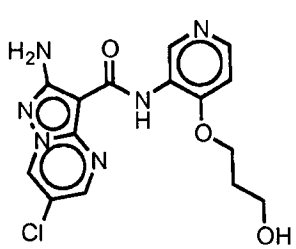
I-O-48



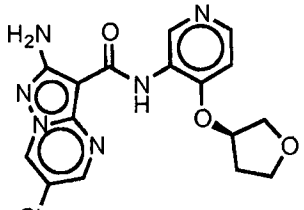
I-O-49



I-O-50



I-O-51



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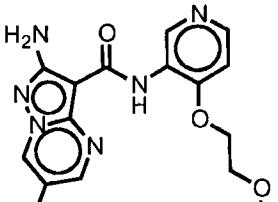
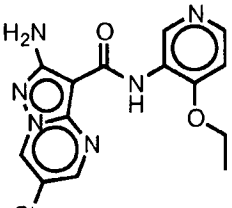


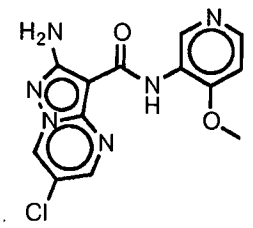
I-O-53

I-O-54

I-O-55



I-O-56



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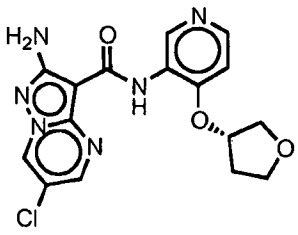

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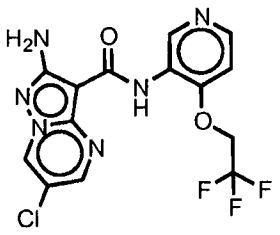

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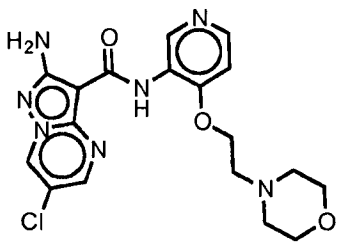

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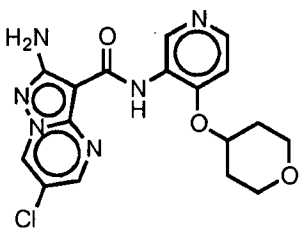

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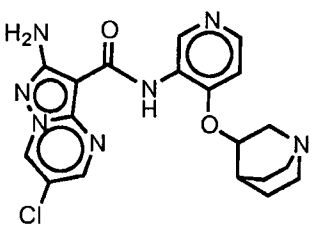
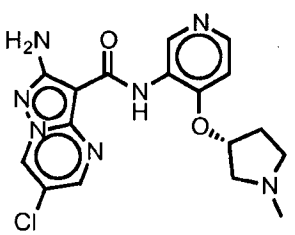


I-O-62



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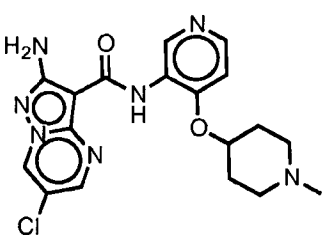

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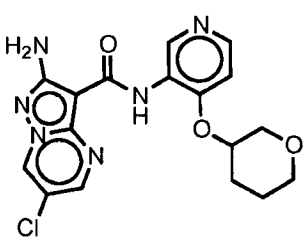

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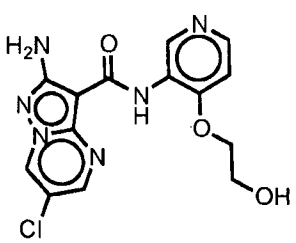
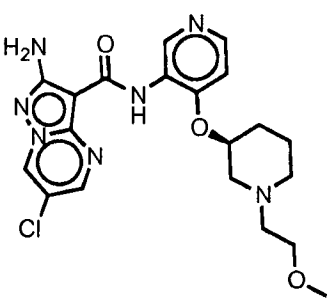
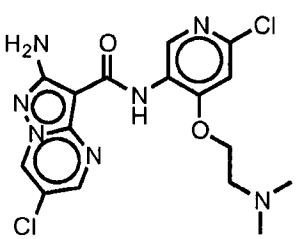


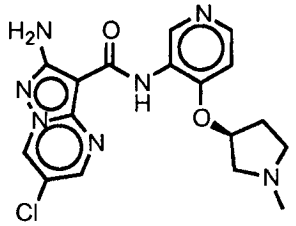
I-O-66



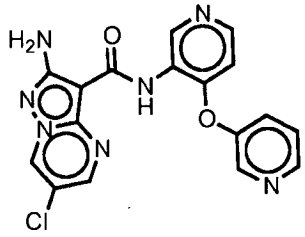
I-O-67



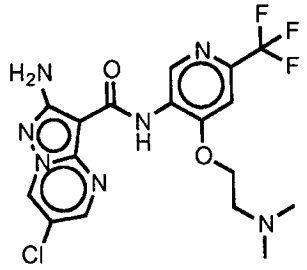
I-O-68



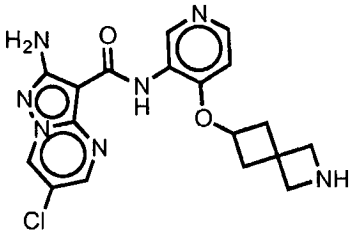
I-O-69



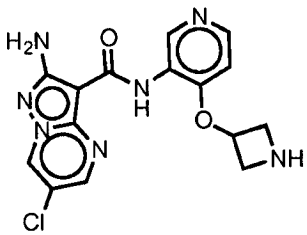
I-O-70



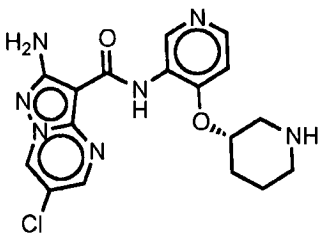
I-O-71



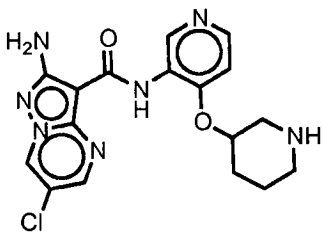
I-O-72



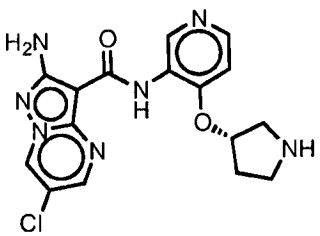
I-O-73



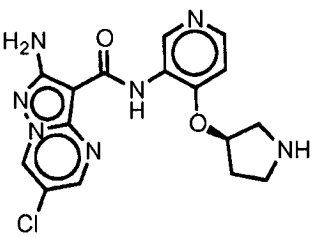
I-O74



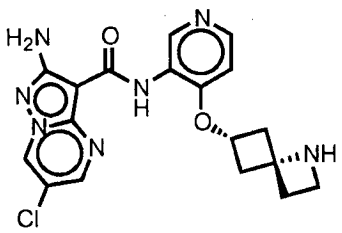
I-O-75



I-O-76



I-O-77



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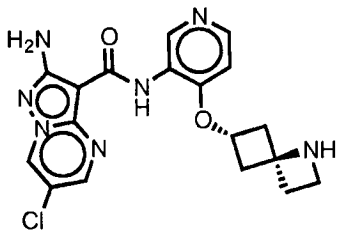
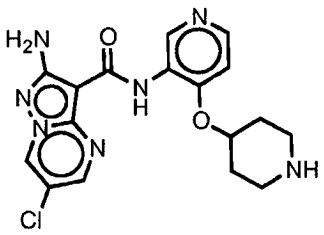
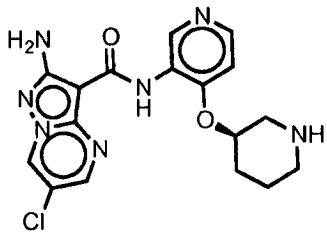


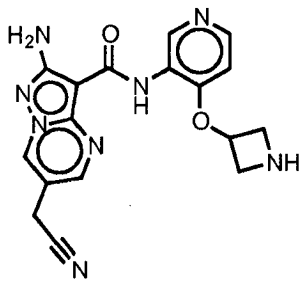
I-O-79



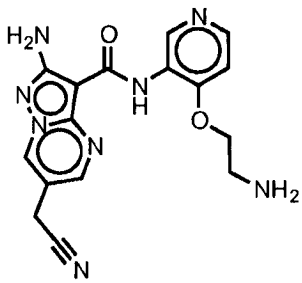
I-O-80



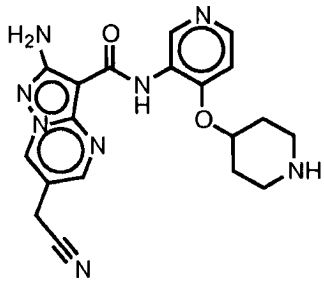
I-O-81



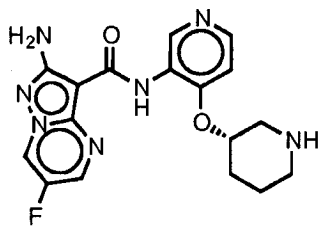
I-O-82



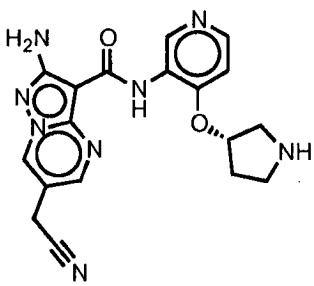
I-O-83



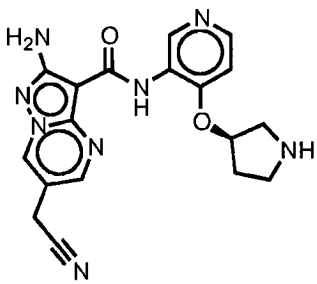
I-O-84



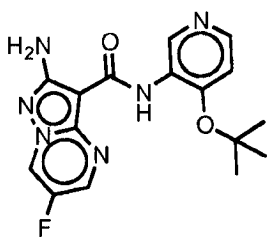
I-O-85



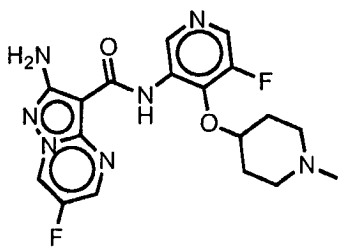
I-O-86



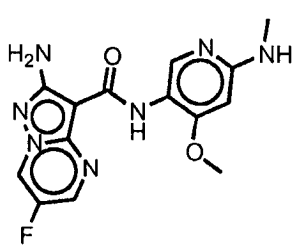
I-O-87



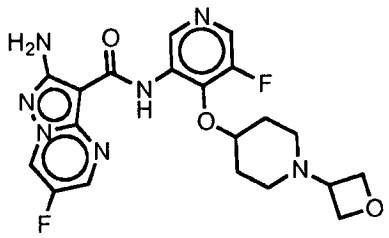
I-O-88



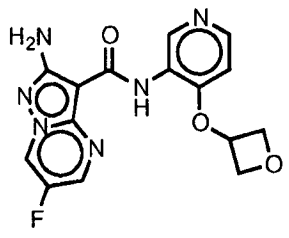
I-O-89



I-O-90

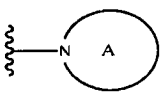


I-O-91



I-O-92

68. The compound of claim 34, wherein R^4 is:



69. The compound of claim 68, wherein Ring A is a is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur.

70. The compound of claim 69, wherein Ring A is a 3-7 membered heterocyclyl.

71. The compound of claim 70, wherein Ring A is independently selected from pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, and azetidinyl.

72. The compound of claim 71, wherein Ring A is independently selected from piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, morpholinyl.

73. The compound of claim 72, wherein Ring A is independently selected from piperazinyl or piperidinyl.

74. The compound of claim 69, wherein Ring A is a 5 membered heteroaryl.

75. The compound of claim 74, wherein Ring A is independently selected from pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.

76. The compound of claim 75, wherein Ring A is independently selected from pyrazolyl or imidazolyl.

77. The compound of claim 68, wherein Ring A is an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

78. The compound of claim 77, wherein Ring A is independently selected from octahydropyrrolo[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, octahydro-1H-pyrazino[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl, 2,5-diazabicyclo[4.1.0]heptane, or octahydropyrazino[2,1-c][1,4]oxazinyl.

79. The compound of any one of claims 68-76, wherein J^Q is C_{1-8}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -C(O)-.

80. The compound of claim 79, wherein J^Q is independently selected from -O-, -C(O)-, -$S(O)_2$-, C_{1-4}alkyl, -(C_{0-4}alkyl)NH_2, -(C_{0-4}alkyl)NH(C_{1-4}alkyl), -(C_{0-4}alkyl)N(C_{1-4}alkyl)$_2$, -(C_{0-4}alkyl)OH, -(C_{0-4}alkyl)O(C_{1-4}alkyl), -C(O)OH, -$S(O)_2$N(C_{1-3}alkyl)-, -C(O)(C_{1-4}alkyl)-, -(O)C(C_{1-4}alkyl)N(C_{1-2}alkyl)$_2$ or -C(O)O(C_{1-4}alkyl).

81. The compound of claim 80, wherein J^Q is C_{1-4}alkyl, -O-, or -C(O)- .

82. The compound of any one of claims 68-78, wherein J^Q is Q^2.

83. The compound of claim 82, wherein Q^2 is a 3-7 membered heterocyclyl or carbocyclyl; the heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.

84. The compound of claim 83, wherein Q^2 is independently selected from selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidinyl, pyrrolidinyl, piperazinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.

85. The compound of claim 84, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl.

86. The compound of claim 85, wherein Q^2 is oxetanyl.

87. The compound of claim 86, wherein Q^2 is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

88. The compound of claim 87, wherein Q^2 is independently selected from 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl or 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl.

89. The compound of any one of claims 68-73, wherein two occurrences of J^Q, together with Ring A, form a bridged ring system.

90. The compound of any one of claims 68-78, wherein J^Q is =O or →O.

91. The compound of any one of claims 79-89, wherein J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.

92. The compound of claim 91, wherein J^R is independently selected from oxetanyl, piperadinyl, azetidinyl, piperazinyl, pyrrolidinyl, or morpholinyl.

93. The compound of claim 92, wherein J^R is a piperazinyl.

94. The compound of any one of claims 79-89, wherein J^R is independently selected from halo, =O, -OH, C_{1-4}alkyl, -(C_{0-4}alkyl)N(C_{1-4}alkyl)$_2$, or -(C_{0-4}alkyl)O(C_{1-4}alkyl).

95. The compound of any one of claims 82-89, wherein two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

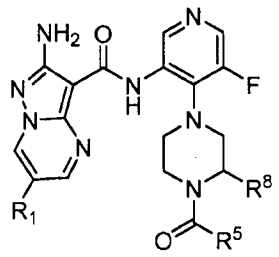
96. The compound of claim 95, wherein J^R is independently selected from oxetanyl or azetidinyl.

97. The compound of any one of claims 82-84, wherein two occurrences of J^R, together with Ring A, form a bridged ring system.

98. The compound of claim 93, wherein J^T is a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

99. The compound of claim 98, wherein J^T is oxytanyl.

100. The compound of claim 34 having formula **I-A-1**:



I-A-1 ;

wherein:

R^5 is selected from C_{1-4}aliphatic, a 3-6 membered cycloalkyl, or a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur;

R^8 is selected from H or C_{1-3} alkyl; or

R^5 and R^8, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

101. The compound of claim 100, wherein R^1 is fluoro.

102. The compound of claim 101, wherein R^5 is C_{1-4}aliphatic.

103. The compound of claim 102, wherein R^5 is independently selected from methyl or ethyl.

104. The compound of claim 100, wherein R^5 is a 3-6 membered cycloalkyl.

105. The compound of claim 104, wherein R^5 is cyclopropyl.

106. The compound of claim 100, wherein R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur.

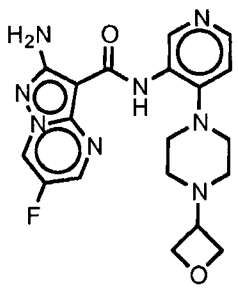
107. The compound of claim 106, wherein R^5 is tetrahydrofuranyl or oxytanyl.

108. The compound of claim 100, wherein R^5 and R^6, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected form oxygen, nitrogen or sulfur.

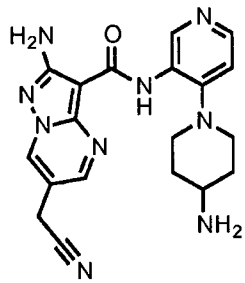
109. The compound of claim 108, wherein the ring formed by R^5 and R^6 is a five-membered ring.

110. The compound of claim 108, wherein the ring formed by R^5 and R^6 is a six-membered ring.

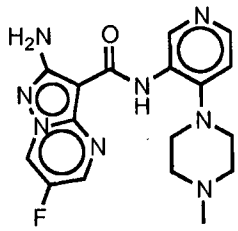
111. The compound of any one of claims 68-110 independently selected from:



I-N-1



I-N-2



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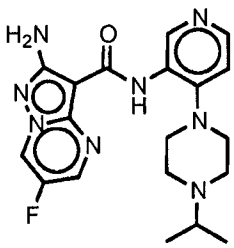
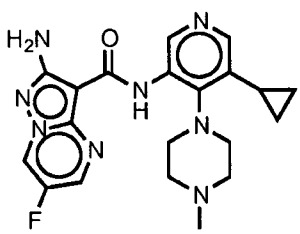


I-N-4



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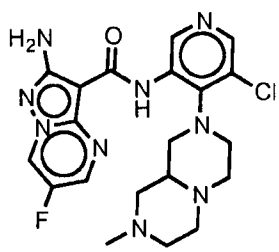

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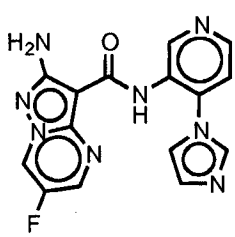

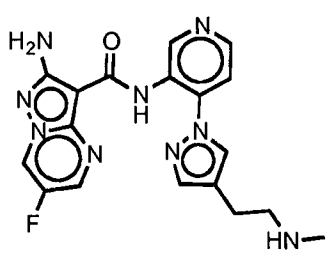

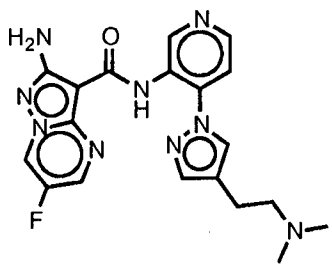

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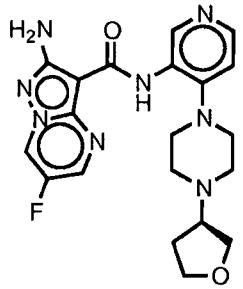

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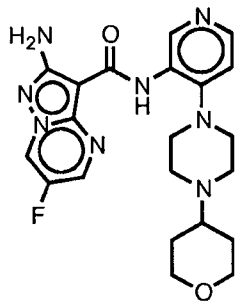

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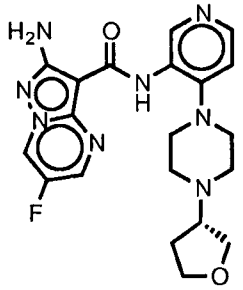

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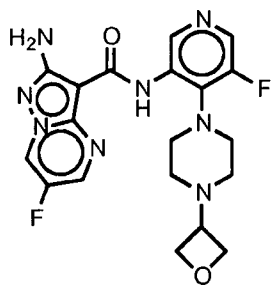

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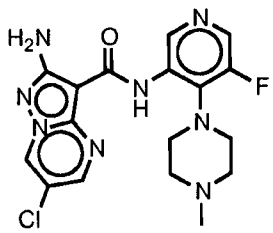

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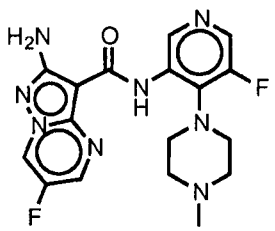

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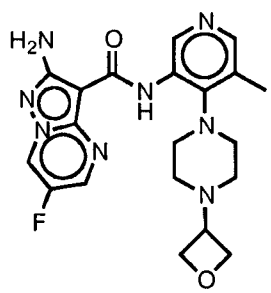

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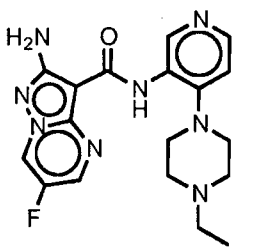

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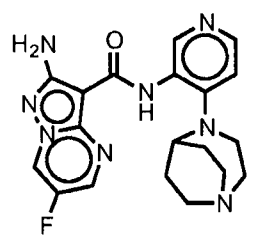

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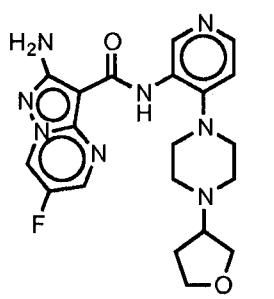
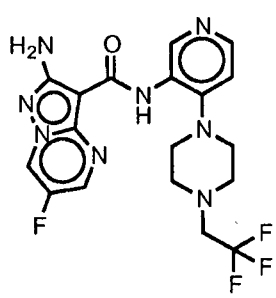


I-N-17

I-N-18

I-N-19

I-N-20



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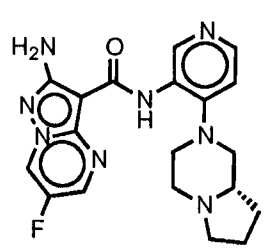

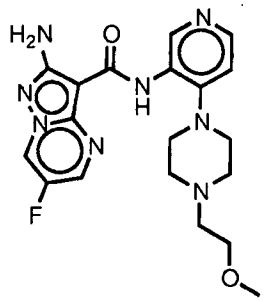

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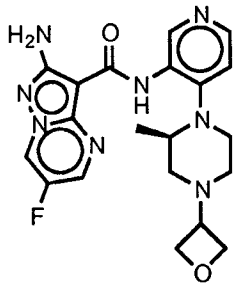

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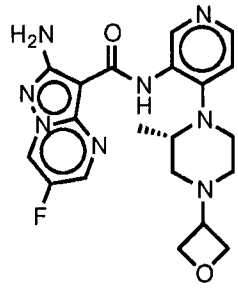

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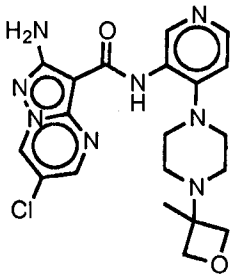

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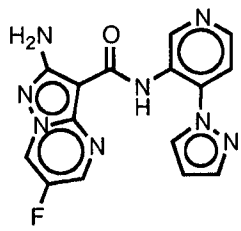

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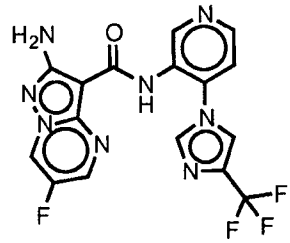

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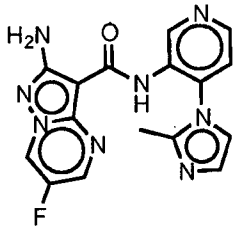

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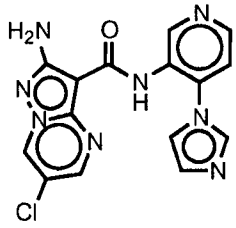

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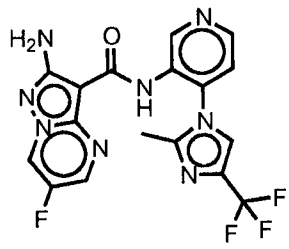

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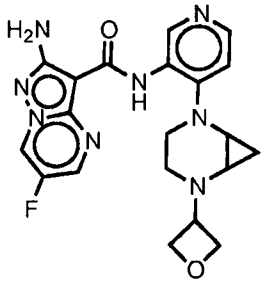

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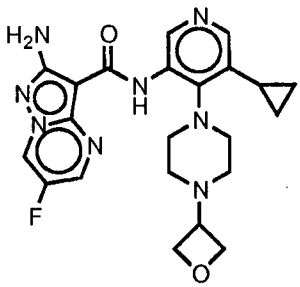

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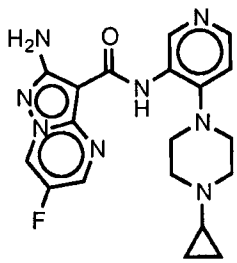

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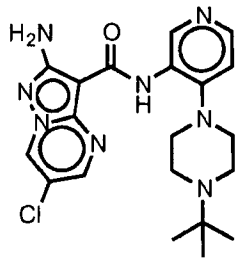
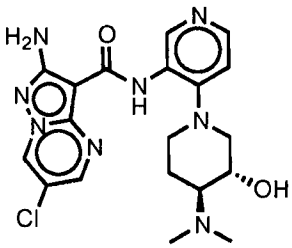
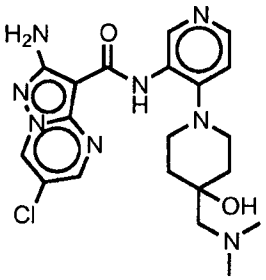


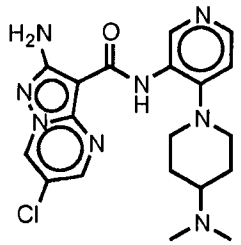
I-N-34



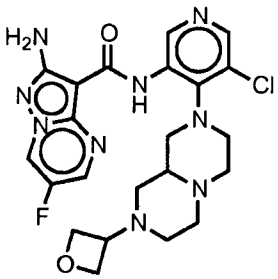
I-N-35



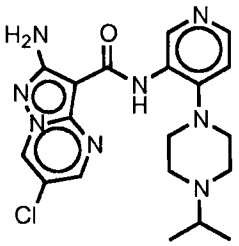
I-N-36



I-N-37



I-N-38



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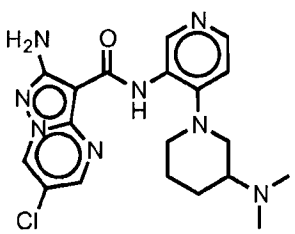

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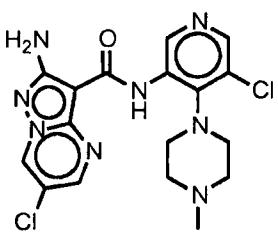

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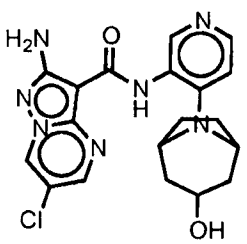
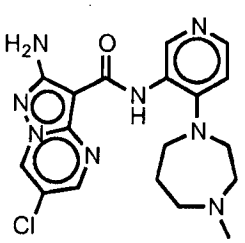
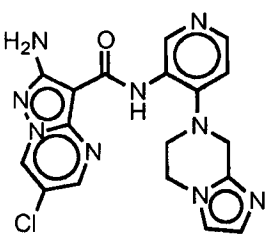


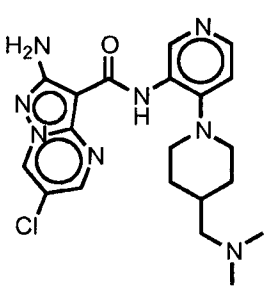
I-N-42



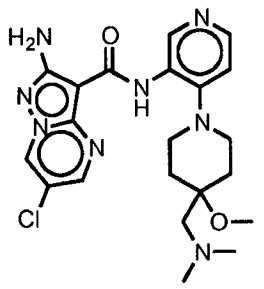
I-N-43



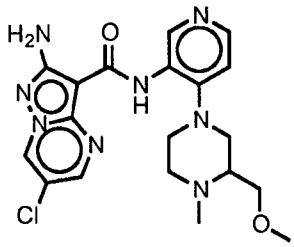
I-N-44



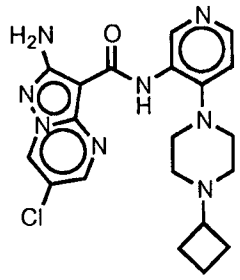
I-N-45



I-N-46



I-N-47



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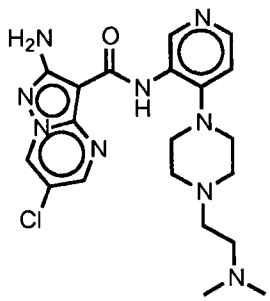
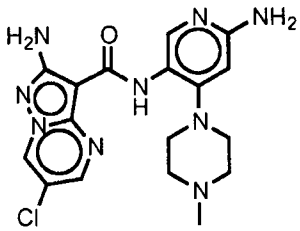


I-N-49



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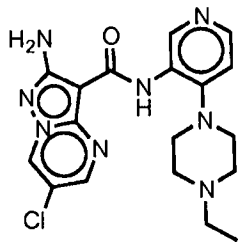

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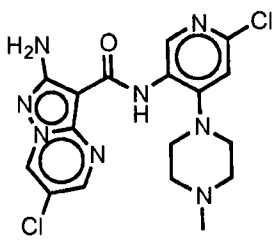
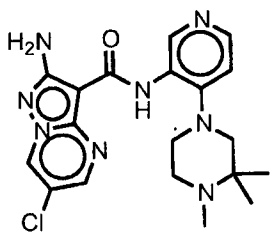


I-N-52



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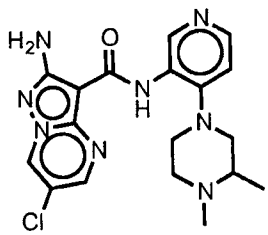

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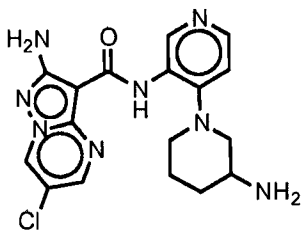

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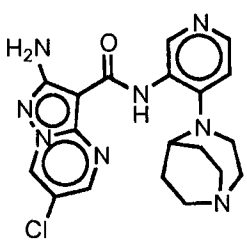
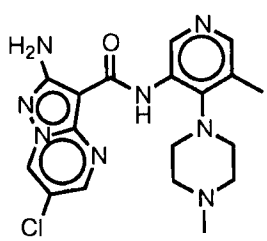


I-N-56



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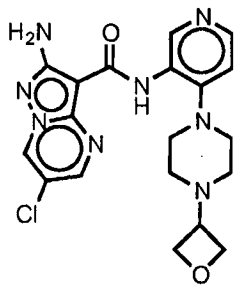

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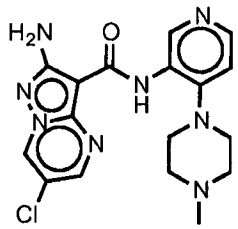

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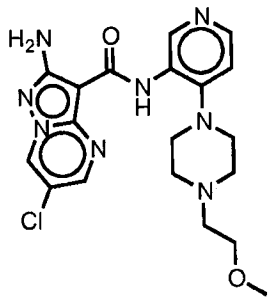

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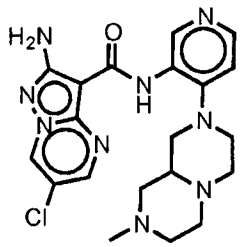
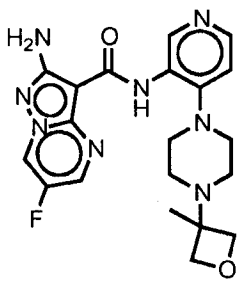
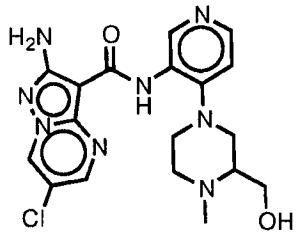


I-N-61



I-N-62



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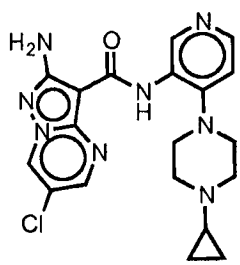

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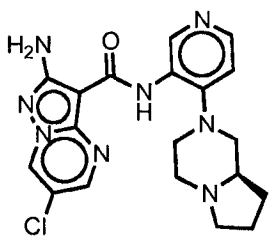

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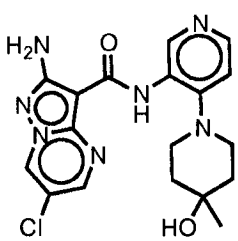
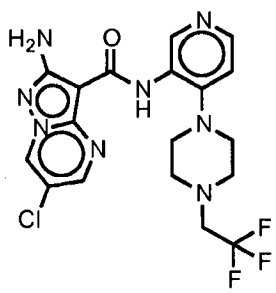
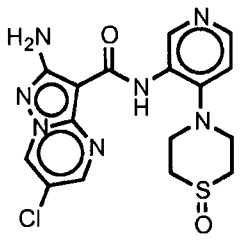


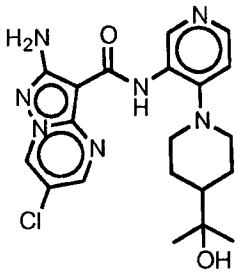
I-N-66



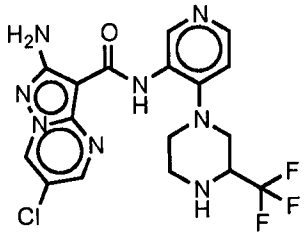
I-N-67



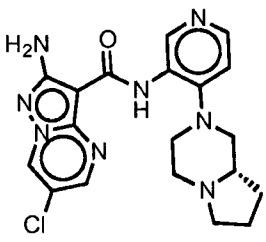
I-N-68



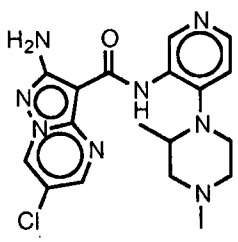
I-N-69



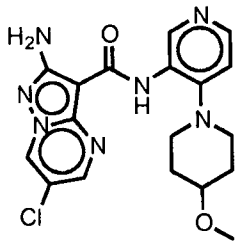
I-N-70



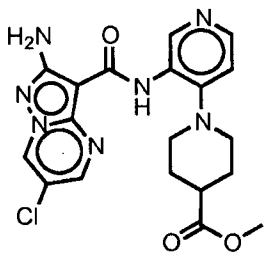
I-N-71



I-N-72



I-N-73



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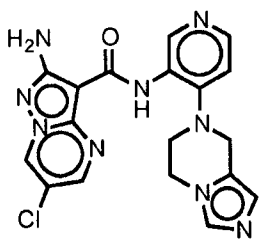
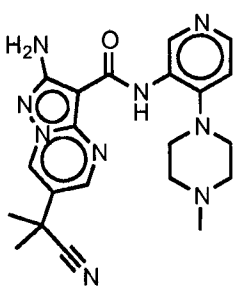
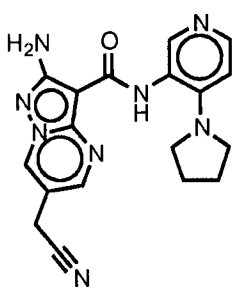


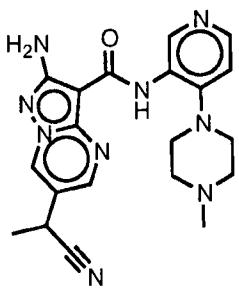
I-N-75



I-N-76



I-N-77



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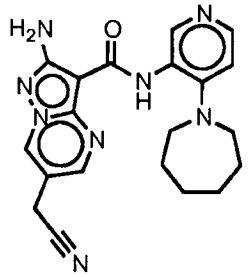

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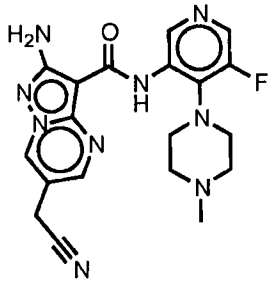
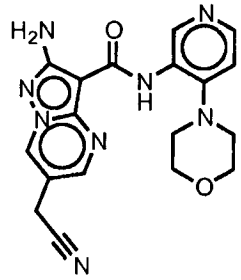
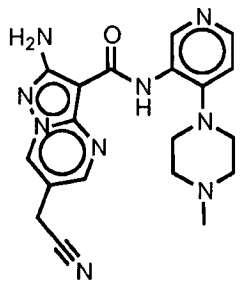


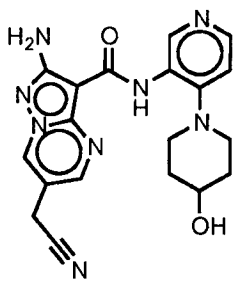
I-N-80



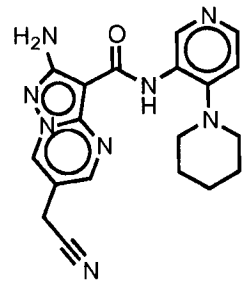
I-N-81



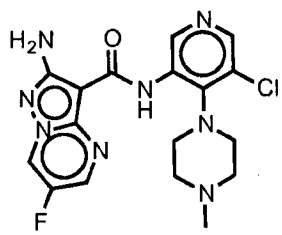
I-N-82



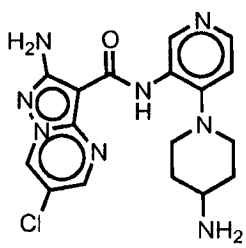
I-N-83



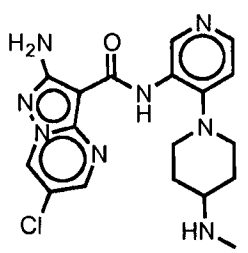
I-N-84



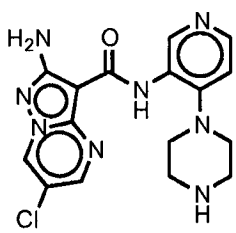
I-N-85



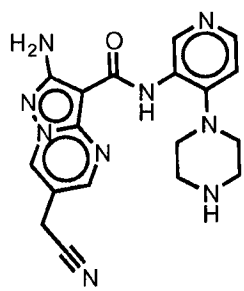
I-N-86



I-N-87



I-N-88



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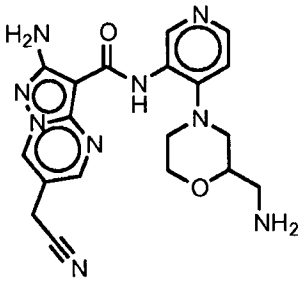

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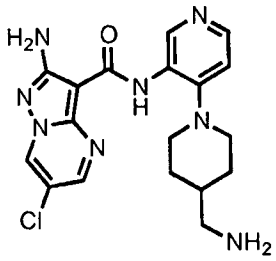
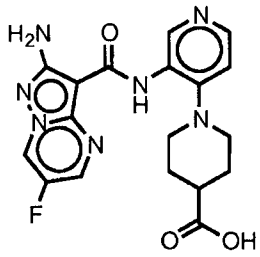


I-N-91



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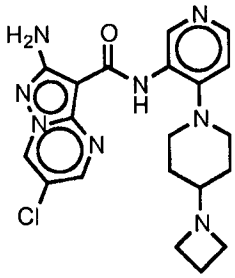

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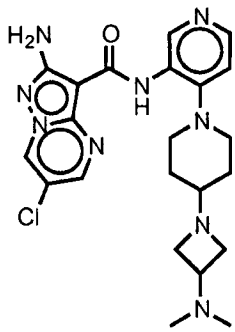

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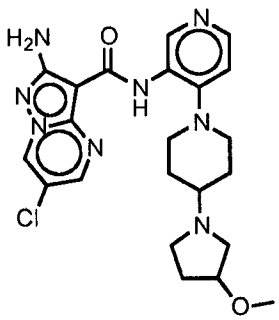

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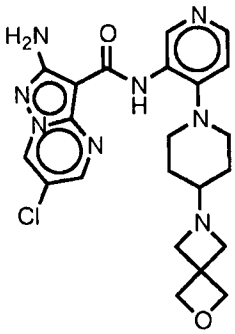

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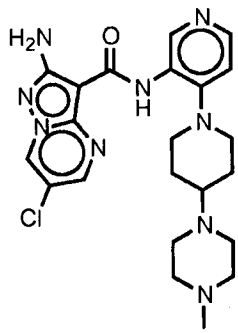

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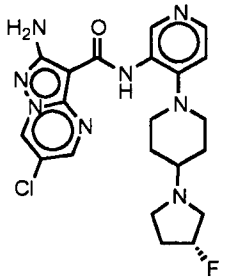

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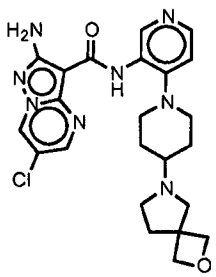

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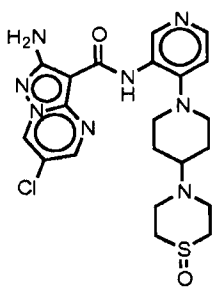

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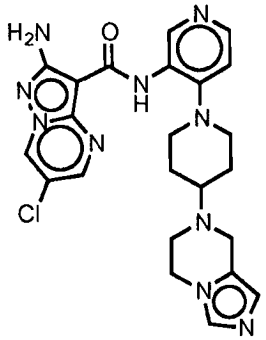

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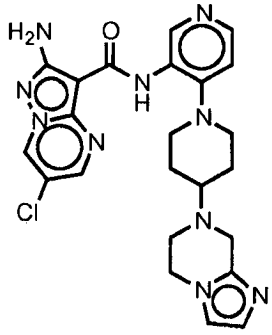

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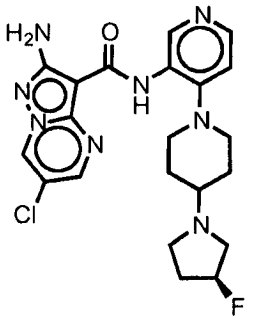

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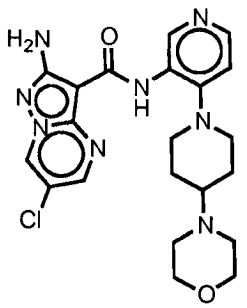

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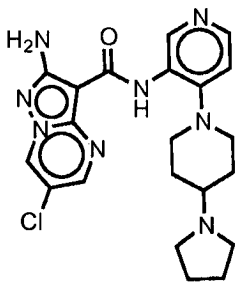

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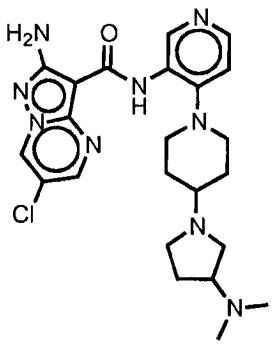

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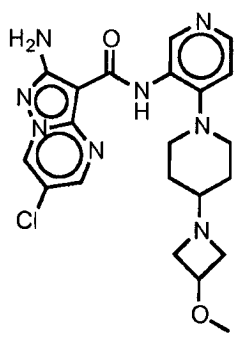

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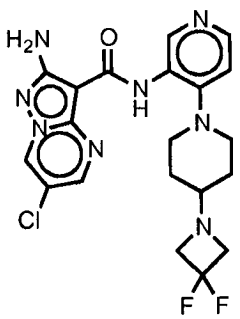

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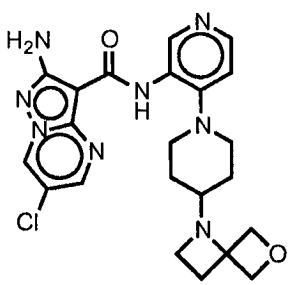

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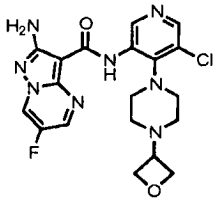

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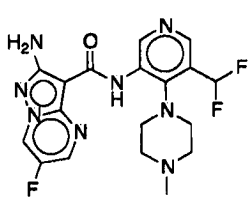

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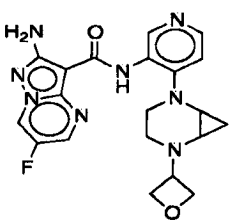

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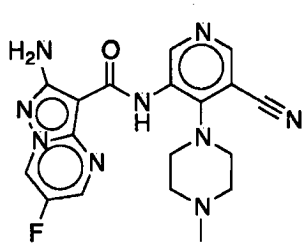

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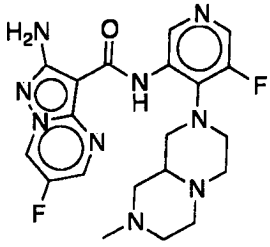

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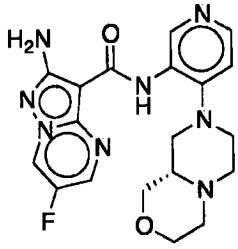

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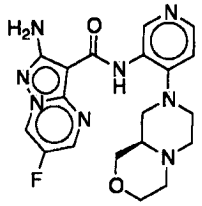

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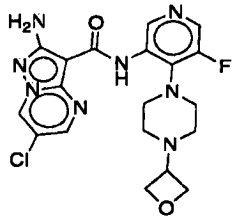

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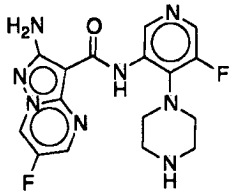

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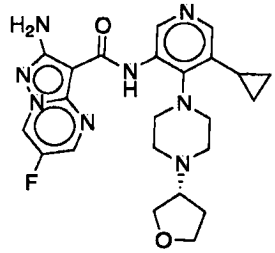

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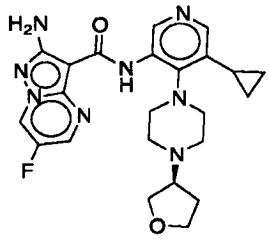

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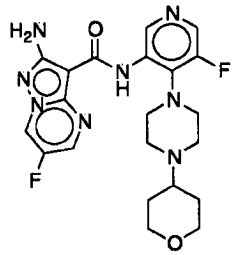

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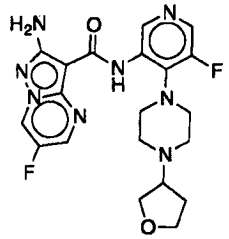

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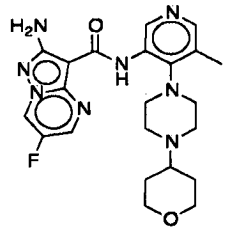

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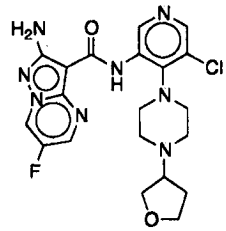

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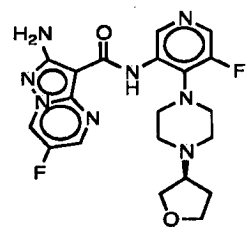

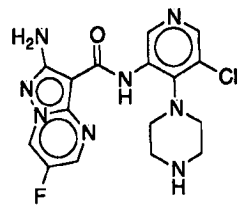

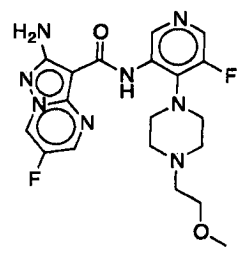

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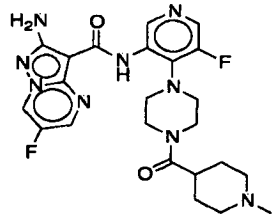

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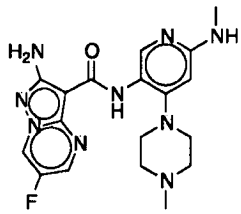

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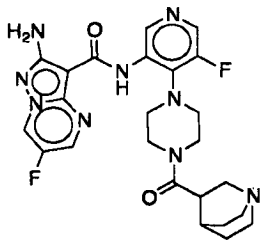

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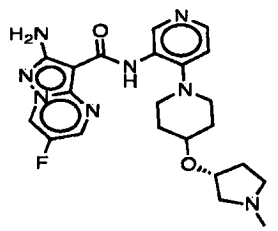

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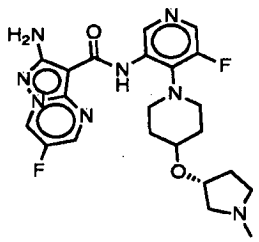

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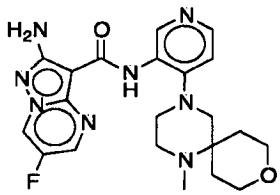

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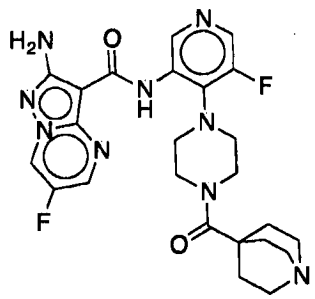

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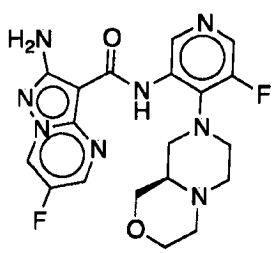

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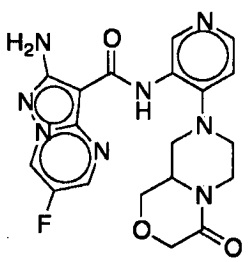

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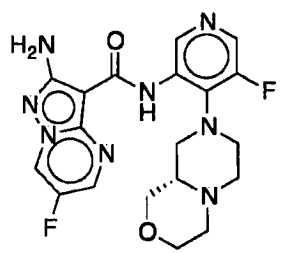

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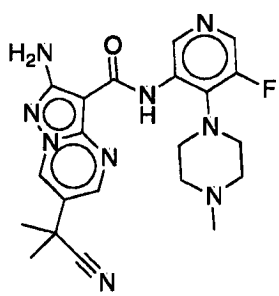
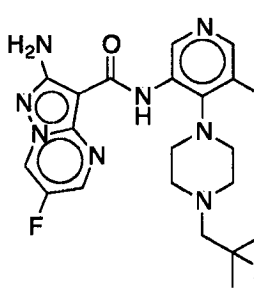


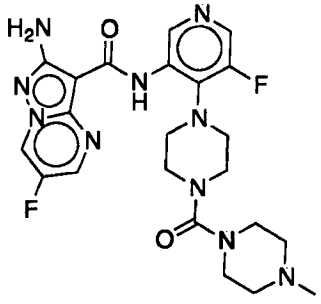
I-N-136



I-N-137

I-N-138

I-N-139



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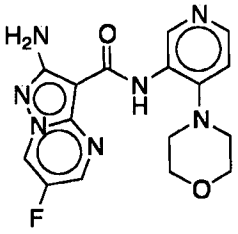
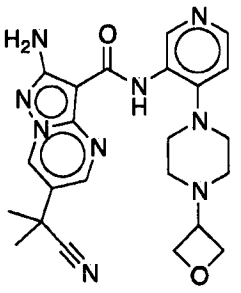
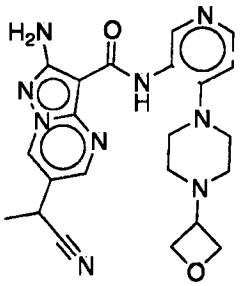


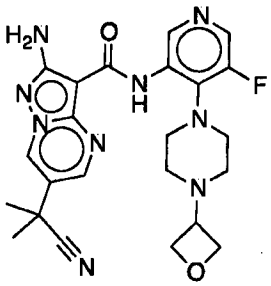
I-N-141



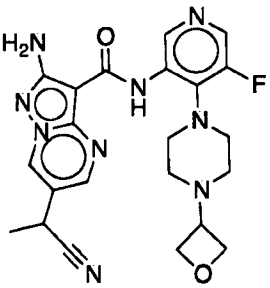
I-N-142



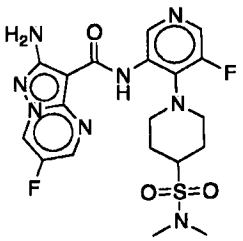
I-N-143



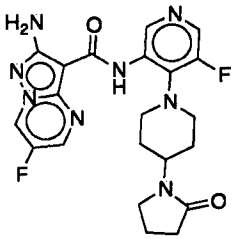
I-N-144



I-N-145



I-N-146



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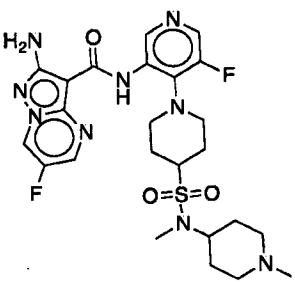

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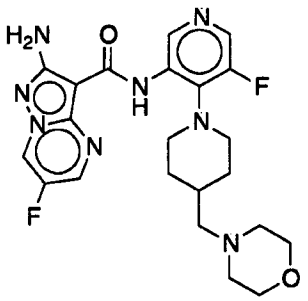

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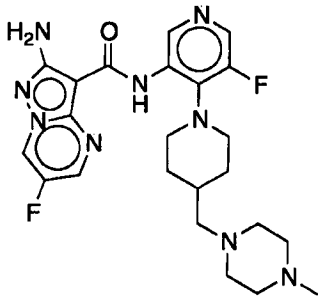

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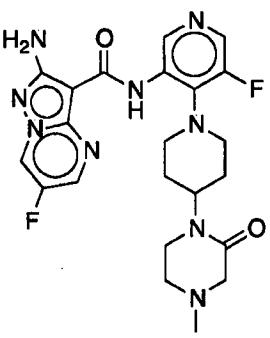

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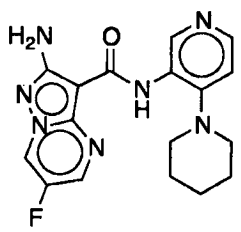

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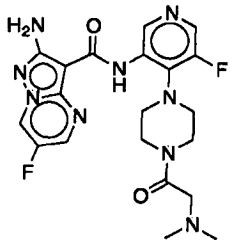

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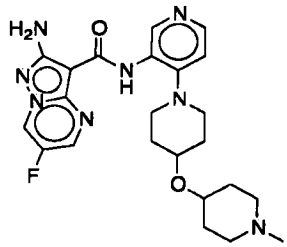

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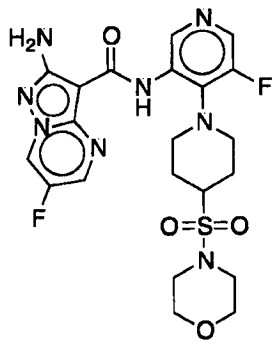

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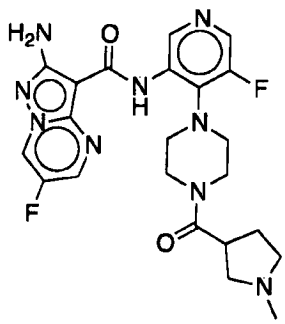

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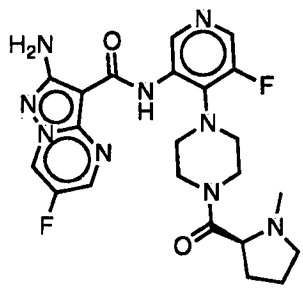

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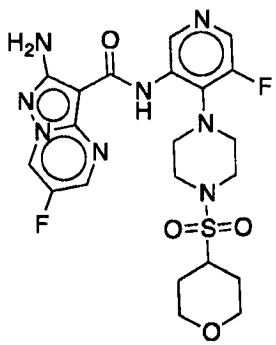

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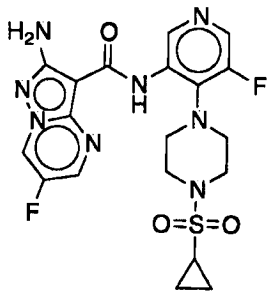

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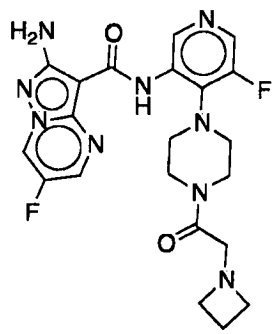

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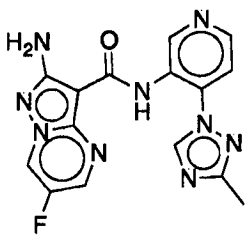

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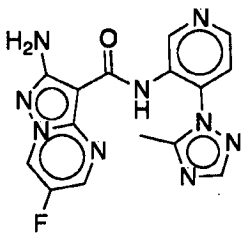

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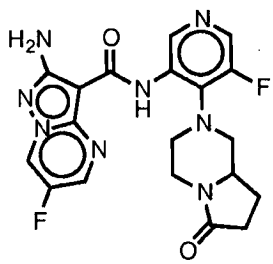

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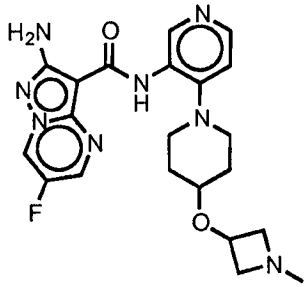

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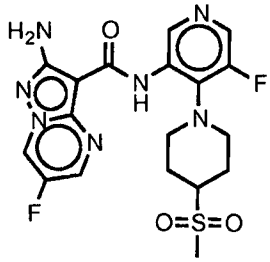

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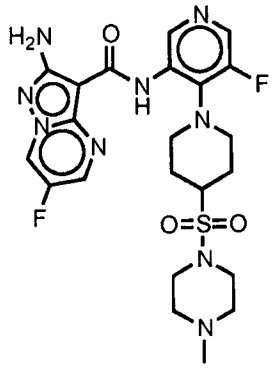

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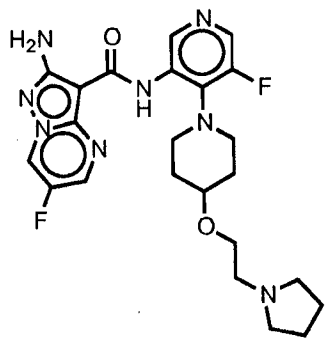

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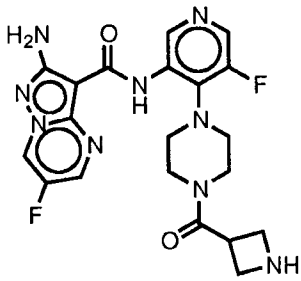

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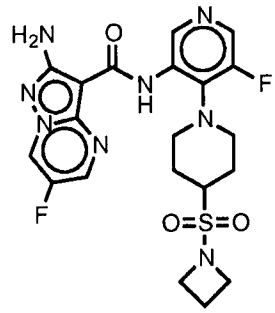

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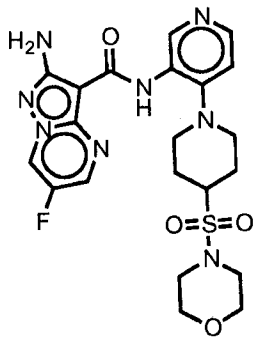

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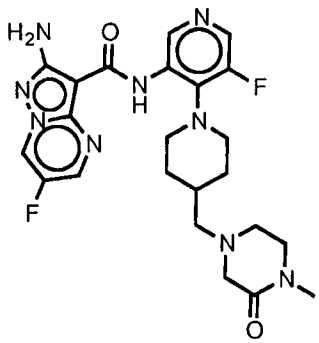

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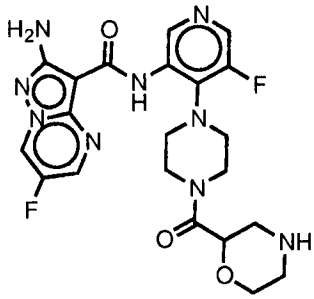

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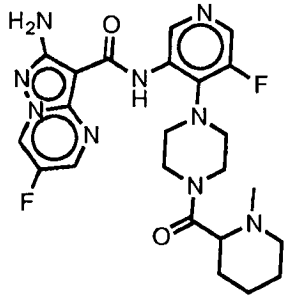

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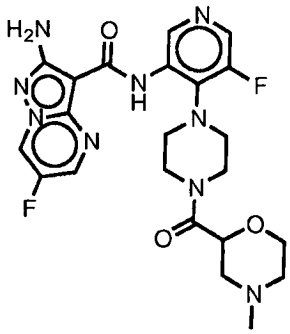

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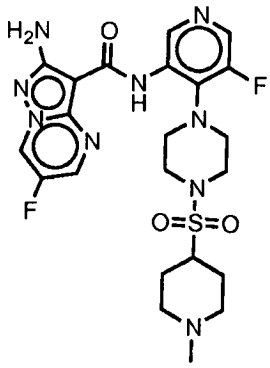

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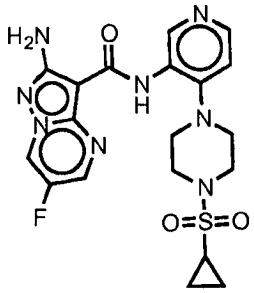

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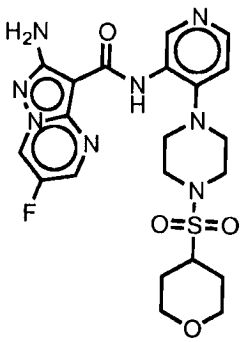

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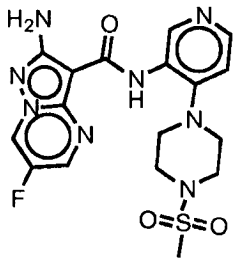

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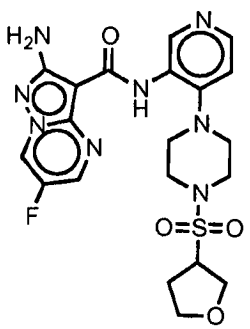

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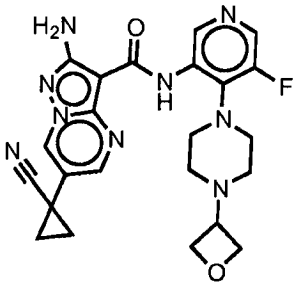

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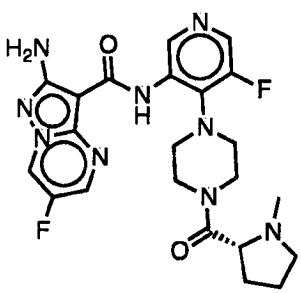

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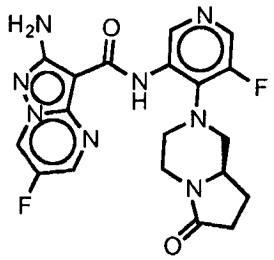

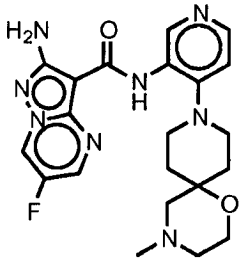

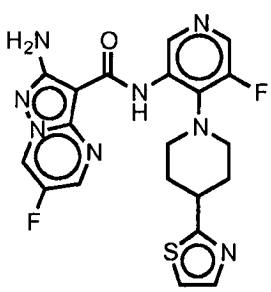

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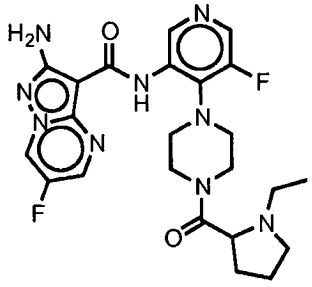

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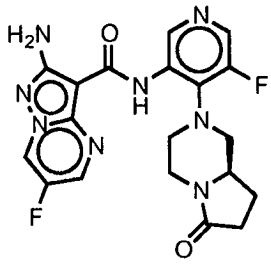

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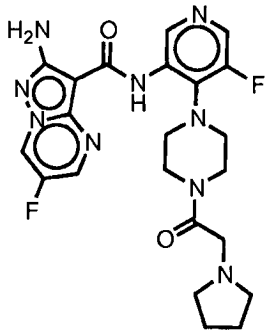

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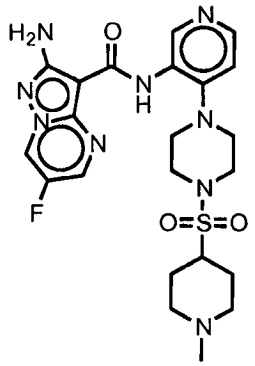

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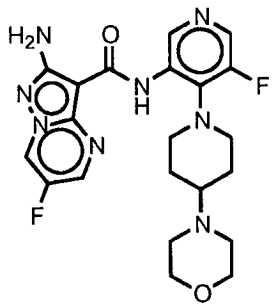

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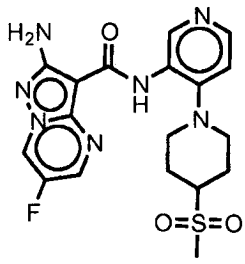

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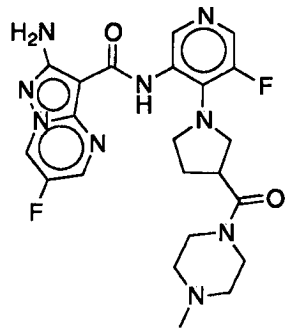

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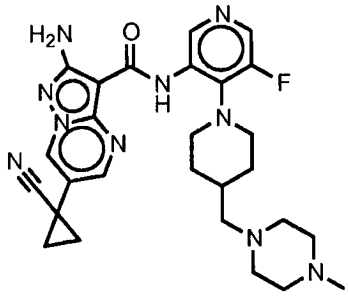

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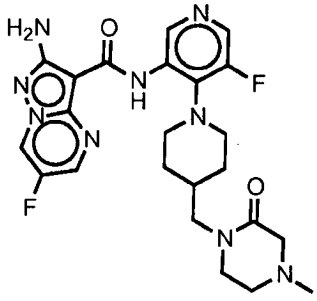
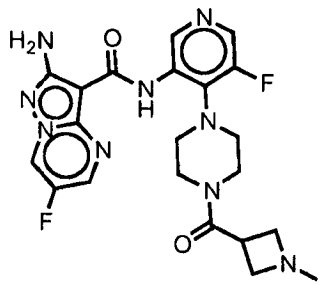


I-N-191

I-N-192

I-N-193



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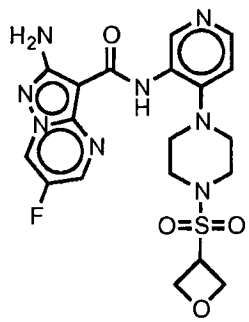

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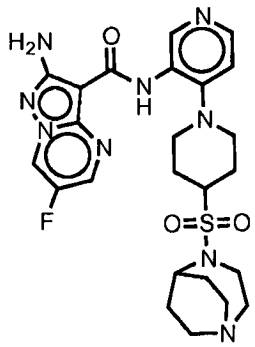
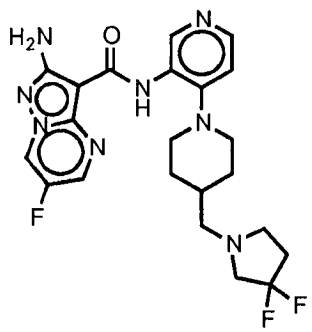


I-N-196



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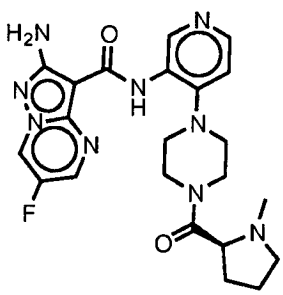

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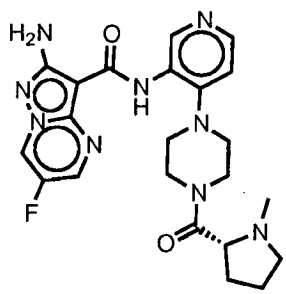

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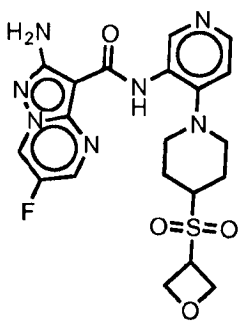

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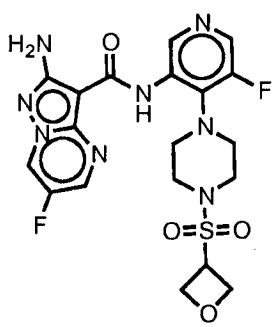

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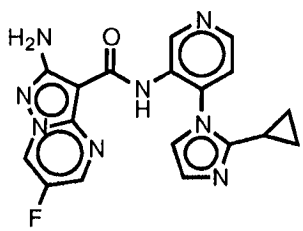

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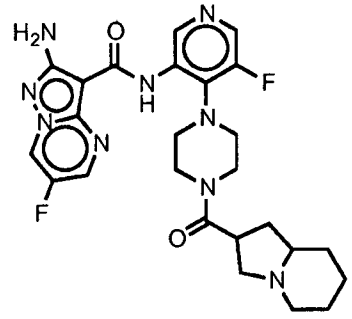

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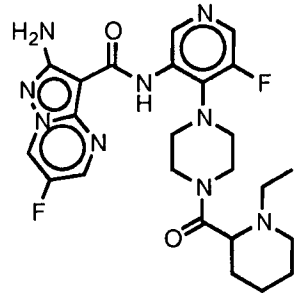

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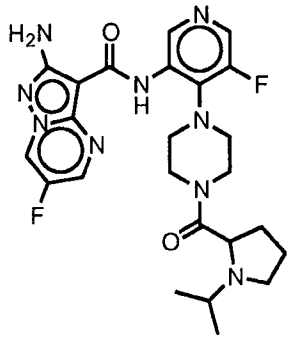

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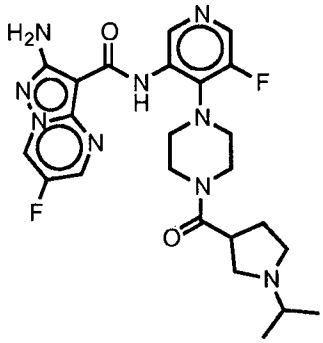

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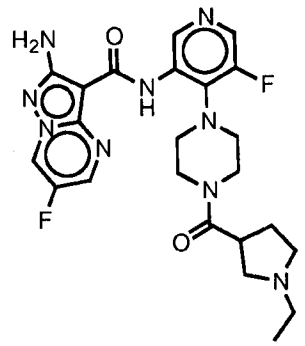

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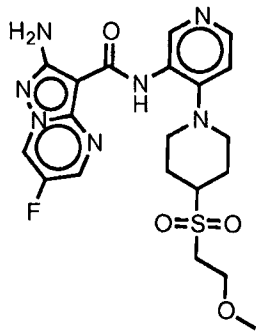

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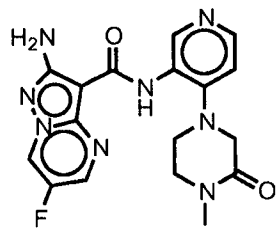

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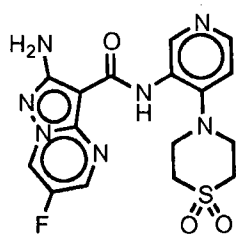

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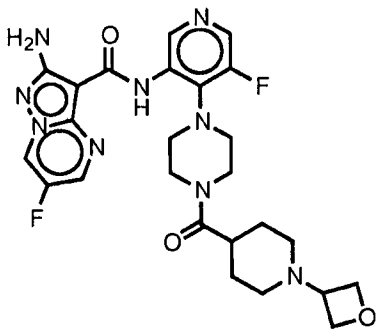

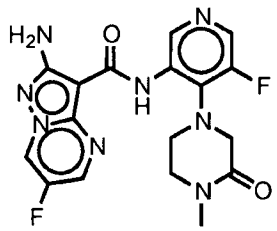

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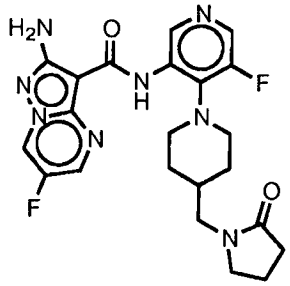

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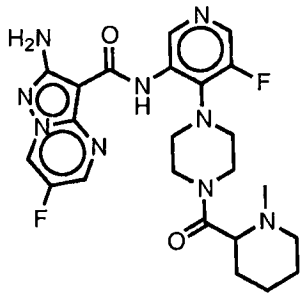

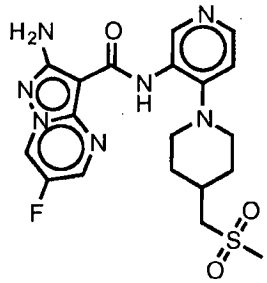

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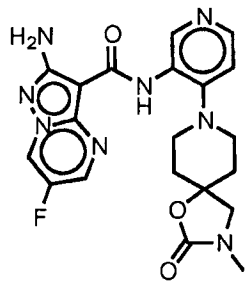

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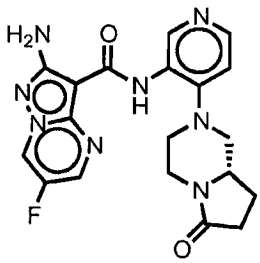

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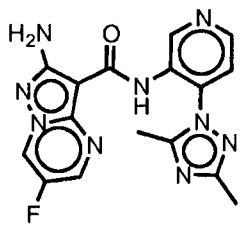

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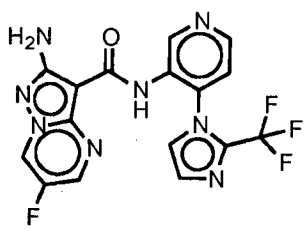

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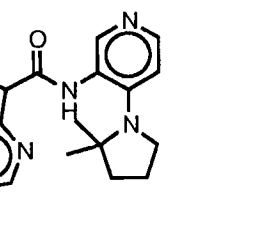
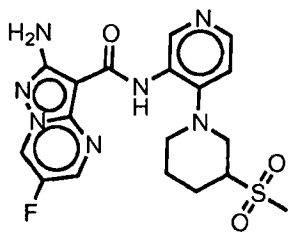


I-N-218

I-N-219

I-N-220

I-N-221



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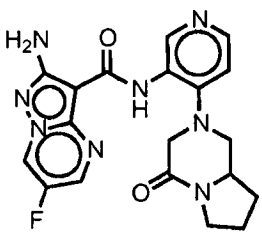

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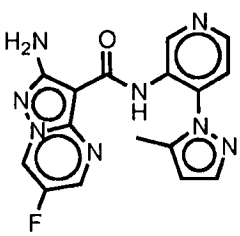

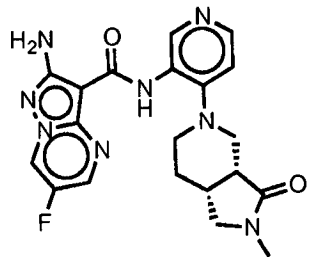

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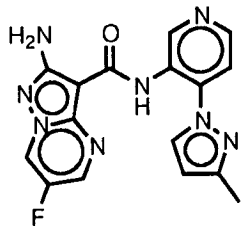

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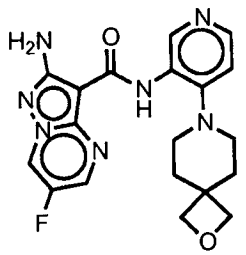

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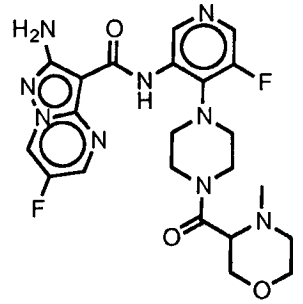

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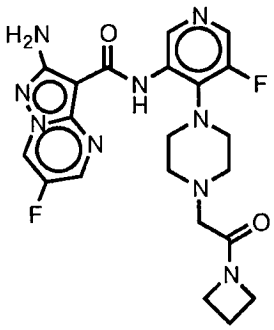

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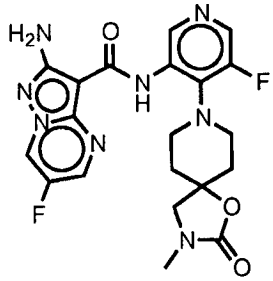

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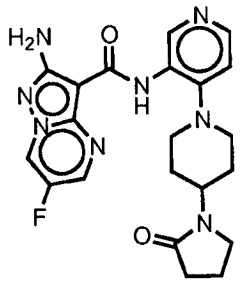

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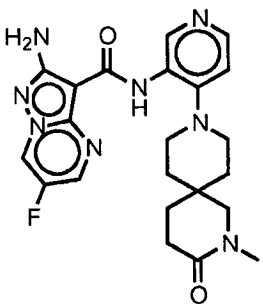

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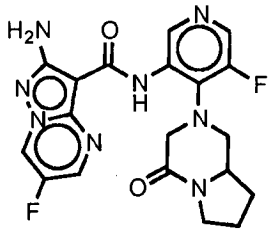

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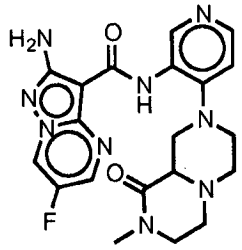

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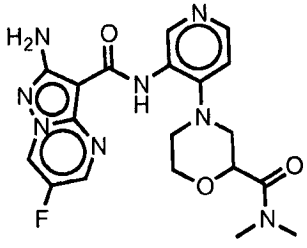

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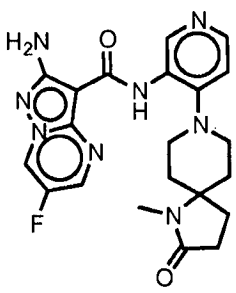

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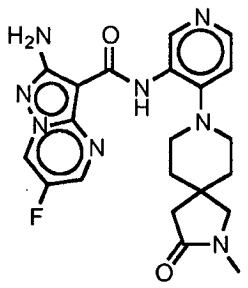

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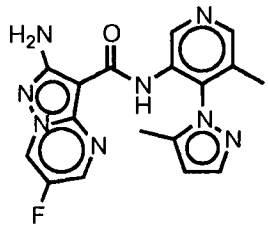

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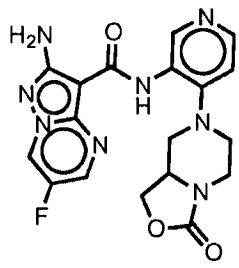

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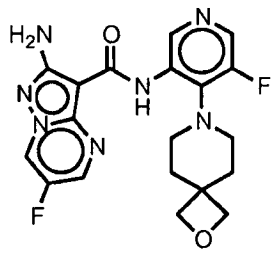

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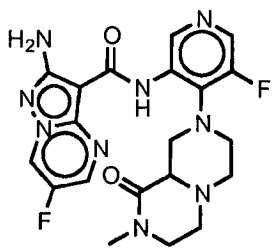

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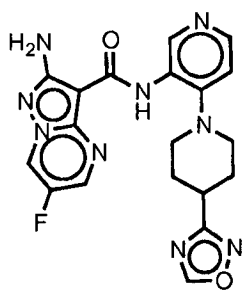

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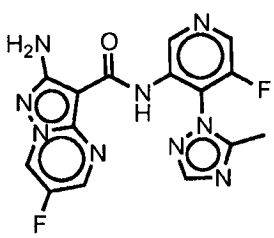

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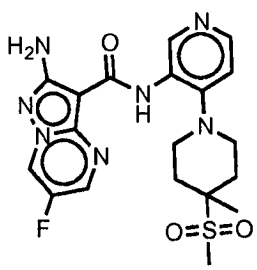

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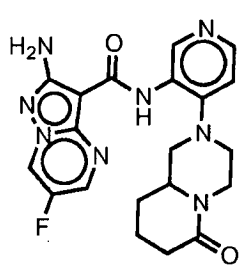
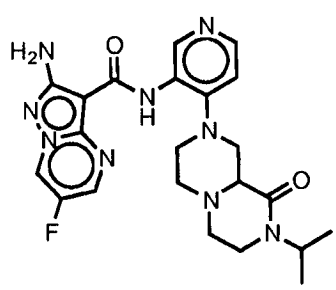


I-N-244



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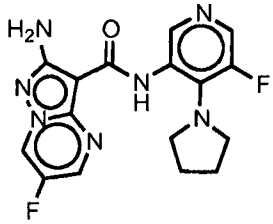
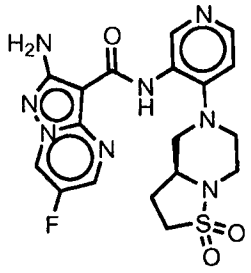


I-N-246



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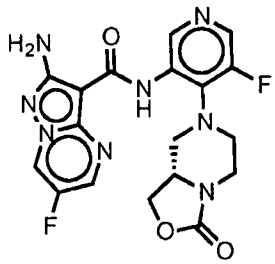

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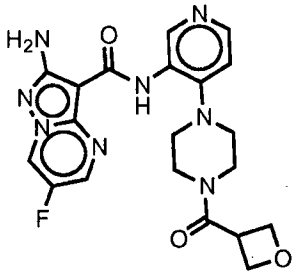
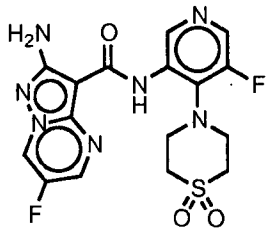
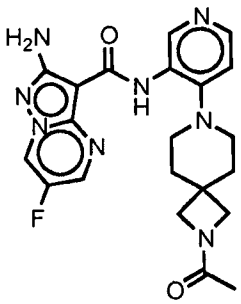


I-N-249



I-N-250



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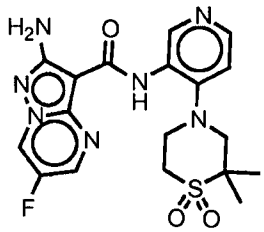

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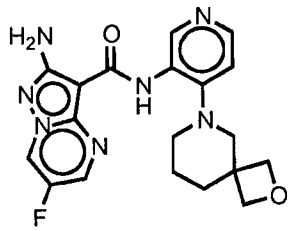

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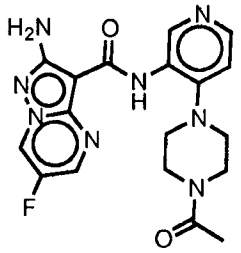

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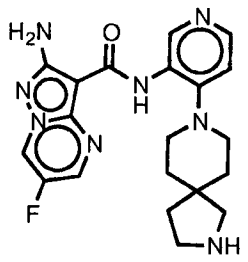

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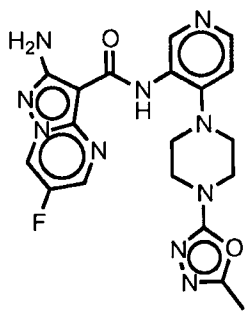

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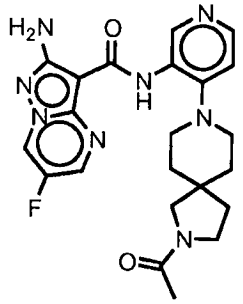

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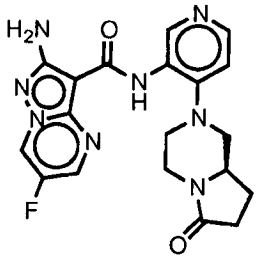

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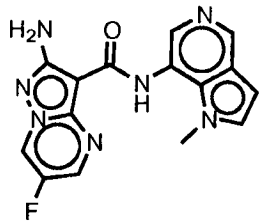

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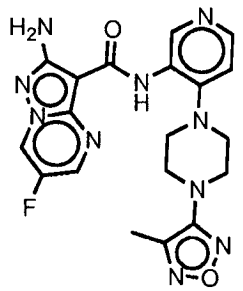

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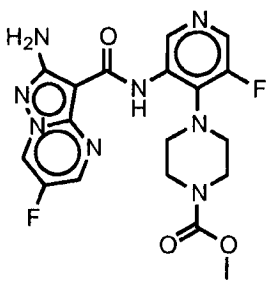

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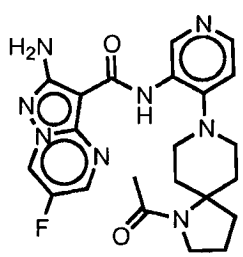

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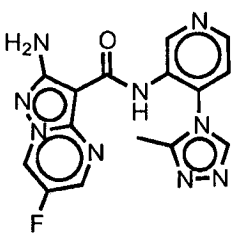

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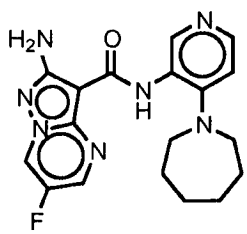

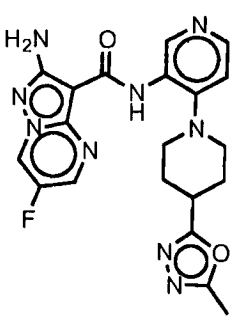

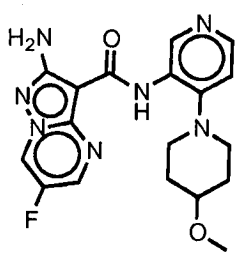

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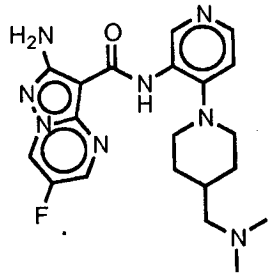

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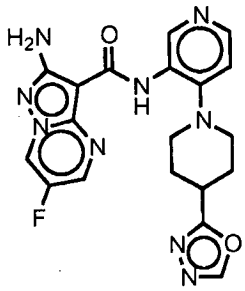

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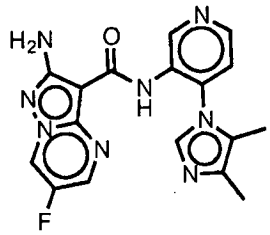

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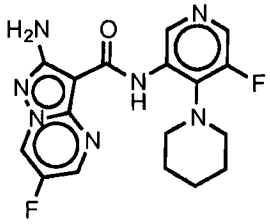

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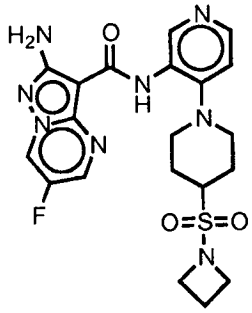

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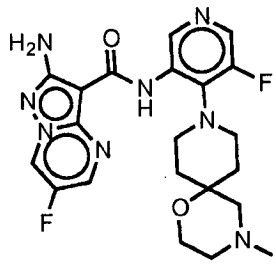

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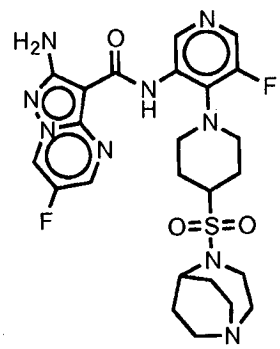

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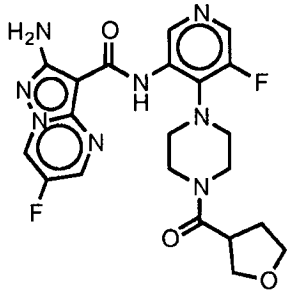

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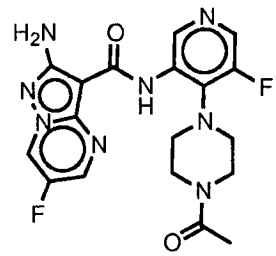

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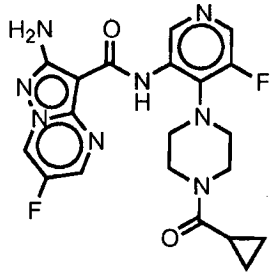

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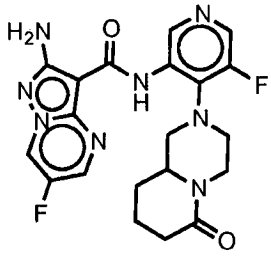

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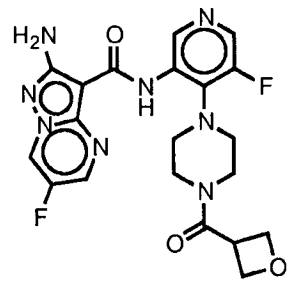

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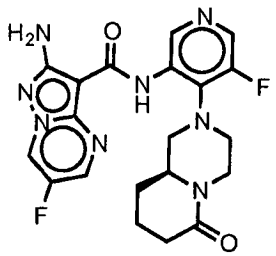

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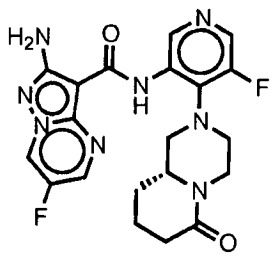

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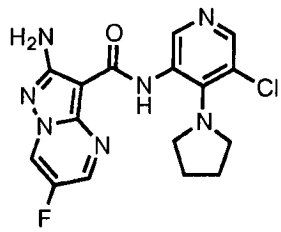

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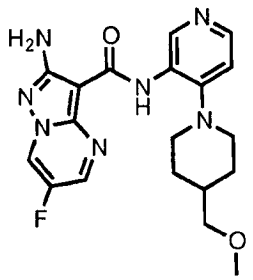

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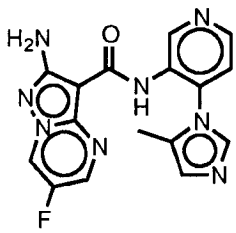

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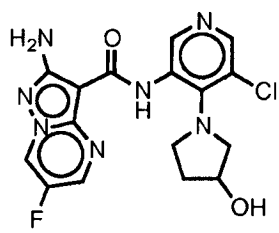

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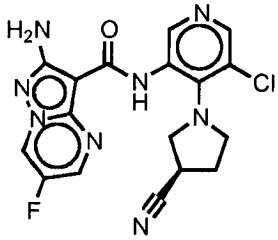

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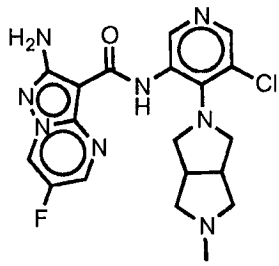

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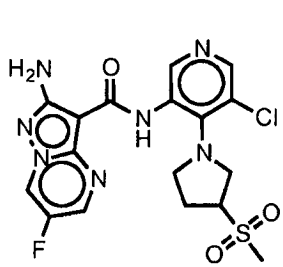
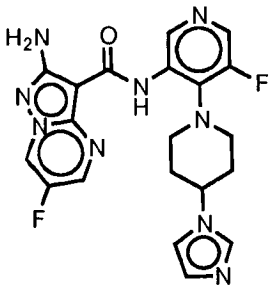


I-N-285

I-N-286

I-N-287

I-N-288



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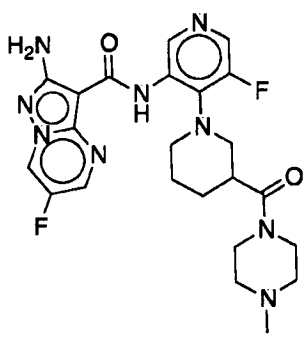

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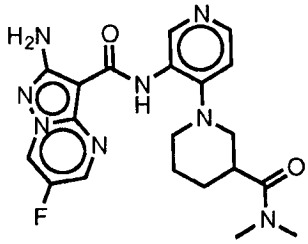
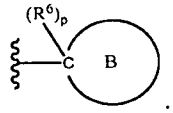


112. The compound of claim 34, wherein R^4 is:



113. The compound of claim 112, wherein p is 1.

114. The compound of claim 113, wherein Ring B is a 3-7 membered cycloaliphatic or heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

115. The compound of claim 114, wherein Ring B is independently selected from selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, 1,2,3,6-tetrahydropyridine, and azetidinyl.

116. The compound of claim 115, wherein Ring B is piperidinyl.

117. The compound of any one of claims 112-116, wherein J^Q is -C(O)- or C_{1-4}alkyl.

118. The compound of any one of claims 112-116, wherein, J^Q is Q^2.

119. The compound of claim 118, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidinyl, pyrrolidinyl, piperazinyl, piperidinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.

120. The compound of claim 119, wherein Q^2 is oxetanyl.

121. The compound of claim 112, wherein p is 0.

122. The compound of claim 121, wherein Ring B is independently selected from phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydropyridinyl, pyridizinyl, or pyrazolyl.

123. The compound of claim 122, wherein Ring B is independently selected from phenyl or pyridinyl.

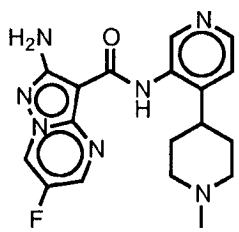
124. The compound of claim 34, wherein R^4 is $-CH_2-R^7$.

125. The compound of claim 124, wherein R^7 is H.

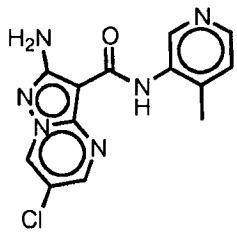
126. The compound of any one of claims 22-29, wherein R^3 and R^4, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen.

127. The compound of claim 124, wherein the J^Z is independently selected from $\rightarrow O$ or C_{1-4}alkyl.

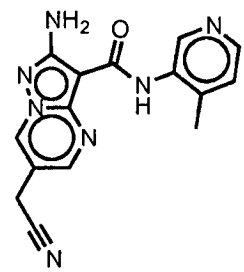
128. The compound of any one of claims 112-127, independently selected from:



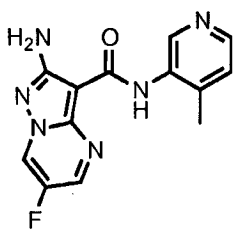
I-C-1



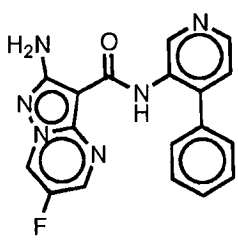
I-C-2



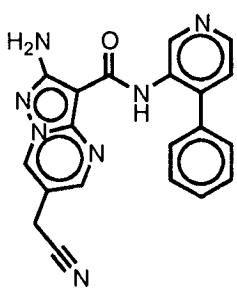
I-C-3



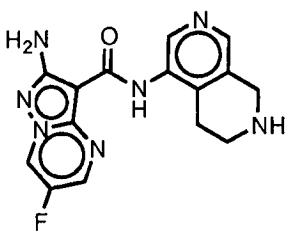
I-C-4



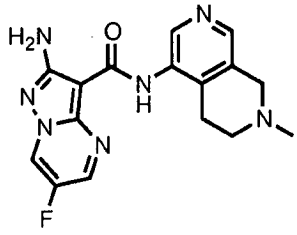
I-C-5



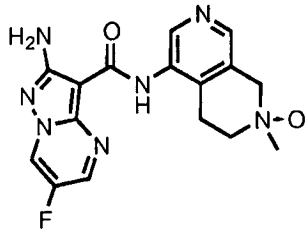
I-C-6



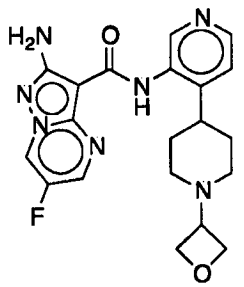
I-C-7



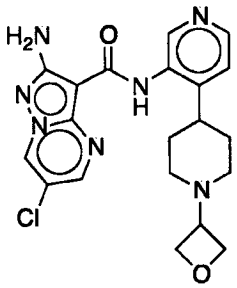
I-C-8



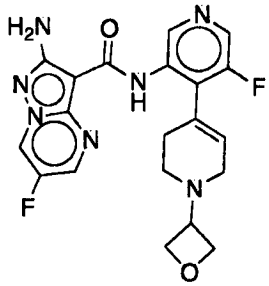
I-C-9 .



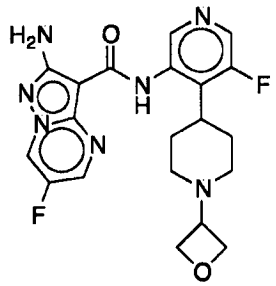
I-C-10



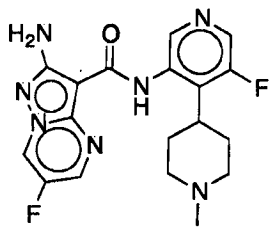
I-C-11



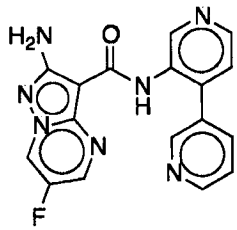
I-C-12



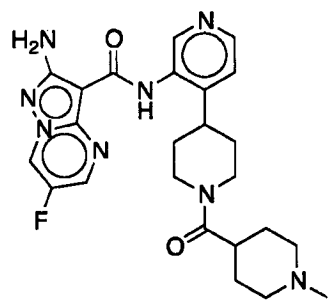
I-C-13



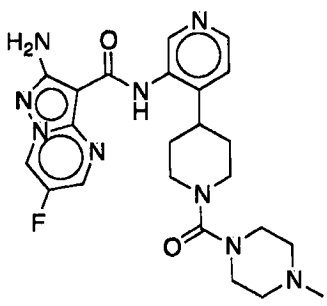
I-C-14



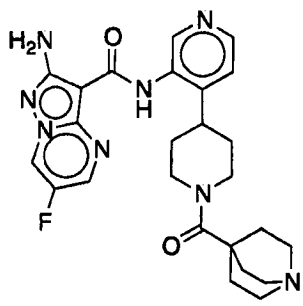
I-C-15



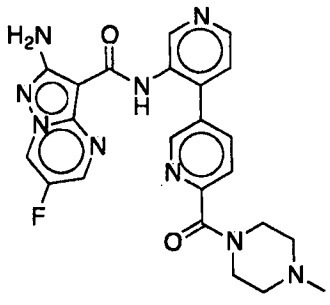
I-C-16



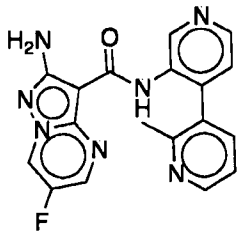
I-C-17



I-C-18



I-C-19



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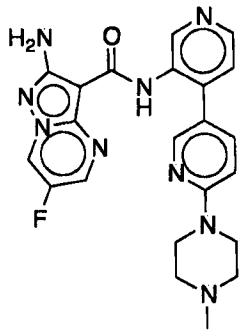

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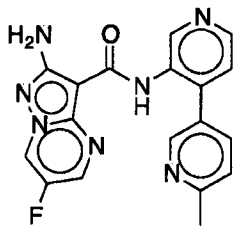

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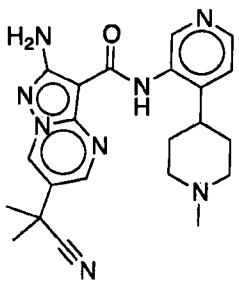

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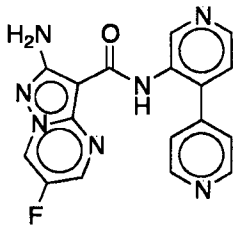
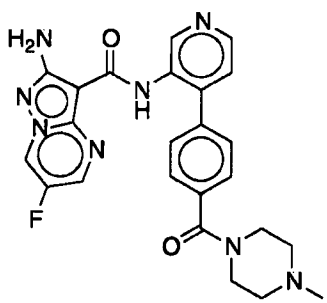
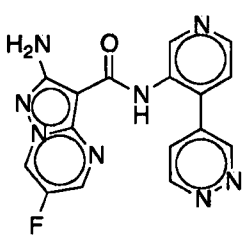


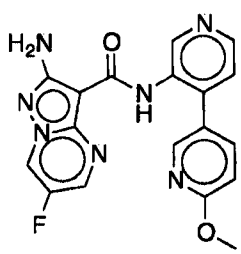
I-C-24



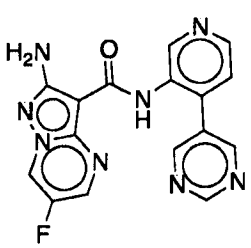
I-C-25



I-C-26



I-C-27



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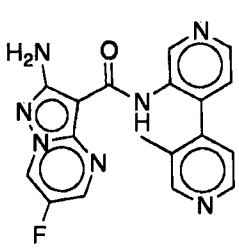
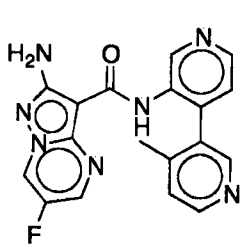


I-C-29



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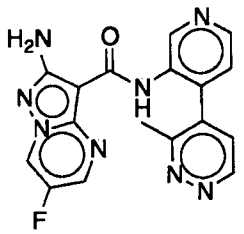
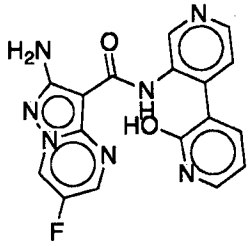
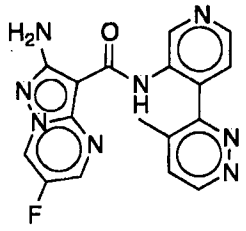


I-C-31



I-C-32



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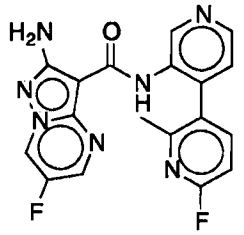

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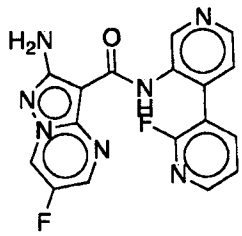
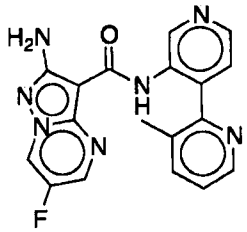
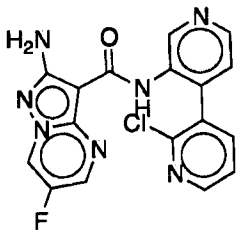


I-C-35



I-C-36



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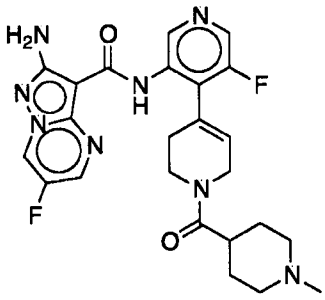
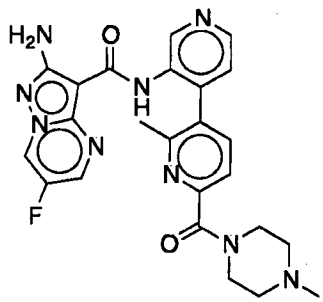
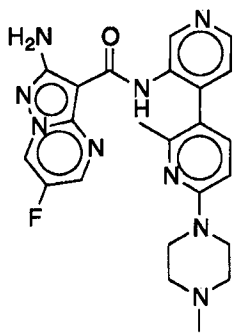


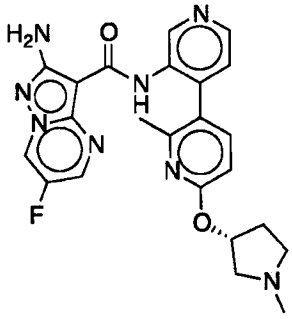
I-C-38



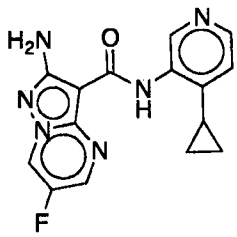
I-C-39



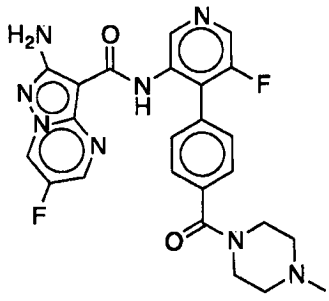
I-C-40



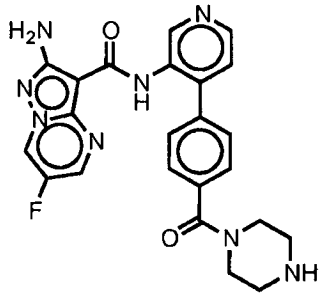
I-C-41



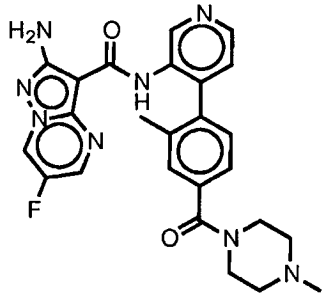
I-C-42



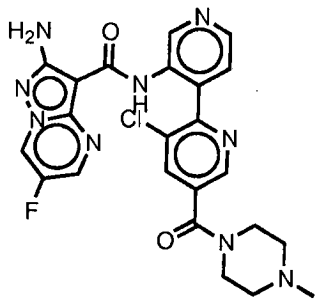
I-C-43



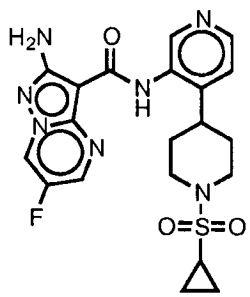
I-C-44



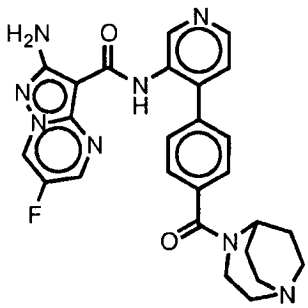
I-C-45



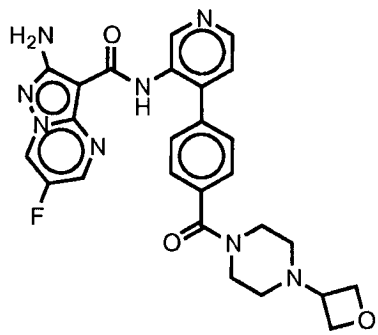
I-C-46



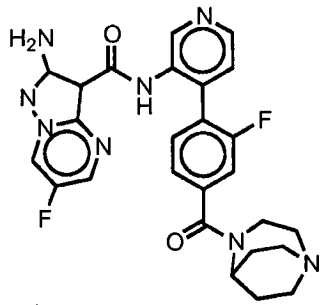
I-C-47



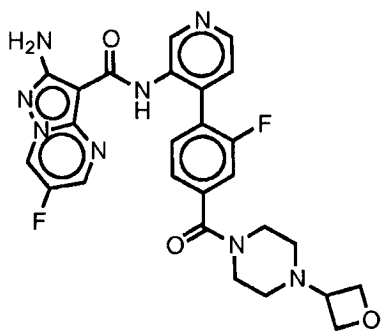
I-C-48



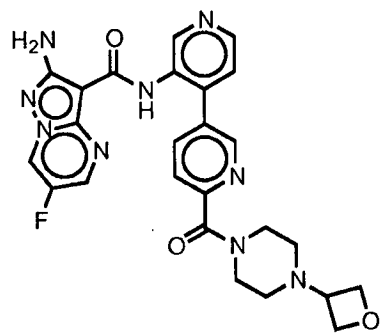
I-C-49



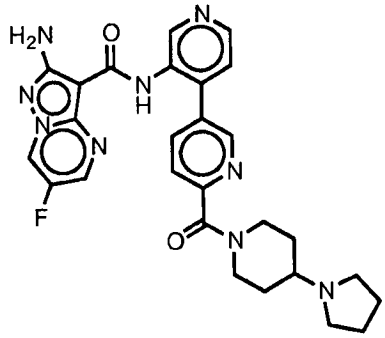
I-C-50



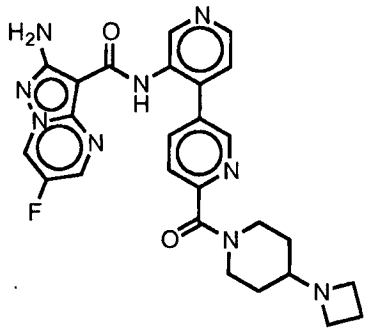
I-C-51



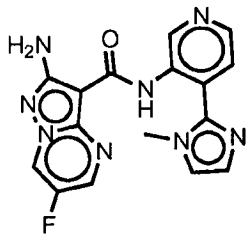
I-C-52



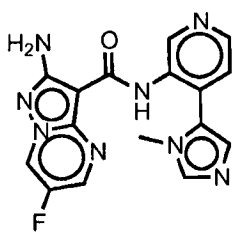
I-C-53



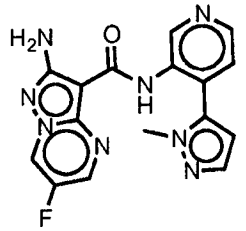
I-C-54



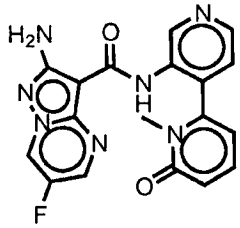
I-C-55



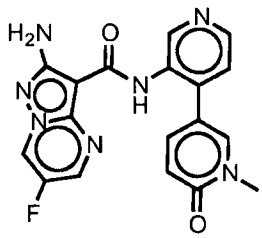
I-C-56



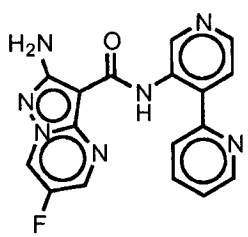
I-C-57



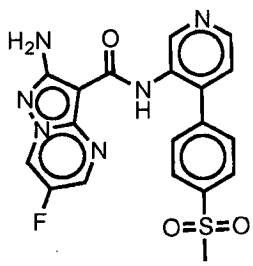
I-C-58



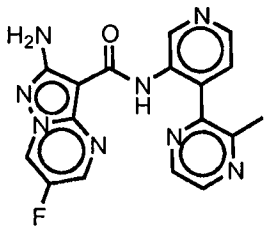
I-C-59



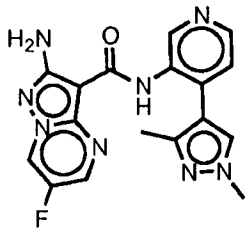
I-C-60



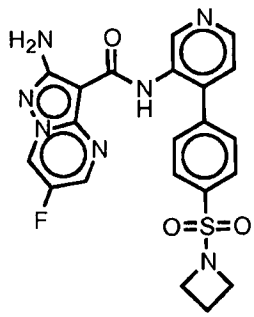
I-C-61



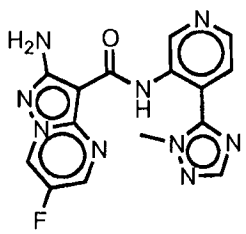
I-C-62



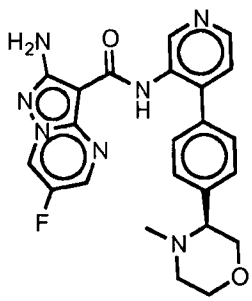
I-C-63



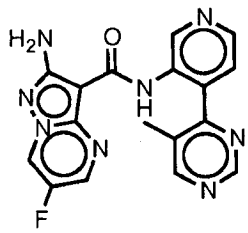
I-C-64



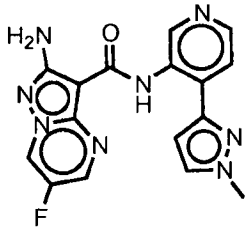
I-C-65



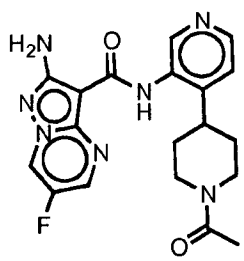
I-C-66



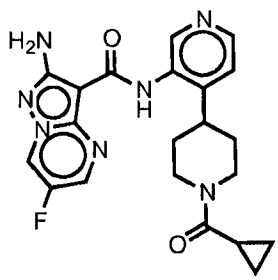
I-C-67



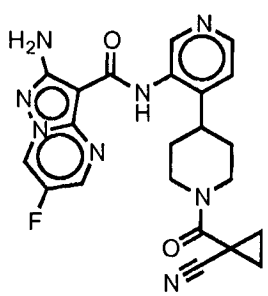
I-C-68



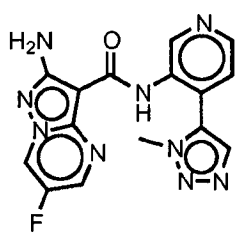
I-C-69



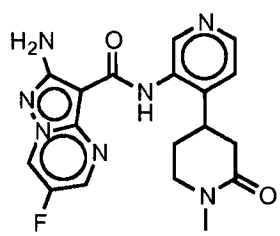
I-C-70



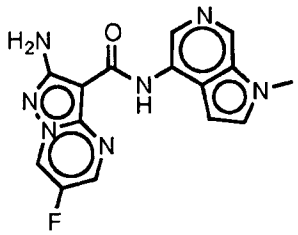
I-C-71



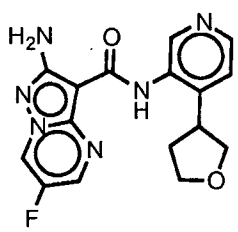
I-C-72



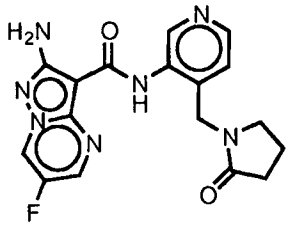
I-C-73



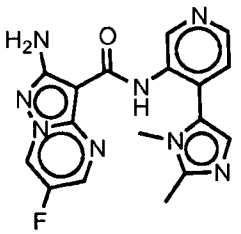
I-C-74



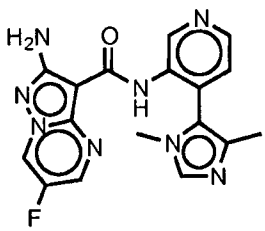
I-C-75



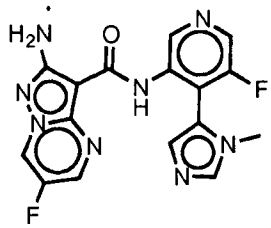
I-C-76



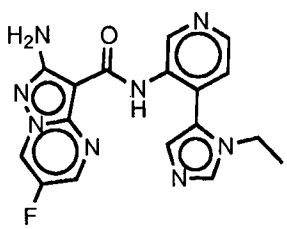
I-C-77



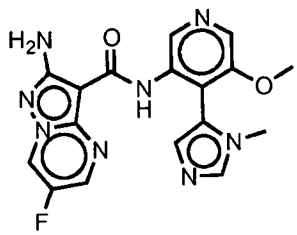
I-C-78



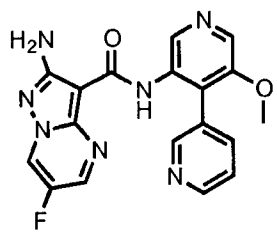
I-C-79



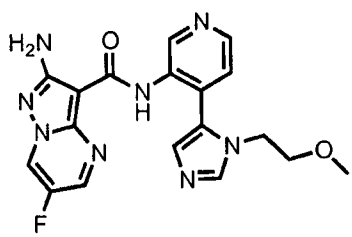
I-C-80



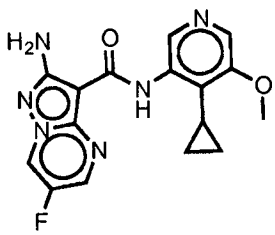
I-C-81



I-C-82

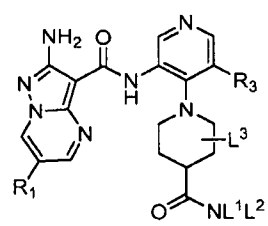


I-C-83



I-C-84

129. A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

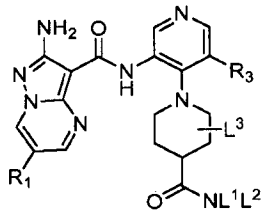
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

130. A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is

optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

L^3 is H; C_{1-3}aliphatic; or CN;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; -CN; $-N(R°)_2$; $\rightarrow$O; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

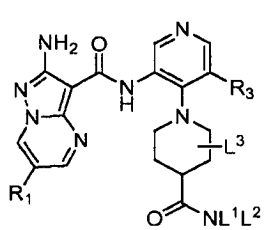
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

131. A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or –$S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or –$S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or –$S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; -CN; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or –$S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

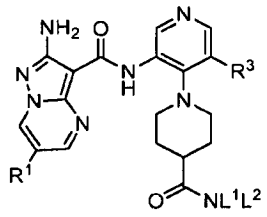
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

132. A compound of formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; or a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from halo; $-N(R°)_2$; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a

C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

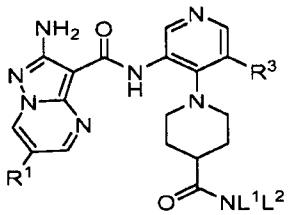
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4}alkyl.

133. A compound of formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from H or C_{1-2}alkyl; or

two occurrences of J^1 ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; or -CN;

L^1 is an optionally substituted C_{1-6}aliphatic;

L^2 is an optionally substituted C_{1-6}aliphatic; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 8-12 membered fully saturated or

partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently selected from C_{1-4}alkyl , $-N(R°)_2$, or a 3-5 membered carbocycyl; or

two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system; and

R° is H or C_{1-4}alkyl.

134. The compound of any one of claims 129-132, wherein R^1 is fluoro.

135. The compound of any one of claims 129-132, wherein R^1 is $-CH_2CN$.

136. The compound of any one of claims 129-132, wherein R^1 is chloro.

137. The compound of any one of claims 129-135, wherein R^3 is independently selected from H, chloro, fluoro, cyclopropyl, or C_{1-4}alkyl.

138. The compound of claim 137, wherein R^3 is independently selected from H, chloro, or fluoro.

139. The compound of claim 137, wherein R^3 is H.

140. The compound of claim 137, wherein R^3 is chloro.

141. The compound of claim 137, wherein R^3 is fluoro.

142. The compound of any one of claims 138-141, wherein L^1 and L^2 are H; -(C_{1-3}alkyl)O(C_{1-2}alkyl); -(C_{1-3}alkyl)N(C_{1-2}alkyl)$_2$; C_{1-4}alkyl; azetidinyl; piperidinyl; oxytanyl; or pyrrolidinyl.

143. The compound of any one of claims 134-141, wherein L^1 and L^2, together with the nitrogen to which they are attached, form Ring D.

144. The compound of claim 143, whererein Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

145. The compound of claim 144, wherein Ring D is independently selected from piperazinyl, piperidinyl, morpholinyl, tetrahydopyranyl, azetidinyl, pyrrolidinyl, or 1,4-diazepanyl.

146. The compound of claim 145, wherein Ring D is piperazinyl, piperidinyl, 1,4-diazepanyl, pyrrolidinyl or azetidinyl.

147. The compound of claim 146, wherein Ring D is piperazinyl or piperidinyl.

148. The compound of claim 144, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

149. The compound of claim 148, wherein Ring D is octahydropyrrolo[1,2-a]pyrazine or octahydropyrrolo[3,4-c]pyrrole.

150. The compound of any one of claims 144-149, wherein J^G is halo, C_{1-4}alkyl, -O(C_{1-3}alkyl), C_{3-6}cycloalkyl, a 3-6 membered heterocyclyl, -NH(C_{1-3}alkyl), -OH, or -N(C_{1-4}alkyl)$_2$.

151. The compound of claim 150, wherein J^G is methyl, -N(C_{1-4}alkyl)$_2$, ethyl, -O(C_{1-3}alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidinyl.

152. The compound of claim 151, wherein J^G is methyl. -O(C_{1-3}alkyl), oxetanyl, pyrrolidinyl, piperidinyl, or azetidinyl.

153. The compound of claim 152, wherein J^G is methyl.

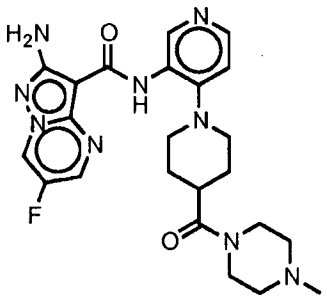
154. The compound of any one of claims 145-148, wherein two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system.

155. The compound of claim 154, wherein the bridged ring system is 1,4-diazabicyclo[3.2.2]nonane, 1,4-diazabicyclo[3.2.1]octane, or 2,5-diazabicyclo[2.2.1]heptane.

156. The compounds of any one of claims 144-147, wherein two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

157. The compound of claim 156, wherein the ring formed by the two occurrences of J^G on the same atom is selected from oxetanyl or cyclopropyl.

158. A compound of any one of claims 129-157 independently selected from:



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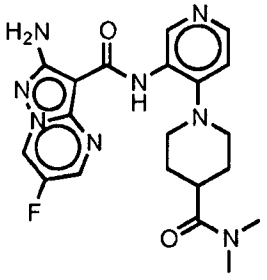

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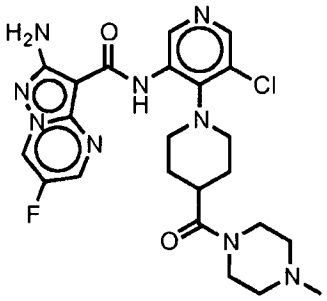

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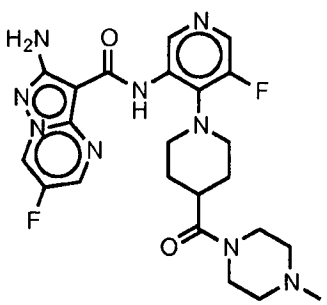

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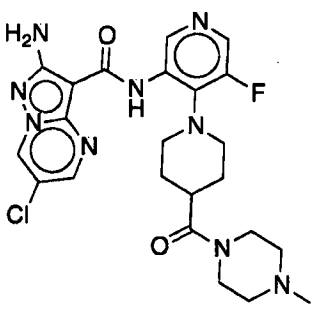

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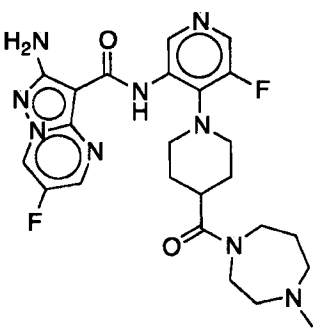

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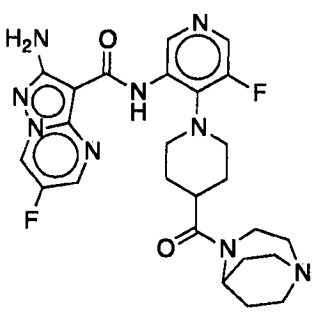

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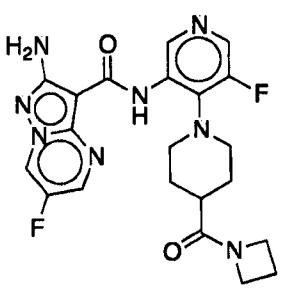

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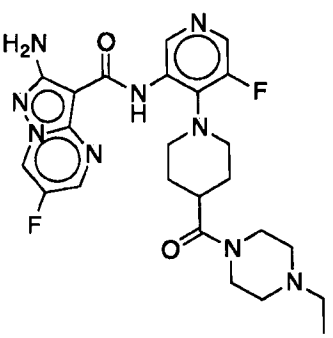

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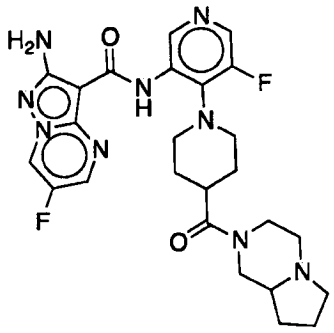

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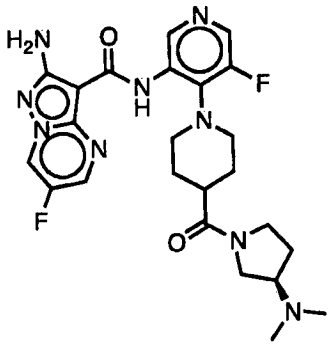

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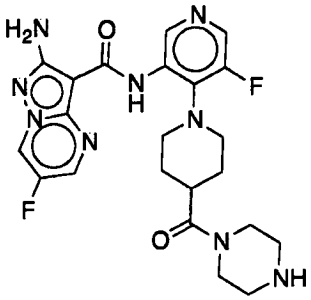

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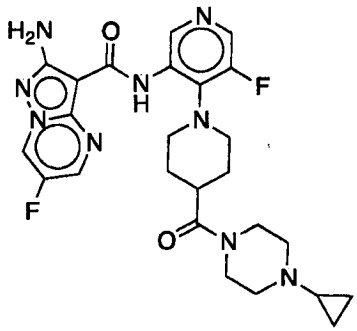

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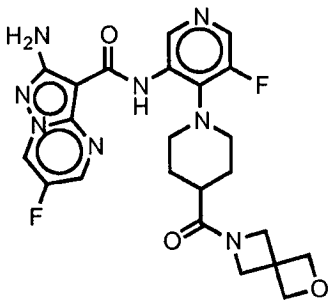

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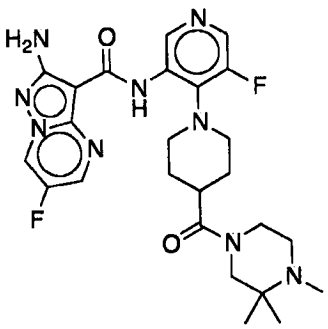

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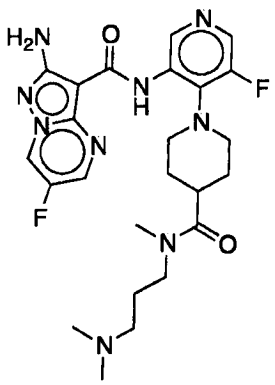

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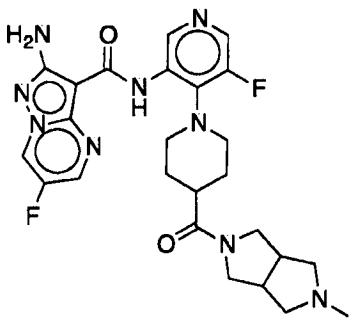

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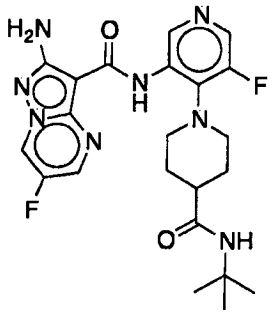

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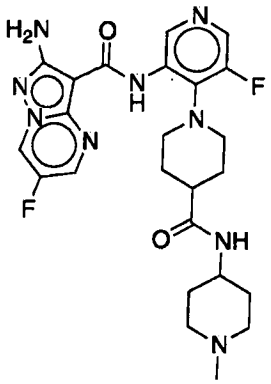

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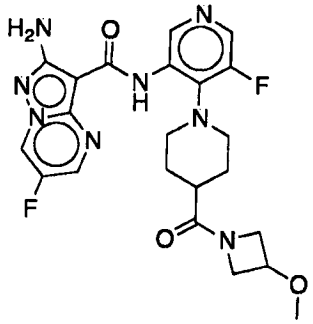

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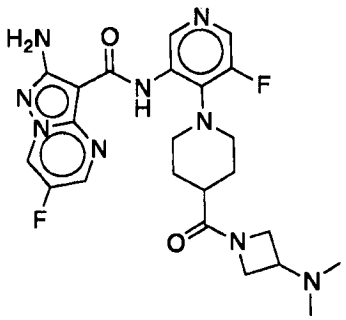

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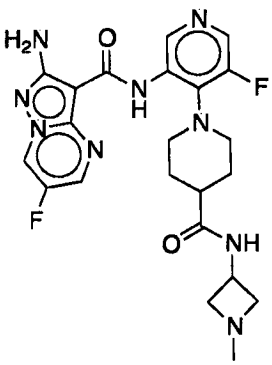

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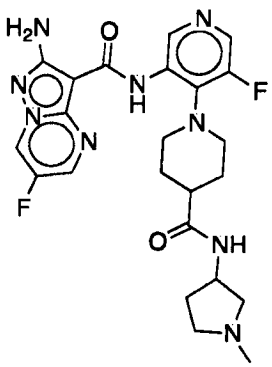

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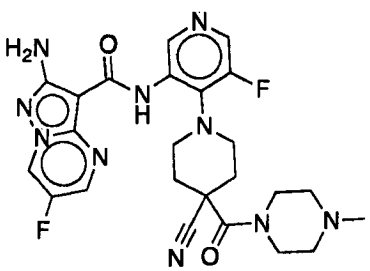

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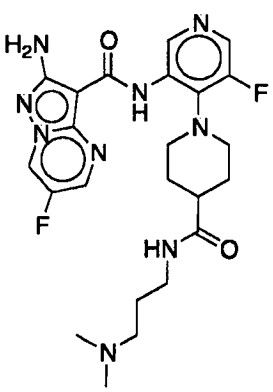

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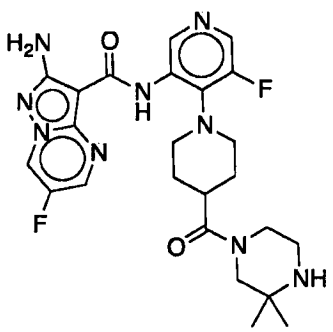

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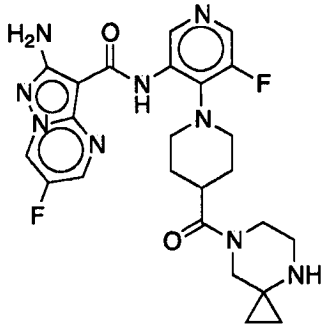

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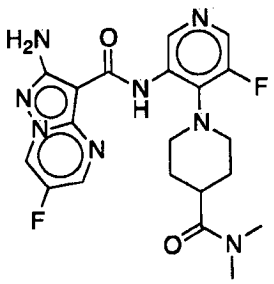

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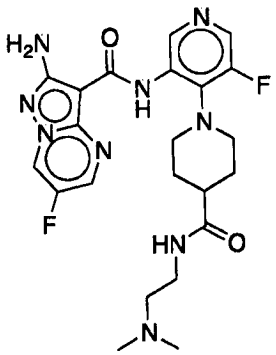

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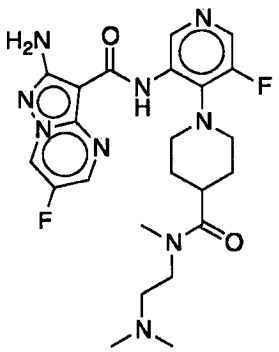

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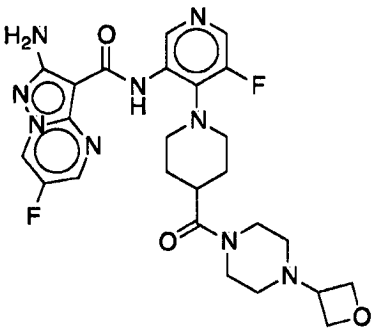

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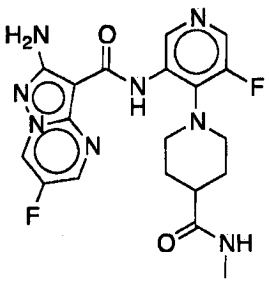

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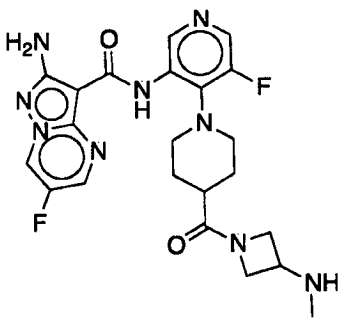

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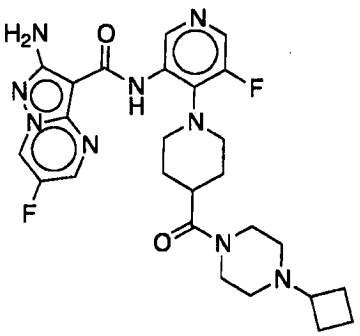

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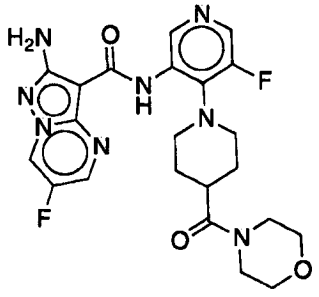

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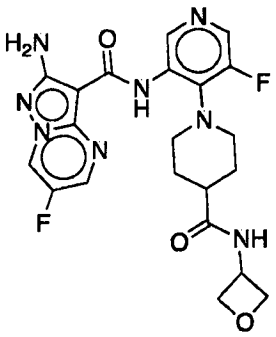

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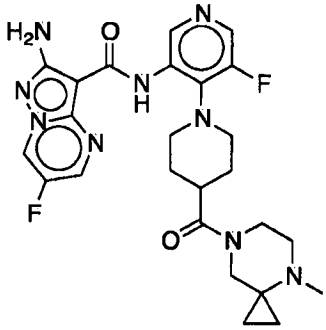

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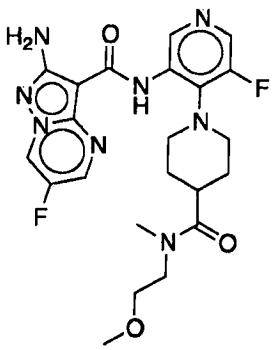

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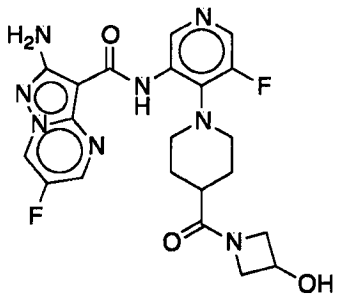

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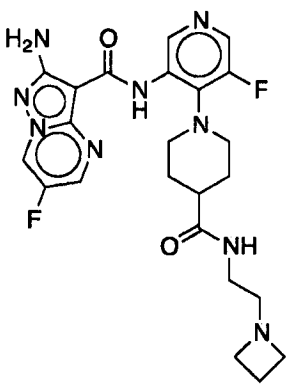

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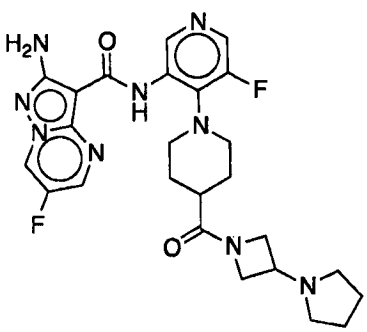

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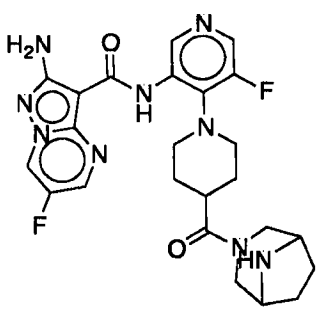

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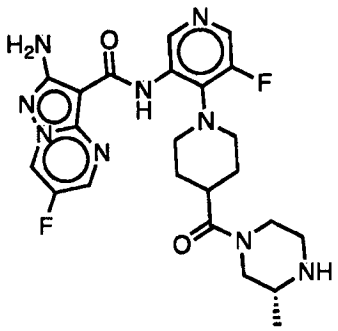

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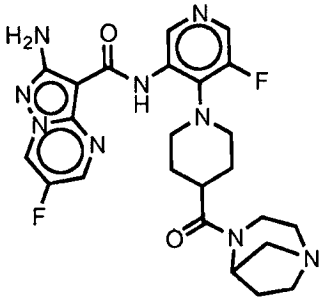

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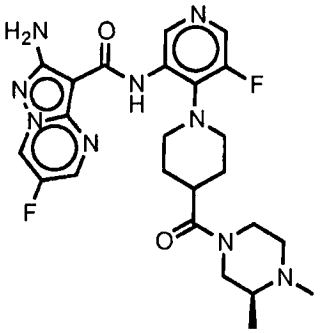

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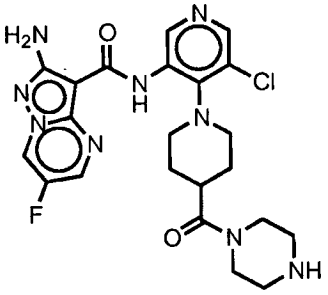

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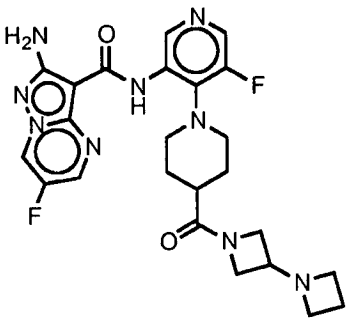

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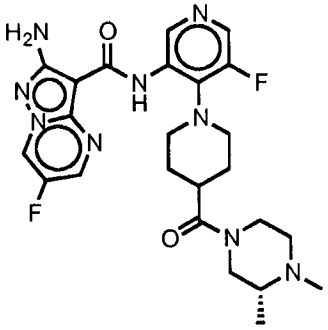

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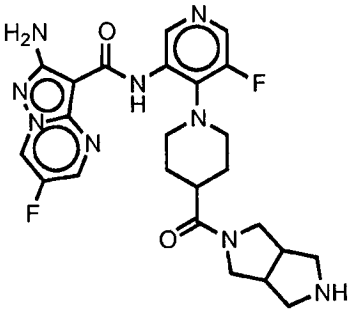

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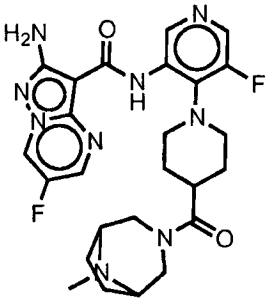

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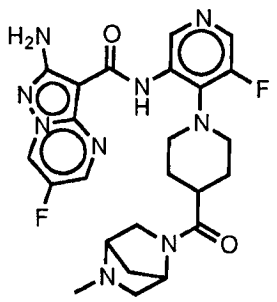

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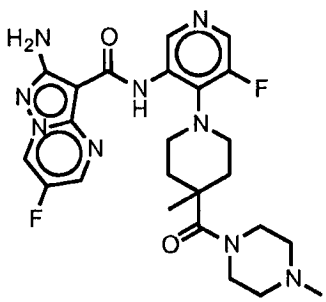

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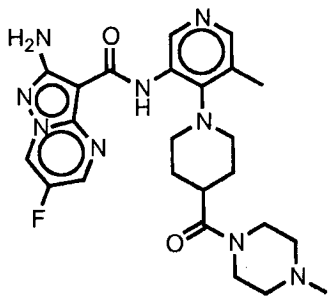

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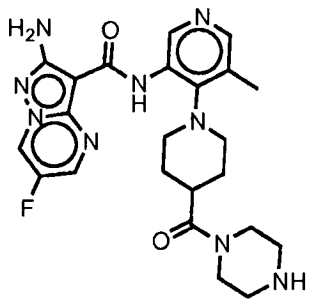

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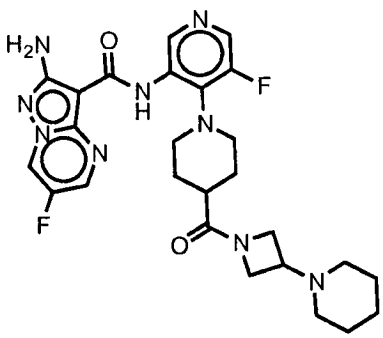

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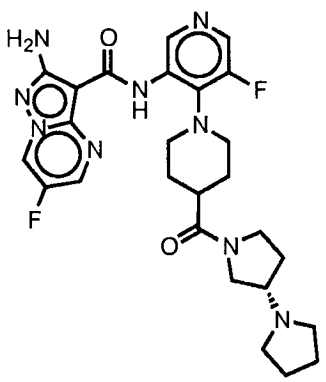

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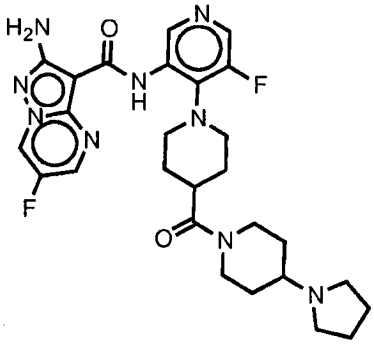

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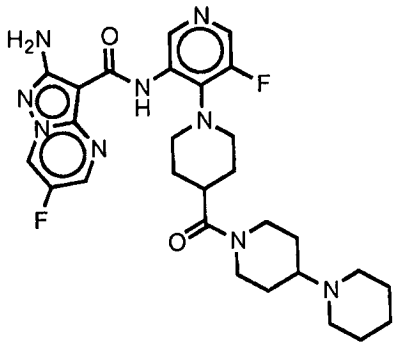

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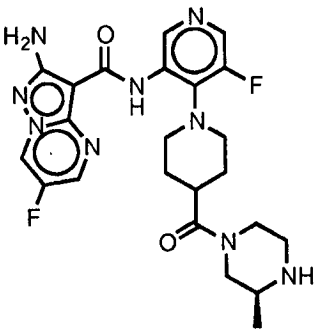

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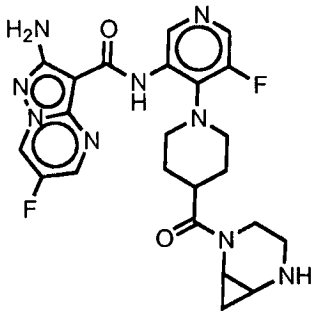

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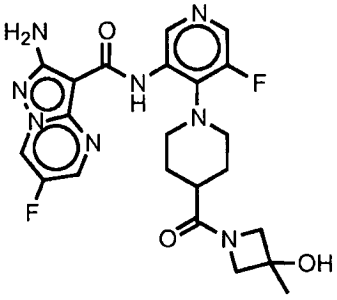

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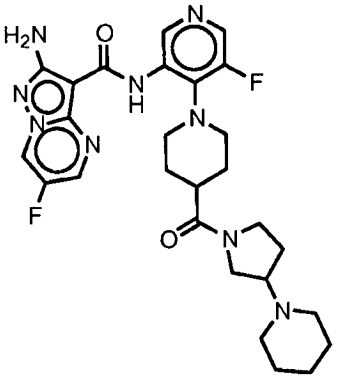

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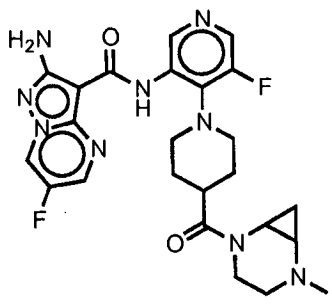

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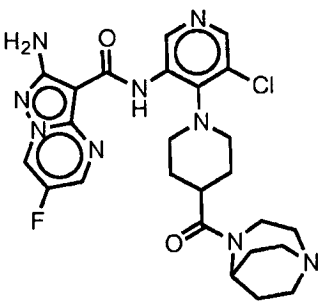

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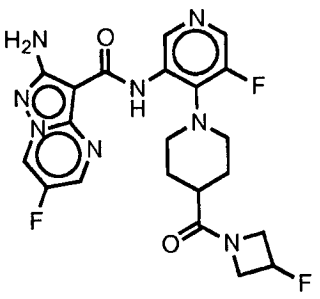

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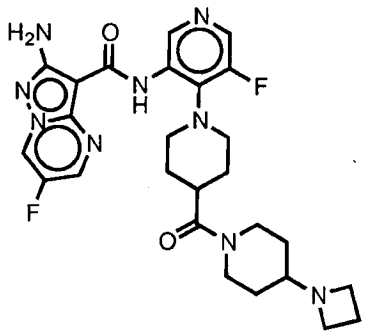

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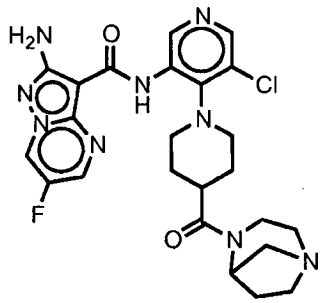

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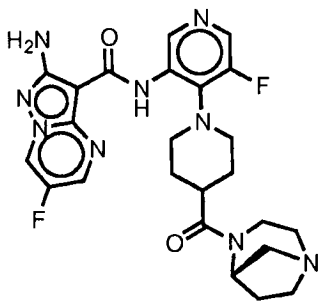

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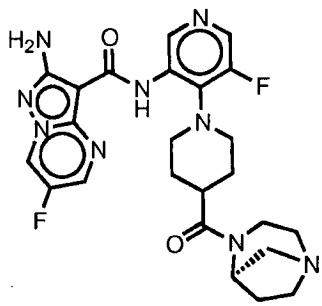

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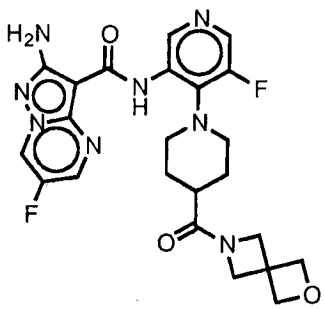

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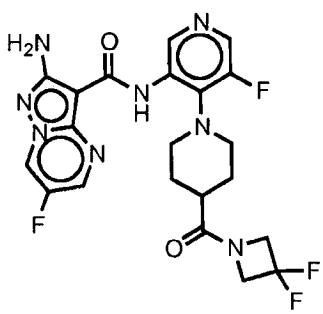

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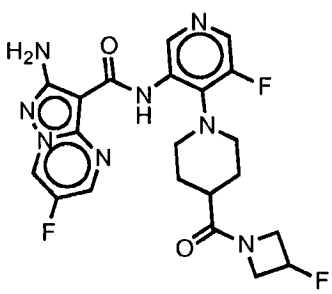

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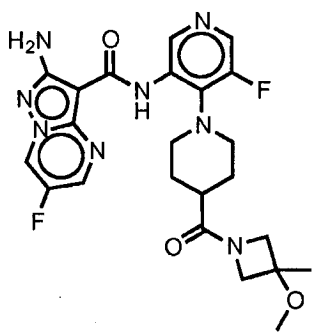

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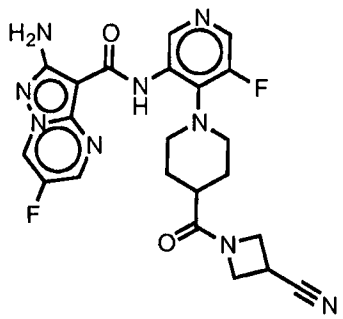

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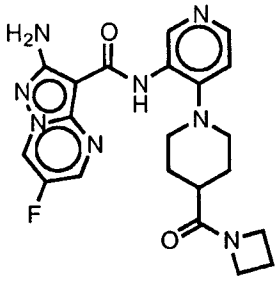

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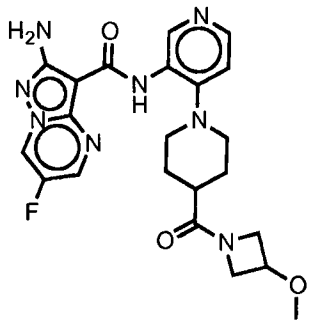

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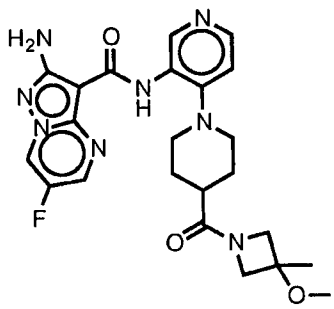

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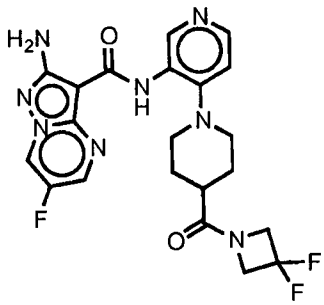

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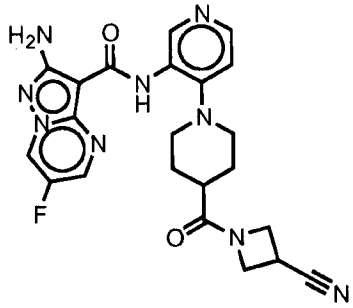

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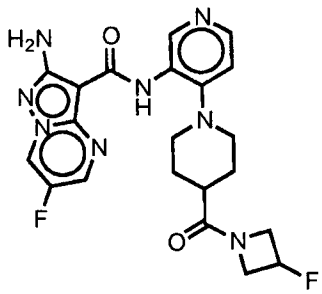

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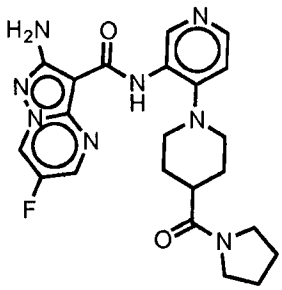

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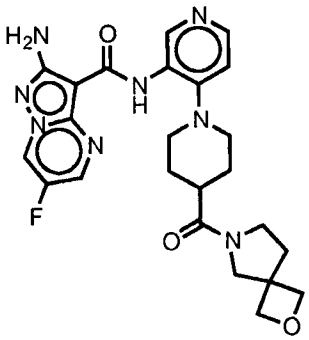

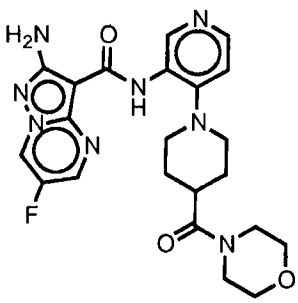

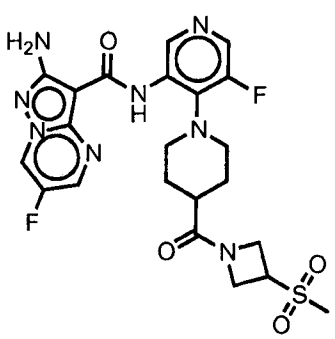

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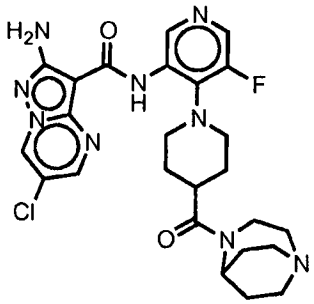

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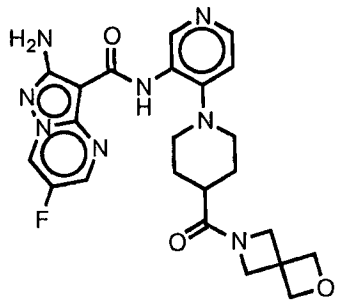

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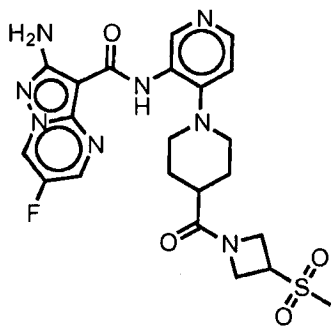

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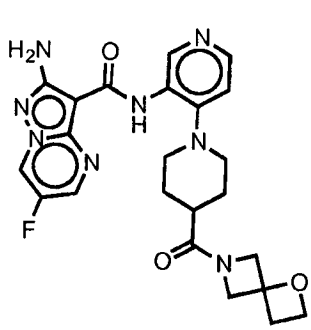

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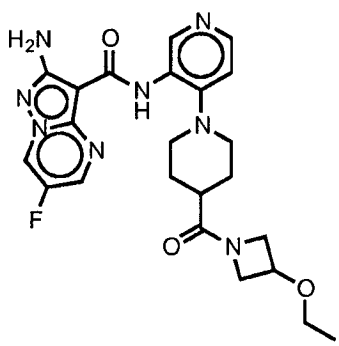

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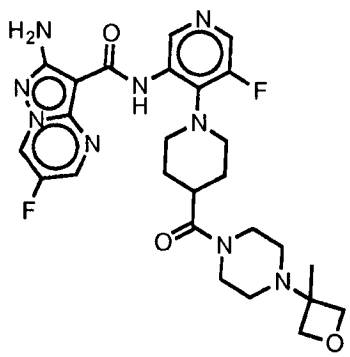

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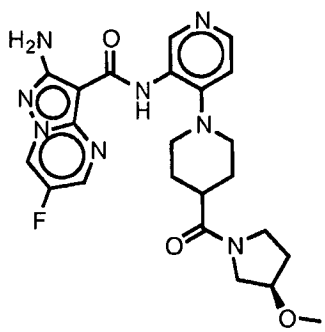

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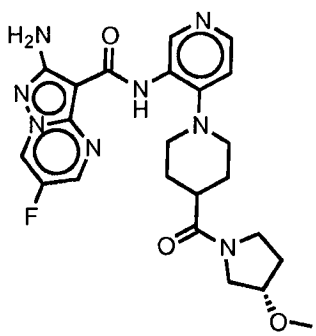

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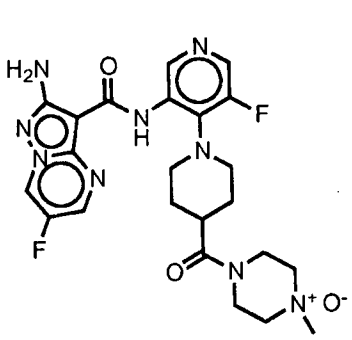

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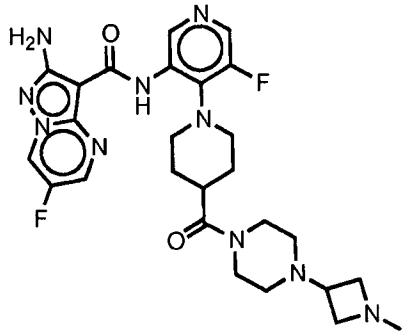

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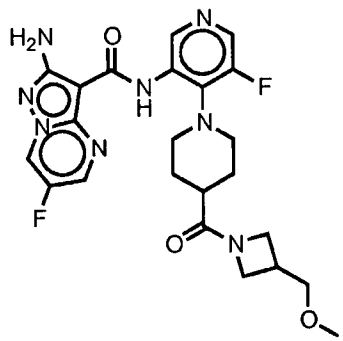

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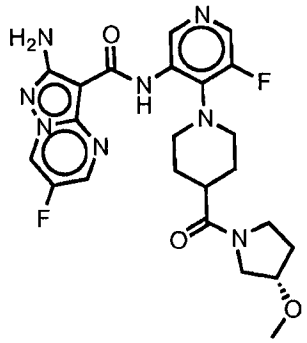


I-G-99.

159. A pharmaceutical composition comprising a compound of any one of claims 1-158 and a pharmaceutically acceptable carrier.

160. A method for treating cancer in a patient comprising administering a compound of any one of claims 1-159 or a pharmaceutically acceptable derivative thereof.

161. The method of claim 160, further comprising administering to said patient an additional therapeutic agent independently selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said compound as a single dosage form or separately from said compound as part of a multiple dosage form.

162. The method of claim 161, wherein said DNA-damaging agent is selected chemotherapy or radiation treatment.

163. The method of claim 161, wherein said DNA-damaging agent is independently selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonates, or an antibiotic.

164. The method of claim 163, wherein said DNA-damaging agent is independently selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, or an alkyl sulphonates.

165. The method of claim 163, wherein said DNA-damaging agent is independently selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.

166. The method of claim 164, wherein said platinating agent is independently selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Lobaplatin, Triplatin Tetranitrate, Picoplatin, Satraplatin, ProLindac and Aroplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan and Belotecan; said Topo II inhibitor is selected from Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin and Teniposide; said antimetabolite is selected from Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine and Hydroxyurea; said alkylating agent is selected from Mechlorethamine, Cyclophosphamide, Ifosfamide, Trofosfamide, Chlorambucil, Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin and Plicamycin.

167. The method of claim 166, wherein said platinating agent is independently selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from

methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, or 5-Fluorouracil; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, or Streptomyces family.

168. The method of claim 166, wherein said DNA-damaging agent is independently selected from a platinating agent or ionizing radiation.

169. The method of claim 164, wherein the antimetabolite is gemcitabine.

170. The method of claim 164, wherein the DNA-damaging agent is ionizing radiation.

171. The method of claim 164, wherein the DNA-damaging agent is a platinating agent independently selected from Cisplatin or Carboplatin.

172. The method of claim 164, wherein the DNA-damaging agent is a Topo II inhibitor selected from Etoposide.

173. The method of claim 162, wherein the DNA-damaging agent is an alkyating agent selected from Temozolomide.

174. The method of claim 164, wherein the DNA-damaging agent is independently selected from one or more of the following: Cisplatin, Carboplatin, gemcitabine, Etoposide, Temozolomide, or ionizing radiation.

175. The method of claim 174, wherein the additional therapeutic agents are selected from one or more of the following: gemcitabine, cisplatin or carboplatin, and etoposide.

176. The method of any one of claims 160-175, wherein said cancer is a solid tumor selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal:

esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological/Female: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma,

multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

177. The method of claim 176, wherein said cancer is selected from a cancer of the lung or the pancreas.

178. The method of claim 177, wherein said cancer is lung cancer.

179. The method of claim 178, wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.

180. The method of claim 179, wherein the lung cancer is small cell lung cancer and the additional therapeutic agents are cisplatin and etoposide.

181. The method of claim 179, wherein the lung cancer is non-small cell lung cancer and the additional therapeutic agents are gemcitabine and cisplatin.

182. The method of claim 181, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.

183. The method of any one of claims 160-175, wherein said cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer.

184. The method of any one of claims 160-175, wherein said cancer is selected from non-small cell lung cancer, small cell lung cancer, pancreatic cancer, biliary tract cancer, head and neck cancer, bladder cancer, colorectal cancer, glioblastoma, esophageal cancer, breast cancer, hepatocellular carcinoma, or ovarian cancer.

185. The method of claim 184, wherein the cancer is breast cancer and the additional therapeutic agent is cisplatin.

186. The method of claim 185, wherein the cancer is triple negative breast cancer.

187. The method of claim 168, wherein the additional therapeutic agent is Gemcitabine and the cancer is pancreatic cancer.

188. A method of treating pancreatic cancer comprising administering to a patient a compound of a compound of any one of claims 1-158 in combination with an additional therapeutic agent selected from Gemcitabine, radiation therapy, or both Gemcitabine and radiation therapy together.

189. A method of increasing the sensitivity of pancreatic cancer cells to a cancer therapy selected from chemotherapy or radiation therapy by administering to a patient a compound of any one of claims 1-158.

190. The method of claim 189, wherein the chemotherapy is gemcitabine.

191. The method of claim 189, wherein the cancer therapy is gemcitabine.

192. The method of claim 189, wherein the cancer therapy is radiation.

193. The method of claim 181, wherein the cancer therapy is gemcitabine and radiation.

194. A method of inhibiting phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell comprising administering a compound of any one of claims 1-159 in combination with gemcitabine (100 nM) and/or radiation (6 Gy).

195. A method of sensitizing pancreatic cancer cells to chemoradiation by administering a compound of any one of claims 1-158 in combination with chemoradiation.

196. The method of claim 166, wherein the chemoradiation is gemcitabine and radiation.

197. A method of radiosensitizing hypoxic pancreatic cancer cells by administering a compound of any one of claims 1-158 in combination with radiation therapy.

198. A method of sensitizing hypoxic pancreatic cancer cells by administering a compound of any one of claims 1-158 in combination with chemotherapy.

199. The method of any one of claims 195-198 wherein said cancer cell is a PSN-1, MiaPaCa-2 or PancM cancer cell.

200. A method of disrupting damage-induced cell cycle checkpoints by administering a compound of any one of claims 1-158 in combination with radiation therapy and/or gemcitabine.

201. A method of inhibiting repair of DNA damage by homologous recombination in a pancreatic cancer cell by administering a compound of any one of claims 1-156 in combination with radiation therapy and/or gemcitabine.

202. The method of any one of claims 195-201 wherein the compound is administered to a patient.

203. The method of any one of claims 196-201 wherein the compound is administered to a pancreatic cancer cell.

204. The method of claim 203, wherein the pancreatic cancer cells are derived from a pancreatic cell line selected from PSN-1, MiaPaCa-2 or Panc-1.

205. A method of treating non-small cell lung cancer comprising administering to a patient a compound of any one of claim 1-158 in combination with one or more of the following additional therapeutic agents: Cisplatin or Carboplatin, Etoposide, and ionizing radiation.

206. A method of promoting cell death in cancer cells comprising administering to a patient a compound of any one of claims 1-158.

207. A method of preventing cell repair from DNA damage comprising administering to a patient a compound of any one of claims 1-158.

208. A method of inhibiting ATR in a biological sample comprising the step of contacting a compound of any one of claims 1-158 with said biological sample.

209. The method of claim 208, wherein said biological sample is a cell.

210. A method of sensitizing cells to DNA damaging agents comprising administering to a patient a compound of any one of claims 1-158.

211. The method of any one of claims 161-210, wherein said cell is a cancer cell having defects in the ATM signaling cascade.

212. The method of claim 211, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1.

213. The method of claim 211, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX.

214. The method of any one of claims 160-210, wherein said cell is a cancer cell expressing DNA damaging oncogenes.

215. The method of claim 214, wherein said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.

216. The method of any one of claims 161-210, wherein said cancer, cancer cell, or cell has a defect in a base excision repair protein.

217. The method of claim 216, wherein the base excision repair protein is UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2(Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.

218. The method of claim 217, wherein the base excision repair protein is PARP1, PARP2, or PolB.

219. The method of claim 218, wherein the base excision repair protein is PARP1 or PARP2.

220. The method of any one of claims 161-219, further comprising administering to said patient an additional therapeutic agent wherein said agent inhibits or modulates a base excision repair protein.

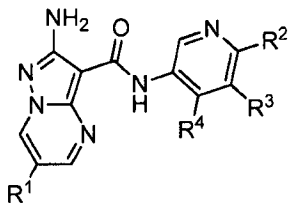
221. The method of claim 220, wherein the base excision repair protein is selected from UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.

222. The method of claim 221, wherein the base excision repair protein is selected from PARP1, PARP2, or PolB.

223. The method of claim 222, wherein the base excision repair protein is selected from PARP1 or PARP2.

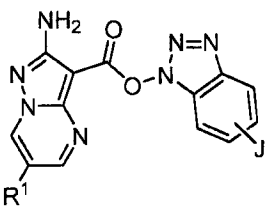
224. The method of claim 213, wherein said agent is selected from Olaparib (also known as AZD2281 or KU-0059436), Iniparib (also known as BSI-201 or SAR240550), Veliparib (also known as ABT-888), Rucaparib (also known as PF-01367338), CEP-9722, INO-1001, MK-4827, E7016, BMN673, or AZD2461.

223.A process for preparing a compound of formula **I-A**:



I-A

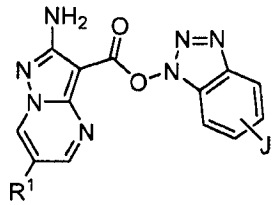
comprising reacting a compound of formula **6**:



6

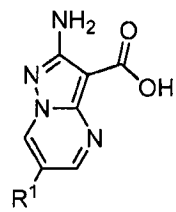
under suitable conditions to form an amide bond, wherein J, R^1, R^2, R^3, and R^4 are as defined in claims 1-158.

224.The process of claim 223, further comprising the step of preparing a compound of formula **6**:



6

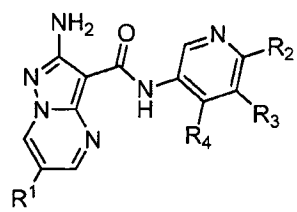
by reacting a compound of formula **5**:



5

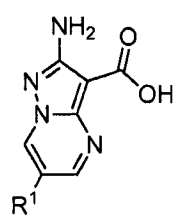
under suitable conditions to form an activated ester.

225.A process for preparing a compound of formula **I-A**:



I-A

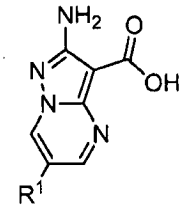
comprising reacting a compound of formula **5**:



5

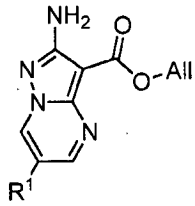
under suitable conditions to form an amide bond, wherein R^1, R^2, R^3, and R^4 are as defined in claims 1-158.

226. The process of any one of claims 223-225, further comprising the step of preparing a compound of formula **5**:



5

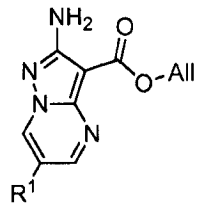
by reacting a compound of formula **4**:



4

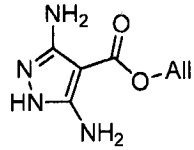
under suitable deprotection conditions.

227. The process of claim 226, further comprising the step of preparing a compound of formula **4**:



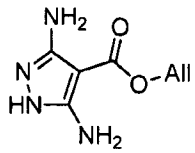
4

by reacting a compound of formula **3**:



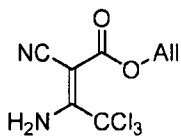
under suitable condensation conditions to form a pyrimidine ring.

228. The process of claim 227, further comprising the step of preparing the compound of formula **3**:



3

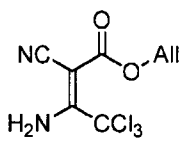
by reacting a compound of formula **2**:



2

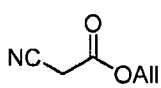
under suitable condensation conditions to form a pyrazole ring.

229. The process of claim 228, further comprising the step of preparing a compound of formula **2**:



2

by reacting a compound of formula **1**:



1

under suitable anion condensation conditions.

230.The process of any one of claims 223, wherein R^1 is independently selected from halo or $-CH_2CN$.

231.The process of claim 230, wherein R^1 is independently selected from fluoro or chloro.

232. The process of claim 223, wherein suitable conditions for forming an amide bond comprise reacting the compound of formula **6** with a substituted 3-aminopyridine in an aprotic solvent in the presence of heat.

233.The process of claim 232, wherein the aprotic solvent is selected from NMP, pyridine, or DMF.

234.The process of claim 232, wherein the aprotic solvent is optionally substituted pyridine.

235.The process of any one of claims 232-234, wherein the reaction is carried out at a temperature of at least 80°C.

236.The process of claim 235, wherein the reaction is carried out at a temperature of at least 100°C.

237. The process of any one of claims 224, wherein suitable conditions for forming the activated ester comprises reacting the compound of formula **5** with an amide coupling agent in the presence of an organic base.

238.The process of claim 237, wherein the organic base is an aliphatic amine.

239.The process of claim 238, wherein the organic base is independently selected from DIPEA or triethylamine.

240.The process of any one of claims 237-239, wherein the amide coupling agent is independently selected from EDCI, TBTU, TCTU, HATU, T3P, or COMU.

241.The process of claim 240, wherein the amide coupling agent is independently selected from TBTU or TCTU.

242.The process of claim 241, wherein the amide coupling agent is TCTU.

243.The process of claim 226, wherein suitable hydrolytic conditions comprise reacting the compound of formula **4** with a silane in the presence of a metal catalyst.

244.The process of claim 243, wherein the silane is phenylsilane.

245.The process of claim 244, wherein the metal catalyst is a palladium catalyst.

246.The process of claim 245, wherein the metal catalyst is $Pd(PPh_3)_4$.

247.The process of claim 226, wherein suitable hydrolytic conditions comprise reacting the compound of formula **4** with an aqueous alkali.

248.The process of claim 247, wherein the aqueous alkali is independently selected from LiOH, NaOH, or KOH.

249. The process of claim 227, wherein suitable condensation conditions for forming a pyrimidine ring comprise reacting the compound of formula **3** with a 1,3-dielectrophilic species in the presence of a solvent.

250.The process of claim 249, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal.

251.The process of any one of claims 249 or 250, wherein the solvent is selected from DMF or DMSO.

252.The process of claim 249, wherein the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species.

253.The process of claim 252, wherein the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid.

254.The process of claim 253, wherein the sulfonic acid is PTSA.

255.The process of claim 228, wherein suitable condensation conditions for forming a pyrazole ring comprise reacting the compound of formula **2** with a hydrazine or hydrazine hydrate in the presence of an aprotic solvent under basic conditions.

256.The process of claim 255, wherein the aprotic solvent is DMF.

257.The process of claim 255, wherein the basic conditions comprise reacting the compound of formula **2** in the presence of potassium acetate or sodium acetate.

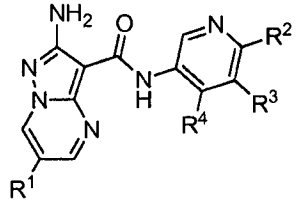
258. The process of claim 229, wherein suitable anion condensation conditions comprise 1) reacting the compound of formula **1** with a base, in the presence of a solvent, to generate the anion of the compound of formula **1**; and 2) reacting the anion of the compound of formula **1** with trichloroacetonitrile.

259.The process of claim 258, wherein the base is potassium acetate.

260.The process of claim 258, wherein the solvent is an alcohol.

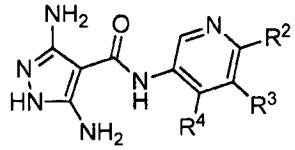
261.The process of claim 260, wherein the solvent is isopropylalcohol.

262.A process for preparing a compound of formula **I-A**:



I-A

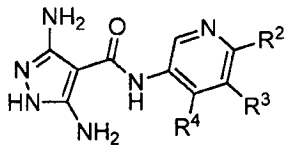
comprising reacting a compound of formula **9**:



9

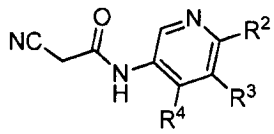
under suitable condensation conditions to form a pyrimidine ring, wherein R^1, R^2, R^3 and R^4 are as defined in claims 1-156.

263.The process of claim 262, further comprising the step of preparing a compound of formula **9**:



9

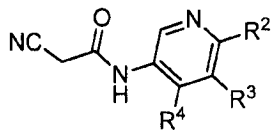
by reacting a compound of formula **8**:



8

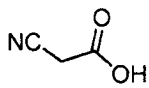
under suitable condensation conditions to form a pyrazole ring.

264. The process of claim 263, further comprising the step of preparing a compound of formula **8**:



8

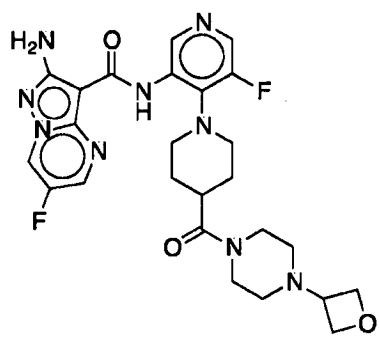
by reacting a compound of formula **7**:



7

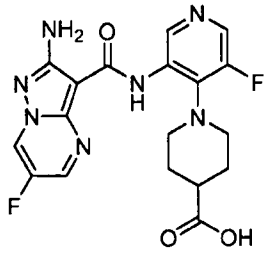
under suitable conditions to form an amide bond.

265. A process of preparing a compound of formula **I-G-32**:



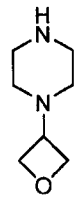
I-G-32

comprising the step of reacting the compound of formula **29**:



29

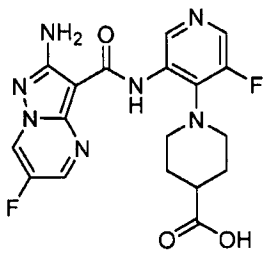
with a compound of formula **25**:



25

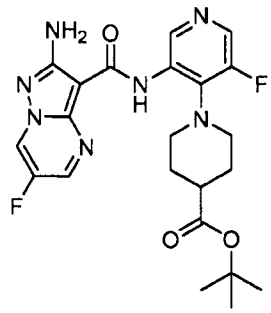
under suitable conditions to form an amide bond.

266.The process of claim 265, further comprising the step of preparing the compound of formula **29**:



29

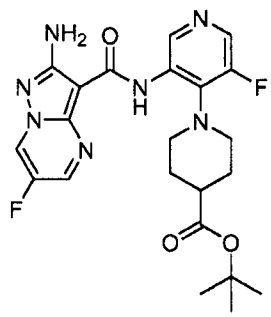
by reacting the compound of formula **28**:



28

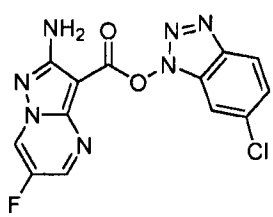
under suitable deprotection conditions to form the carboxylic acid.

267. The process of claim 266, further comprising the step of preparing a compound of formula **28**:



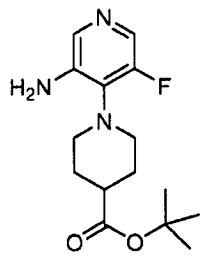
28

by reacting the compound of formula **6a***:



6a*

with a compound of formula **27**:



27

under suitable conditions to form an amide bond.

268. The compound of claim 265, wherein suitable conditions for forming the amide bond comprise reacting the compound of formula **29** with the compound of formula **25** in the presence of an amide coupling partner, an aprotic solvent, and a base.

269. The compound of claim 268, wherein the aprotic solvent is independently selected from NMP, DMF, or tetrahydrofuran.

270. The process of claim 269, wherein the aprotic solvent is tetrahydrofuran.

271. The process of claim 269, wherein the base is an aliphatic amine.

272. The process of claim 271, wherein the base is DIPEA.

273. The process of any one of claims 268-272, wherein the amide coupling partner is independently selected from TBTU or TCTU.

274. The process of claim 273, wherein the amide coupling partner is TCTU.

275. The process of claim 266, wherein suitable deprotection conditions comprise reacting the compound of formula **28** with an acid in the presence of a solvent.

276. The process of claim 275, wherein the acid is HCl.

277. The process of claim 276, wherein the solvent is 1,4-dioxane.

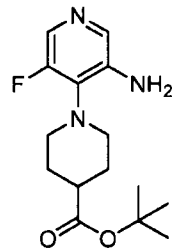
278. The process of claim 267, wherein the suitable conditions for forming the amide bond comprise reacting the compound of formula **6a*** with the compound of formula **27** in an aprotic solvent under heat.

279. The process of claim 278, wherein the aprotic solvent is independently selected from NMP, pyridine, or DMF.

280.The process of claim 279, wherein the aprotic solvent is pyridine.

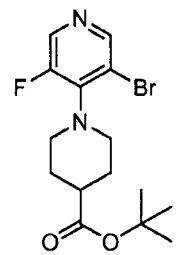
281.The process of any one of claims 278, wherein the reaction is carried out at a temperature of at least 80°C.

282.A process of preparing a compound of formula **27**:



27

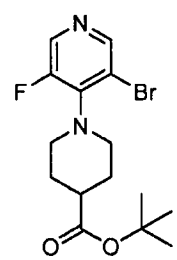
comprising the step of reacting a compound of formula **26**:



26

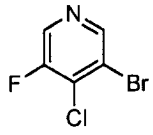
under suitable conditions to form an amine.

283. The process of claim 282, further comprising the step of preparing a compound of formula **26**:



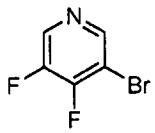
26

by 1) reacting a compound of formula **18**:



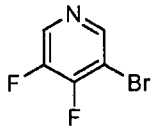
18

under suitable halogen exchange conditions to generate the compound of formula **32**



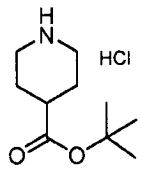
32 , and

2) reacting the compound of formula **32**:



32

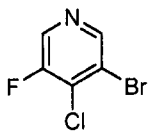
with a compound of formula **22**:



22

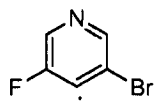
under suitable displacement conditions.

284. The process of claim 282, further comprising the step of preparing a compound of formula **18**:



18

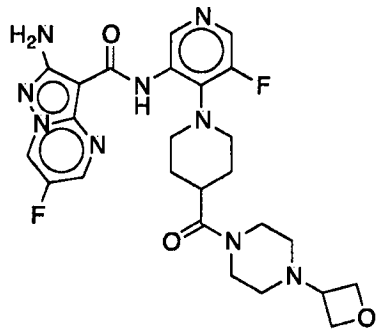
by reacting the compound of formula **31**:



31

under suitable halogenation conditions.

285. A compound having the structure **I-G-32**:



I-G-32

or a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/073457

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/495 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/138938 A1 (VERTEX PHARMA [US]; CHARRIER JEAN-DAMIEN [GB]; MACCORMICK SOMHAIRLE [G) 11 October 2012 (2012-10-11) the whole document	1-285
A	WO 2010/071837 A1 (VERTEX PHARMA [US]; CHARRIER JEAN-DAMIEN [GB]; DURRANT STEVEN [GB]; KA) 24 June 2010 (2010-06-24) the whole document	1-285

☐ Further doouments 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" doument 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	Date of mailing of the international search report
17 January 2014	29/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baston, Eckhard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/073457

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012138938 A1	11-10-2012	AU 2012240030 A1	24-10-2013
		CA 2832100 A1	11-10-2012
		EP 2694498 A1	12-02-2014
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		US 2010222318 A1	02-09-2010
		WO 2010071837 A1	24-06-2010

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104903325 A
(43)申请公布日 2015.09.09

(21)申请号 201380069648.8
(22)申请日 2013.12.06
(30)优先权数据
61/734,726 2012.12.07 US
61/787,568 2013.03.15 US
61/868,132 2013.08.21 US
(85)PCT国际申请进入国家阶段日
2015.07.07
(86)PCT国际申请的申请数据
PCT/US2013/073457 2013.12.06
(87)PCT国际申请的公布数据
WO2014/089379 EN 2014.06.12
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代理人 袁志明
(51)Int.Cl.
C07D 487/04(2006.01)
A61K 31/495(2006.01)
A61P 35/00(2006.01)

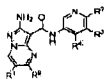
权利要求书85页 说明书357页

(54)发明名称

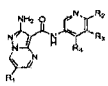
可用作ATR激酶抑制剂的化合物

(57)摘要

本发明涉及可用作ATR蛋白激酶抑制剂的化合物。本发明还涉及包含本发明所述化合物的药学上可接受的组合物；使用本发明所述化合物治疗各种疾病、障碍和病症的方法；用于制备本发明所述化合物的方法；用于制备本发明所述化合物的中间体；以及在体外应用中使用所述化合物的方法，所述体外应用为例如对生物学和病理学现象中的激酶的研究；对这种激酶介导的胞内信号转导途径的研究；以及对新激酶抑制剂的对比评价。本发明的所述化合物具有式I或其药学上可接受的盐，其中所述变量如本申请中所定义。另外，本发明的所述化合物具有式I-A或其药学上可接受的盐，其中所述变量如本申请中所定义。



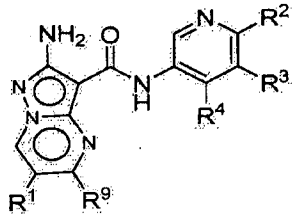
(I)



(I-A)

CN 104903325 A

1. 具有式 I 的化合物：



I

或其药学上可接受的盐或前药，其中：

R^1独立地选自 $-C(J^1)_2CN$、卤素、$-(L)_k-W$ 或 M；

R^9独立地选自 H、$-C(J^1)_2CN$、卤素、$-(L)_k-W$ 或 M；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

k 是 0 或 1；

M 和 L 是 C_{1-8}脂族基团，其中至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代，M 和 L^1各自任选地被 0-3 次出现的 J^{LM}取代；

J^{LM}独立地选自卤素、-CN 或 C_{1-4}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

W 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；其中 W 任选地被 0-5 次出现的 J^W取代；

J^W独立地选自 -CN、卤素、$-CF_3$；C_{1-4}脂族基团，其中至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；

R^2独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2}烷基；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^3独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；3-4 元杂环基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元芳族或非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^Z独立地选自 C_{1-6}脂族基团、=O、卤素或→O；

J^Q独立地选自 -CN；卤素；=O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被 0-3 次出现的 J^R

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取代；或

同一原子上的 2 次出现的 J^Q 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^Q 形成的环任选地被 0-3 次出现的 J^X 取代；或

2 次出现的 J^Q 与 Q^1 一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^2 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^R 独立地选自 -CN；卤素；=O；→O；Q^3；或 C_{1-6} 脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；J^R 各自任选地被 0-3 次出现的 J^T 取代；或

同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^R 形成的环任选地被 0-3 次出现的 J^X 取代；或

2 次出现的 J^R 与 Q^2 一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^3 是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^X 独立地选自 -CN；=O；卤素；或 C_{1-4} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

J^T 独立地选自卤素、-CN；→O；=O；-OH；C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T 任选地被 0-3 次出现的 J^M 取代；或

同一原子上的 2 次出现的 J^T 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；或

2 次出现的 J^T 与 Q^3 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^M 独立地选自卤素或 C_{1-6} 脂族基团；

n 是 0、1 或 2；且

R 独立地选自 H 或 C_{1-4} 脂族基团。

2. 权利要求 1 任一项的化合物，其中 R^9 是 H。

3. 权利要求 1-2 任一项的化合物，其中 R^9 是 M。

4. 权利要求 3 的化合物，其中 M 是 C_{1-8} 脂族基团，其中至多 3 个亚甲基单元任选地被 -O- 或 -NR- 替代。

5. 权利要求 4 的化合物，其中 M 是 C_{1-4} 烷基、$-(C_{1-4}$ 烷基$)O(C_{1-3}$ 脂族基团$)$、$-(C_{1-3}$ 烷基$)OH$、$-O(C_{1-4}$ 烷基$)N(C_{1-2}$ 烷基$)_2$、$-NH(C_{1-4}$ 烷基$)$ 或 $-(C_{1-4}$ 烷基$)NH(C_{1-4}$ 烷基$)$。

6. 权利要求 5 的化合物，其中 M 是 C_{1-4} 烷基。

7. 权利要求 4-6 任一项的化合物，其中 J^{LM} 是卤素。

8. 权利要求 1-2 任一项的化合物，其中 R^9 是 $-(L^1)_k-W$。

9. 权利要求 8 的化合物，其中 k 是 0。

10. 权利要求 8 的化合物，其中 k 是 1。

11. 权利要求 10 的化合物，其中 L 是 C_{1-8} 脂族基团，其中至多 3 个亚甲基单元任选地被 -O- 或 -NR- 替代。

打印ID?619020 Pg 4

12. 权利要求 11 的化合物，其中 L 是 -O-、-O(C_{1-4}脂族基团)- 或 -NR(C_{1-3}烷基)-。

13. 权利要求 8-12 任一项的化合物，其中 W 是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。

14. 权利要求 13 的化合物，其中 W 是 3-7 元杂环基。

15. 权利要求 14 的化合物，其中 W 独立地选自吡咯烷基、哌啶基、哌嗪基、氧杂环丁烷基或氮杂环丁烷基。

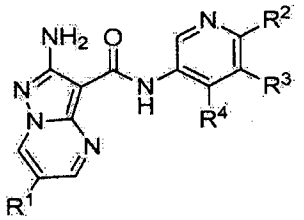
16. 权利要求 8-12 任一项的化合物，其中 W 是具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。

17. 权利要求 8-16 任一项的化合物，其中 J^W选自 C_{1-3}烷基或 CF_3。

18. 权利要求 8-16 任一项的化合物，其中同一原子上的 2 次出现的 J^W与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环。

19. 权利要求 18 的化合物，其中由同一原子上的 2 次出现的 J^W形成的环是氧杂环丁烷基。

20. 具有式 I-A 的化合物：



I-A

或其药学上可接受的盐或前药，其中：

R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

R^2独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2}烷基；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^3独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元芳族或非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^Z独立地选自 C_{1-6}脂族基团、=O、卤素或→O；

J^Q独立地选自 -CN；卤素；=O；Q^2；或 C_{1-6}脂族链，其中所述脂族链的至多 3 个亚甲基

打印ID?619020 Pg 5

单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q 任选地被 0-3 次出现的 J^R 取代；或

同一原子上的 2 次出现的 J^Q 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^Q 形成的环任选地被 0-3 次出现的 J^X 取代；或

2 次出现的 J^Q 与 Q^1 一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^2 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^R 独立地选自 -CN；卤素；=O；→O；Q^3；或 C_{1-6} 脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；J^R 各自任选地被 0-3 次出现的 J^T 取代；或

同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^R 形成的环任选地被 0-3 次出现的 J^X 取代；或

2 次出现的 J^R 与 Q^2 一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^3 是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^X 独立地选自 -CN；=O；卤素；或 C_{1-4} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

J^T 独立地选自卤素、-CN；=O；C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T 任选地被 0-3 次出现的 J^M 取代；或

同一原子上的 2 次出现的 J^T 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；或

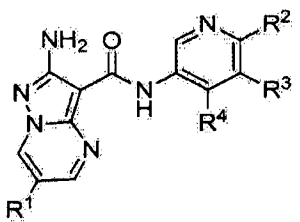
2 次出现的 J^T 与 Q^3 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^M 独立地选自卤素或 C_{1-6} 脂族基团；

R 独立地选自 H 或 C_{1-4} 脂族基团。

n 是 0、1 或 2；且

21. 具有式 I-A 的化合物：



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或其药学上可接受的盐或前药，其中：

R^1 独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1 独立地选自 H 或 C_{1-2} 烷基；或

2 次出现的 J^1 与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

R^2独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2}烷基；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^3独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^Z独立地选自 C_{1-6}脂族基团、= O、卤素或→ O；

J^Q独立地选自 -CN；卤素；= O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被 0-3 次出现的 J^R取代；或

同一原子上的 2 次出现的 J^Q与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^Q形成的环任选地被 0-3 次出现的 J^X取代；或

2 次出现的 J^Q与 Q^1一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^2独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^R独立地选自 -CN；卤素；= O；→ O；Q^3；或 C_{1-6}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；J^R各自任选地被 0-3 次出现的 J^T取代；或

同一原子上的 2 次出现的 J^R与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^R形成的环任选地被 0-3 次出现的 J^X取代；或

2 次出现的 J^R与 Q^2一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^3是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^X独立地选自 -CN；卤素；或 C_{1-4}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

J^T独立地选自 -CN；= O；-OH；C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T任选地被 0-3 次出现的 J^M取代；或

同一原子上的 2 次出现的 J^T与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

2 次出现的 J^T与 Q^3一起形成 6-10 元饱和或部分不饱和桥连环系；

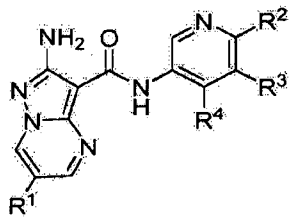
J^M独立地选自卤素或 C_{1-6}脂族基团；

打印ID?619020 Pg 7

n 是 0、1 或 2；且

R 独立地选自 H 或 C_{1-4}脂族基团。

22. 具有式 I-A 的化合物：



I-A

或其药学上可接受的盐或前药，其中：

R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^2独立地选自 H；氯；NH_2；或任选地被氟取代的 C_{1-2}烷基；

R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；或 -CN；

R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR- 或 -S- 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

Q^1独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

J^Z独立地选自 C_{1-6}脂族基团、=O、卤素或→O；

J^Q独立地选自卤素；=O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被 0-3 次出现的 J^R取代；或

同一原子上的 2 次出现的 J^Q与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^Q形成的环任选地被 0-3 次出现的 J^X取代；或

2 次出现的 J^Q与 Q^1一起形成 6-10 元饱和或部分不饱和桥连环系；

Q^2独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和、部分不饱和或芳族双环；

J^R独立地选自卤素；=O；→O；具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或 C_{1-4}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代；J^R各自任选地被 0-3 次出现的 J^T取代；或

同一原子上的 2 次出现的 J^R与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^R形成的环任选地被 0-3 次出现的 J^X取代；或

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2 次出现的 J^R 与 Q^2 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^X 独立地选自卤素或 C_{1-4} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代；或

J^T 独立地选自 C_{1-6} 脂族基团或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T 任选地被 0-3 次出现的 J^M 取代；

J^M 独立地选自卤素或 C_{1-6} 脂族基团；

n 是 1 或 2；且

R 独立地选自 H 或 C_{1-4} 脂族基团。

23. 权利要求 1-22 任一项的化合物，其中 R^1 是氟。

24. 权利要求 1-22 任一项的化合物，其中 R^1 是 $-CH_2CN$、$-C(CH_3)_2CN$ 或 $-CH(C_{1-2}$ 烷基）CN。

25. 权利要求 1-22 任一项的化合物，其中 R^1 是氯。

26. 权利要求 1-25 任一项的化合物，其中 R^2 独立地选自 $-CF_3$、$-NH(C_{1-2}$ 烷基）、氯或 H。

27. 权利要求 26 的化合物，其中 R^2 是 H。

28. 权利要求 26 的化合物，其中 R^2 是 - 氯。

29. 权利要求 1-28 任一项的化合物，其中 R^3 独立地选自 H、氯、氟、CHF_2、-CN、环丙基或 C_{1-4} 烷基。

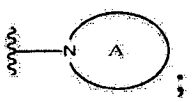
30. 权利要求 29 的化合物，其中 R^3 独立地选自 H、氯或氟。

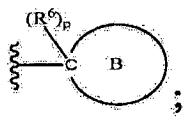
31. 权利要求 30 的化合物，其中 R^3 是 H。

32. 权利要求 30 的化合物，其中 R^3 是氯。

33. 权利要求 30 的化合物，其中 R^3 是氟。

34. 权利要求 1-33 任一项的化合物，其中 R^4 独立地选自：

-O-； 

； 

；或 $-CH_2-R^7$，其中：

-O- 被 1 个 J^Q 取代；

环 A 独立地选自具有 1-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

环 B 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

R^6 是 H；

R^7 独立地选自 H 或 C_{1-6} 脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代；且

p 是 0 或 1。

35. 权利要求 34 的化合物，其中 R^4 是 -O-。

36. 权利要求 35 的化合物，其中 J^Q 独立地选自 $-(C_{1-4}$ 烷基）、$-(C_{1-4}$ 烷基）$N(C_{1-4}$ 烷基）$_2$、$-(C_{1-3}$ 烷基）$O(C_{1-2}$ 烷基）$N(C_{1-3}$ 烷基）$_2$、$(C_{1-4}$ 烷基）OH、$-(C_{1-4}$ 烷基）NH_2 或 $-(C_{1-4}$ 烷

打印ID?619020 Pg 9

基)O(C_{1-4}烷基)。

37. 权利要求 35 的化合物，其中 J^Q是 Q^2。

38. 权利要求 37 的化合物，其中 Q^2是具有 0-3 个选自氧、硫或氮的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。

39. 权利要求 38 的化合物，其中 Q^2独立地选自 5-6 元芳基、5-6 元杂芳基、4-6 元脂环族基团或 3-7 元杂环基。

40. 权利要求 39 的化合物，其中 Q^2独立地选自 4-7 元脂环族基团或 3-7 元杂环基。

41. 权利要求 40 的化合物，其中 Q^2是 3-7 元杂环基。

42. 权利要求 41 的化合物，其中 Q^2独立地选自吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1,3-噁嗪烷基、1,3-噻嗪烷基、二氢吡啶基、二氢咪唑基、1,3-四氢嘧啶基、二氢嘧啶基、1,4-二氮杂庚环基、1,4-氧杂氮杂庚环基、1,4-硫杂氮杂庚环基、四氢噻喃基、四氢呋喃基、四氢吡喃基、氮杂环丁烷基和氧杂环丁烷基。

43. 权利要求 42 的化合物，其中 Q^2独立地选自四氢噻喃基、吡咯烷基、哌啶基、哌嗪基、四氢呋喃基、四氢吡喃基或氮杂环丁烷基。

44. 权利要求 43 的化合物，其中 Q^2是哌啶基。

45. 权利要求 39 的化合物，其中 Q^2是 5-6 元杂芳基。

46. 权利要求 45 的化合物，其中 Q^2独立地选自咪唑基、吡咯基、吡啶基、吡嗪基、嘧啶基、吡唑基、1,2,3-三唑基或 1,2,4-三唑基。

47. 权利要求 46 的化合物，其中 Q^2是吡啶基。

48. 权利要求 39 的化合物，其中 Q^2是 4-6 元脂环族基团。

49. 权利要求 48 的化合物，其中 Q^2独立地选自环丁基或环己基。

50. 权利要求 39 的化合物，其中 Q^2是苯基。

51. 权利要求 37 的化合物，其中 Q^2是具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。

52. 权利要求 51 的化合物，其中 Q^2是 6,7-二氢-5H-吡咯并[1,2-a]咪唑。

53. 权利要求 36-52 任一项的化合物，其中 J^R是 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代。

54. 权利要求 53 的化合物，其中 J^R独立地选自 C_{1-4}烷基、$-N(C_{1-4}烷基)_2$、-C(O)OH、-C(O)O(C_{1-4}烷基)、$-C(O)N(C_{1-4}烷基)_2$、$-(C_{1-4}烷基)O(C_{1-4}烷基)$ 或 -C(O)-。

55. 权利要求 54 的化合物，其中 J^R是 C_{1-4}烷基。

56. 权利要求 36-52 任一项的化合物，其中 J^R是 Q^3。

57. 权利要求 56 的化合物，其中 Q^3是具有 0-3 个选自氧、硫或氮的杂原子的 3-6 元完全饱和、部分不饱和或芳族单环、

58. 权利要求 57 的化合物，其中 Q^3是具有 1-3 个选自氧、氮或硫的杂原子的 3-6 元杂环基。

59. 权利要求 58 的化合物，其中 Q^3独立地选自氧杂环丁烷基、哌啶基、氮杂环丁烷基、哌嗪基、吡咯烷基、吗啉基。

60. 权利要求 59 的化合物，其中 Q^3是氧杂环丁烷基。

打印ID?619020 Pg 10

61. 权利要求 57 的化合物，其中 Q^3 是环丙基。

62. 权利要求 39-43 任一项的化合物，其中 J^R 是 = O 或卤素。

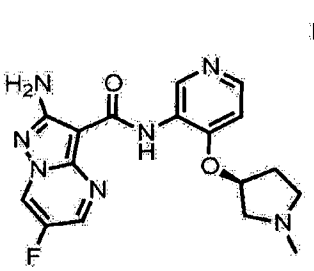
63. 权利要求 39-43 的化合物，其中同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环。

64. 权利要求 63 的化合物，其中由同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成的环选自氧杂环丁烷基、环丁基或氮杂环丁烷基。

65. 权利要求 56-61 任一项的化合物，其中 J^T 是具有 1-2 个选自氧、氮或硫的杂原子的 4-6 元杂环。

66. 权利要求 65 的化合物，其中 J^T 是哌嗪基。

67. 权利要求 34-66 任一项的化合物，其独立地选自：



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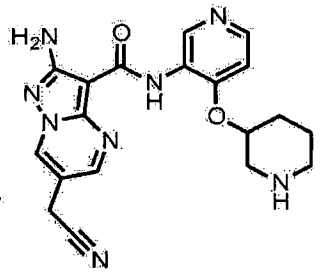

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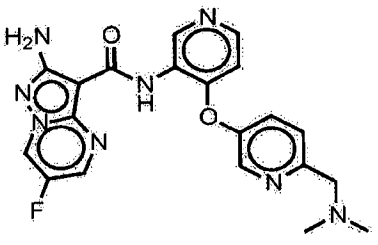

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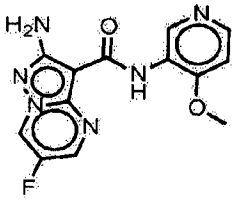

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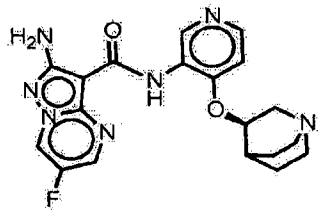

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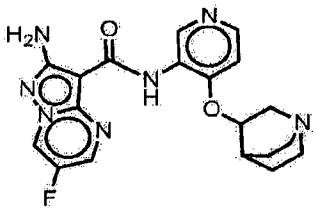

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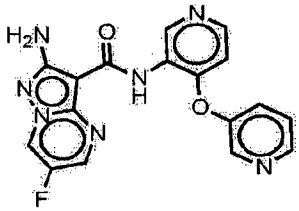

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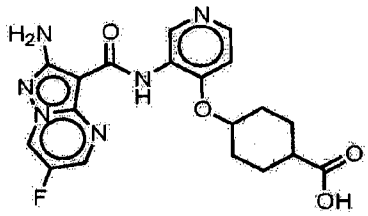

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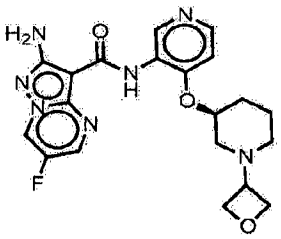

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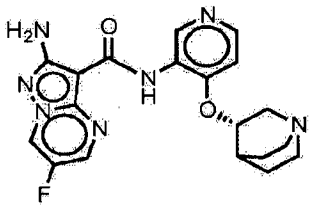

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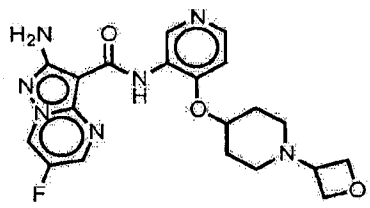

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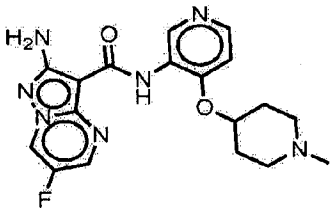

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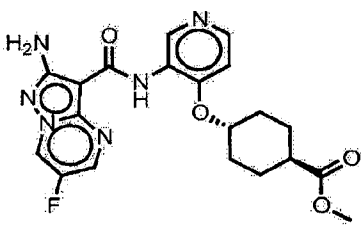

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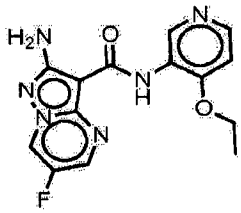

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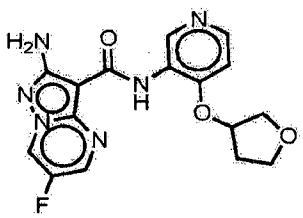

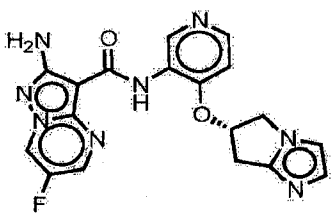

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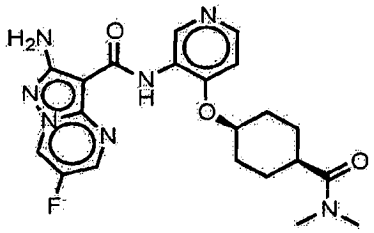

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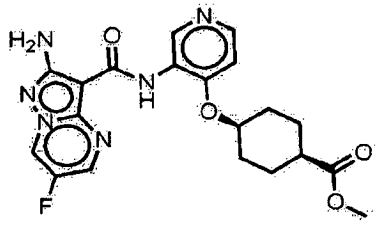

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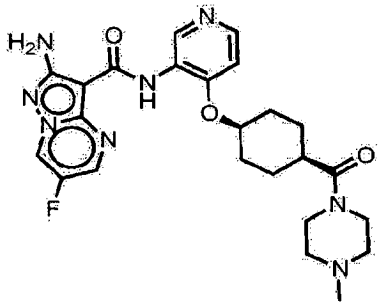

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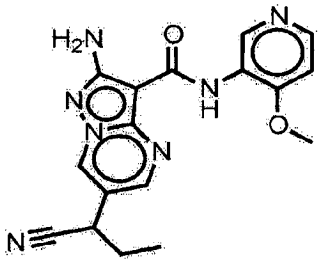

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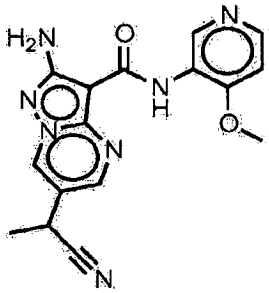

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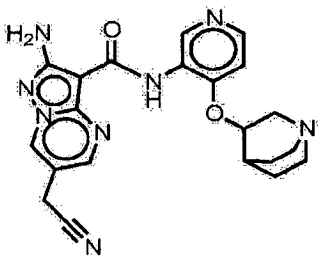

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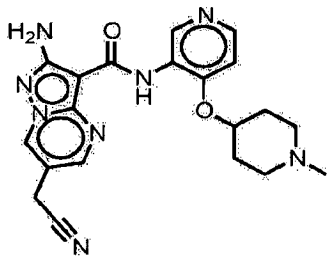

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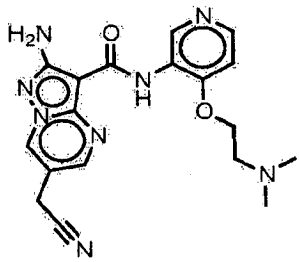

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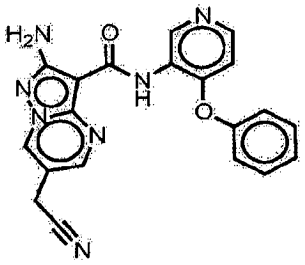

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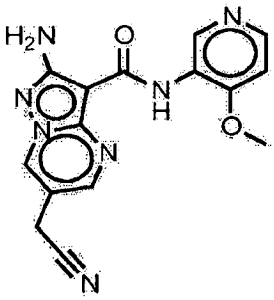

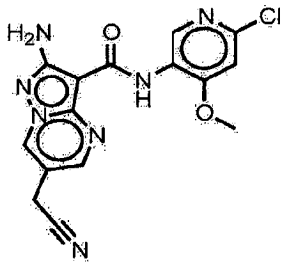

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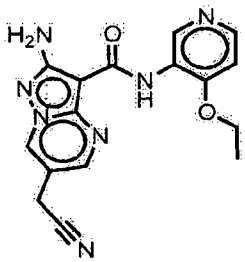

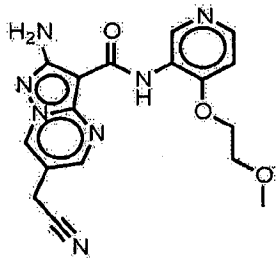

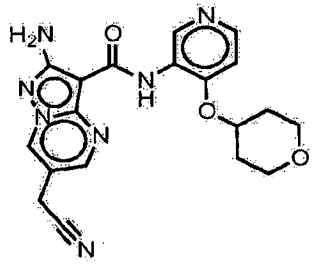

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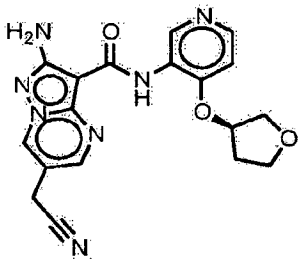

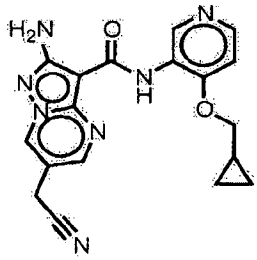

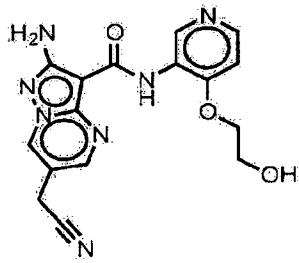

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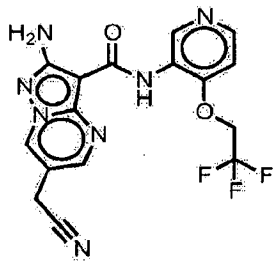

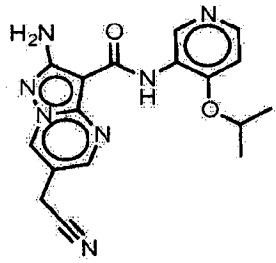

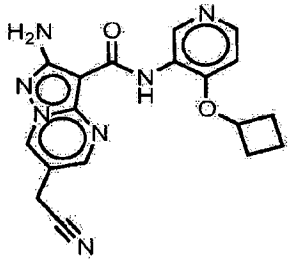

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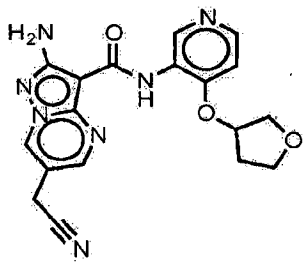

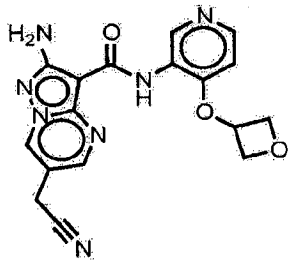

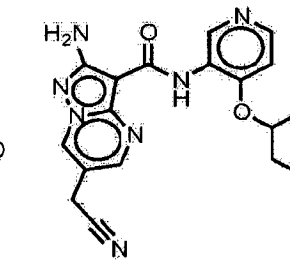

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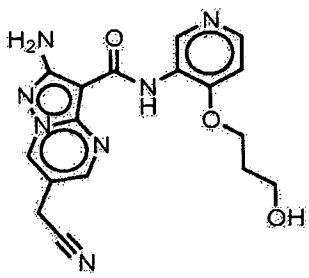
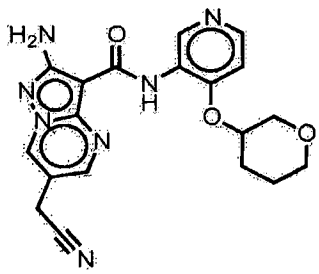
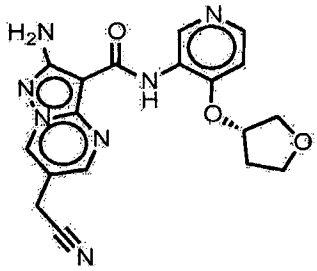


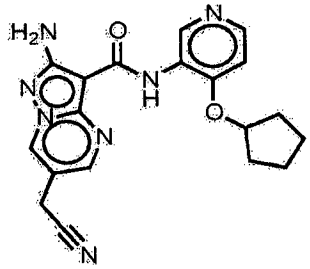
I-O-40



I-O-41



I-O-42



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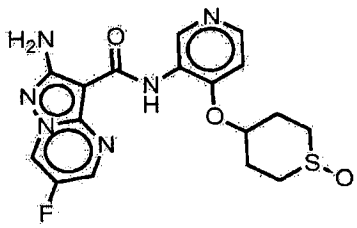

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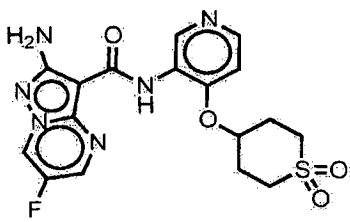

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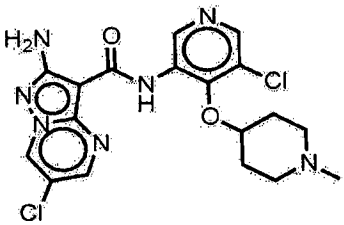
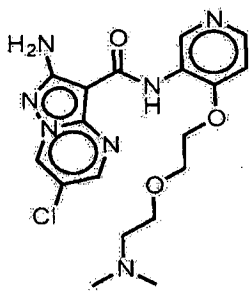


I-O-46



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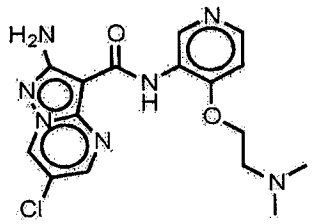

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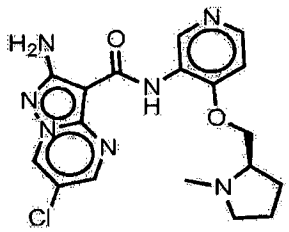

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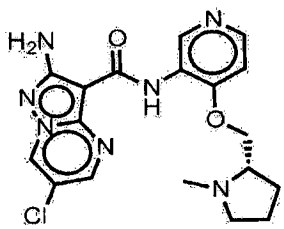

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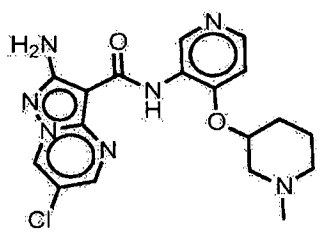

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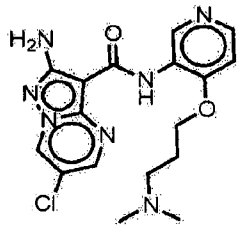

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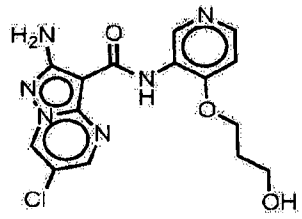

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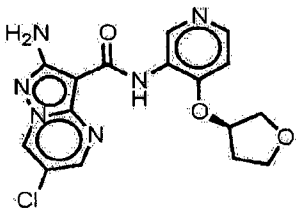

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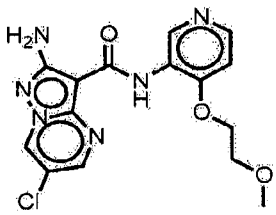

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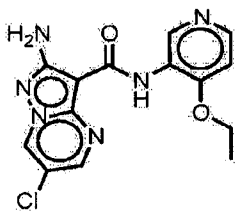

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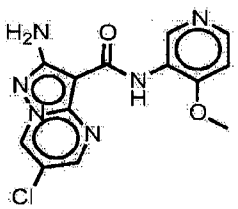

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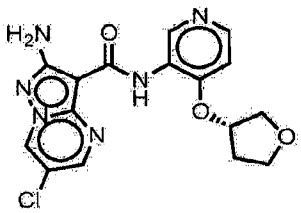

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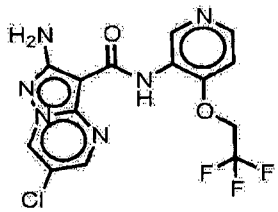

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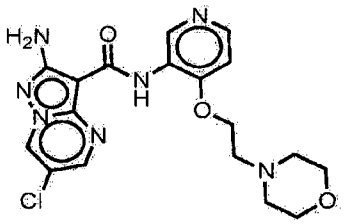

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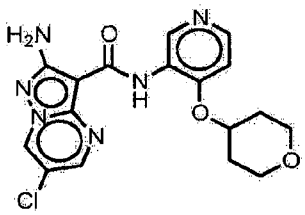
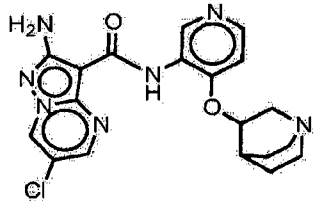


I-O-61



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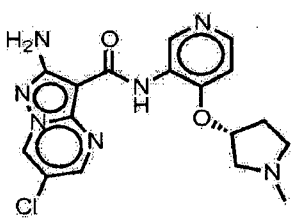

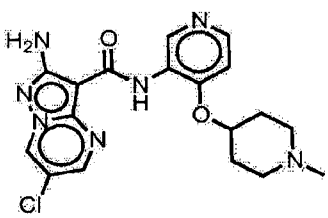

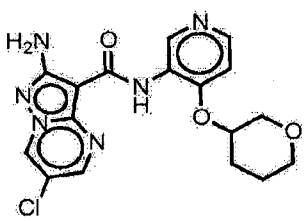

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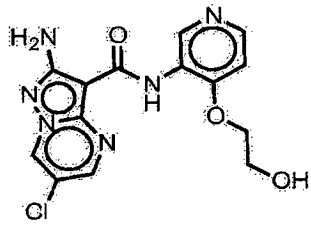

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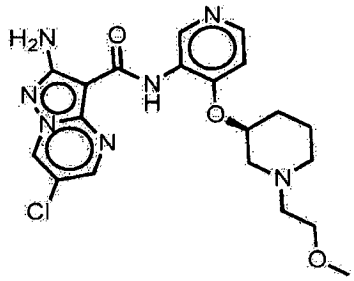

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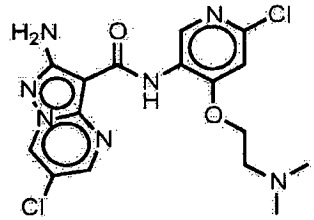

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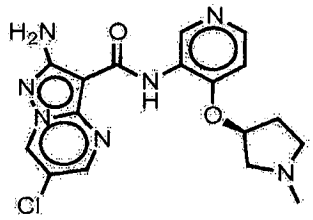

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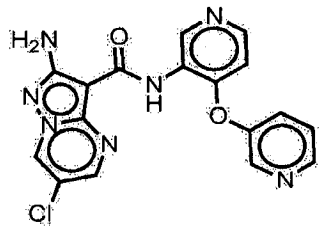
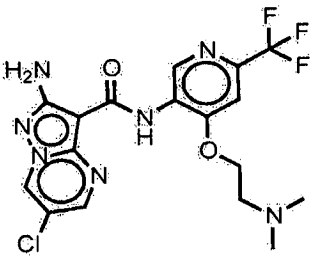
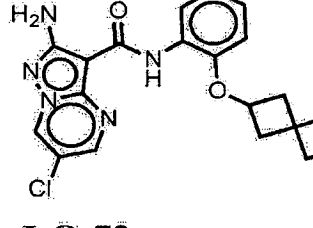


I-O-68



I-O-69

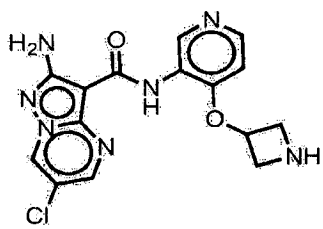


I-O-70

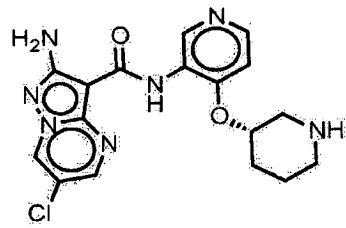
I-O-71

I-O-72

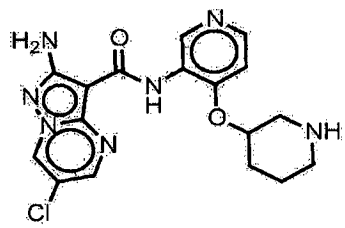
I-O-73



I-O74



I-O-75



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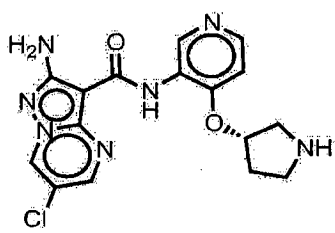

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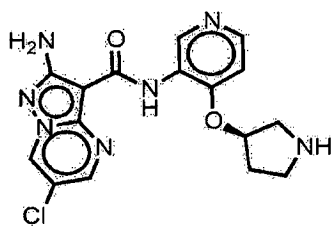

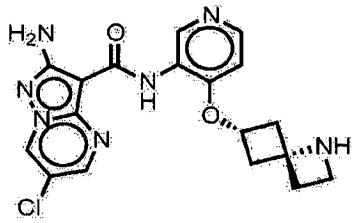

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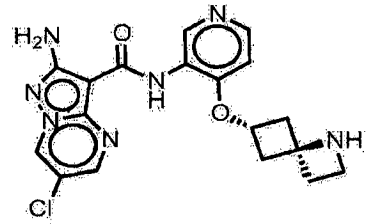
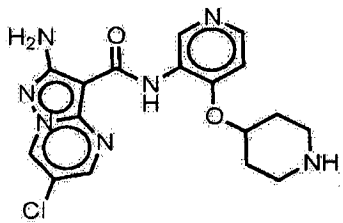
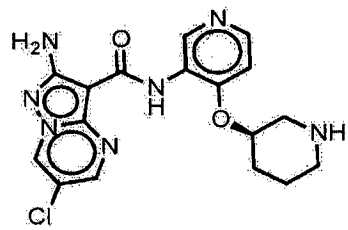


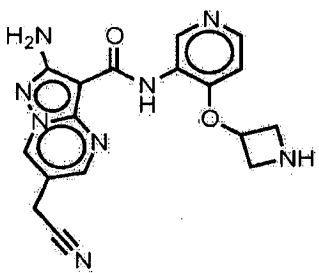
I-O-79



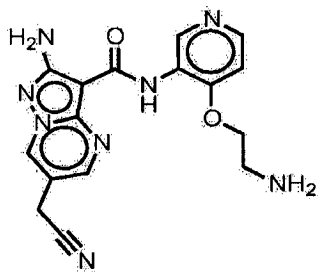
I-O-80



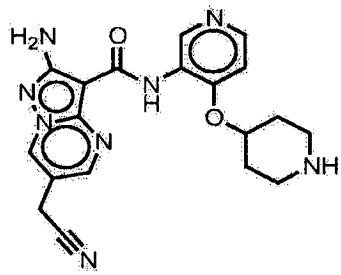
I-O-81



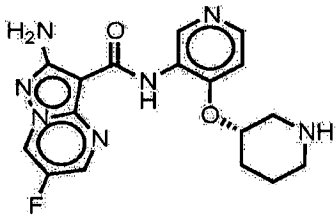
I-O-82



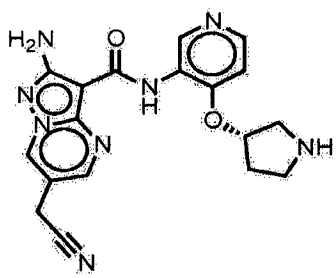
I-O-83



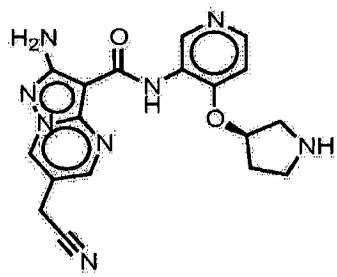
I-O-84



I-O-85



I-O-86



I-O-87

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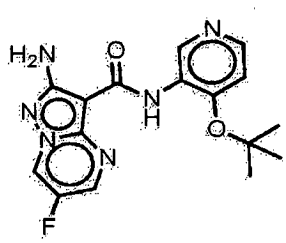
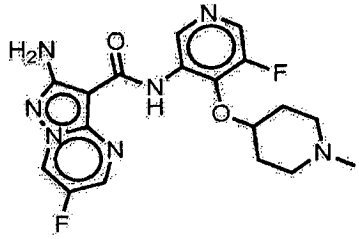
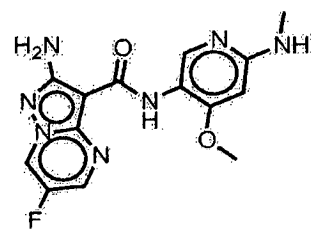


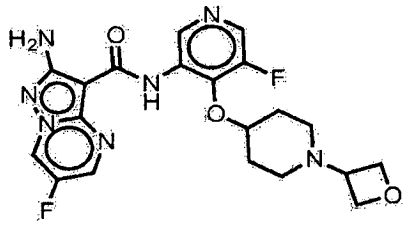
I-O-88



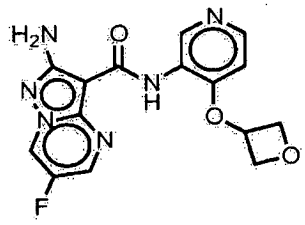
I-O-89



I-O-90

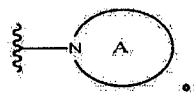


I-O-91



I-O-92。

68. 权利要求 34 的化合物，其中 R^4 是：



69. 权利要求 68 的化合物，其中环 A 是具有 1-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。

70. 权利要求 69 的化合物，其中环 A 是 3-7 元杂环基。

71. 权利要求 70 的化合物，其中环 A 独立地选自吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1, 3- 噁嗪烷基、1, 3- 噻嗪烷基、二氢吡啶基、二氢咪唑基、1, 3- 四氢嘧啶基、二氢嘧啶基、1, 4- 二氮杂庚环基、1, 4- 氧杂氮杂庚环基、1, 4- 硫杂氮杂庚环基和氮杂环丁烷基。

72. 权利要求 71 的化合物，其中环 A 独立地选自哌啶基、哌嗪基、1, 4- 二氮杂庚环基、硫代吗啉基、吡咯烷基、氮杂庚环基、吗啉基。

73. 权利要求 72 的化合物，其中环 A 独立地选自哌嗪基或哌啶基。

74. 权利要求 69 的化合物，其中环 A 是 5 元杂芳基。

75. 权利要求 74 的化合物，其中环 A 独立地选自吡咯基、咪唑基、吡唑基、1, 2, 3- 三唑基或 1, 2, 4- 三唑基。

76. 权利要求 75 的化合物，其中环 A 独立地选自吡唑基或咪唑基。

77. 权利要求 68 的化合物，其中环 A 是具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。

78. 权利要求 77 的化合物，其中环 A 独立地选自八氢吡咯并 [1, 2-a] 吡嗪基、5, 6, 7, 8- 四氢咪唑并 [1, 2-a] 吡啶基、八氢 -1H- 吡嗪并 [1, 2-a] 吡嗪基、5, 6, 7, 8- 四氢咪唑并 [1, 5-a] 吡嗪基、2, 5- 二氮杂双环 [4. 1. 0] 庚烷或八氢吡嗪并 [2, 1-c] [1, 4] 噁嗪基。

79. 权利要求 68-76 任一项的化合物，其中 J^Q 是 C_{1-8} 脂族链，其中所述脂族链的至多 2

打印ID7619020 Pg 19

个亚甲基单元任选地被 -O-、-NR- 或 -C(O)- 替代。

80. 权利要求 79 的化合物，其中 J^Q 独立地选自 -O-、-C(O)-、-S(O)$_2$-，C_{1-4} 烷基、-(C_{0-4} 烷基)NH_2、-(C_{0-4} 烷基)NH(C_{1-4} 烷基)、-(C_{0-4} 烷基)N(C_{1-4} 烷基)$_2$、-(C_{0-4} 烷基)OH、-(C_{0-4} 烷基)O(C_{1-4} 烷基)、-C(O)OH、-S(O)$_2$N(C_{1-3} 烷基)-、-C(O)(C_{1-4} 烷基)-、-(O)C(C_{1-4} 烷基)N(C_{1-2} 烷基)$_2$ 或 -C(O)O(C_{1-4} 烷基)。

81. 权利要求 80 的化合物，其中 J^Q 是 C_{1-4} 烷基、-O- 或 -C(O)-。

82. 权利要求 68-78 任一项的化合物，其中 J^Q 是 Q^2。

83. 权利要求 82 的化合物，其中 Q^2 是 3-7 元杂环基或碳环基；所述杂环基具有 1-3 个选自氧、氮或硫的杂原子。

84. 权利要求 83 的化合物，其中 Q^2 独立地选自氧杂环丁烷基、四氢吡喃基、四氢呋喃基、环丙基、氮杂环丁烷基、吡咯烷基、哌嗪基、环丁基、硫代吗啉基或吗啉基。

85. 权利要求 84 的化合物，其中 Q^2 独立地选自氧杂环丁烷基、四氢吡喃基或四氢呋喃基。

86. 权利要求 85 的化合物，其中 Q^2 是氧杂环丁烷基。

87. 权利要求 86 的化合物，其中 Q^2 是具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。

88. 权利要求 87 的化合物，其中 Q^2 独立地选自 5,6,7,8- 四氢咪唑并 [1,5-a] 吡嗪基或 5,6,7,8- 四氢咪唑并 [1,2-a] 吡嗪基。

89. 权利要求 68-73 任一项的化合物，其中 2 次出现的 J^Q 与环 A 一起形成桥连环系。

90. 权利要求 68-78 任一项的化合物，其中 J^Q 是 = O 或→ O。

91. 权利要求 79-89 任一项的化合物，其中 J^R 是具有 1-3 个选自氧、氮或硫的杂原子的 3-6 元杂环基。

92. 权利要求 91 的化合物，其中 J^R 独立地选自氧杂环丁烷基、哌啶基、氮杂环丁烷基、哌嗪基、吡咯烷基或吗啉基。

93. 权利要求 92 的化合物，其中 J^R 是哌嗪基。

94. 权利要求 79-89 任一项的化合物，其中 J^R 独立地选自卤素、= O、-OH、C_{1-4} 烷基、-(C_{0-4} 烷基)N(C_{1-4} 烷基)$_2$ 或 -(C_{0-4} 烷基)O(C_{1-4} 烷基)。

95. 权利要求 82-89 任一项的化合物，其中同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元芳族或非芳族环。

96. 权利要求 95 的化合物，其中 J^R 独立地选自氧杂环丁烷基或氮杂环丁烷基。

97. 权利要求 82-84 任一项的化合物，其中 2 次出现的 J^R 与环 A 一起形成桥连环系。

98. 权利要求 93 的化合物，其中 J^T 是具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环。

99. 权利要求 98 的化合物，其中 J^T 是氧杂环丁烷基。

100. 权利要求 34 的化合物，其具有式 I-A-1：

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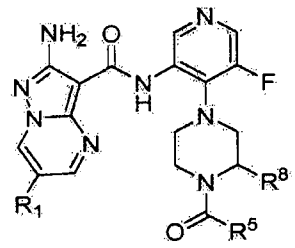

I-A-1 ;

其中：

R^5选自 C_{1-4}脂族基团、3-6 元环烷基或具有 1-2 个选自氧或硫的杂原子的 3-6 元杂环基；

R^8选自 H 或 C_{1-3}烷基；或

R^5和 R^8与它们所连接的原子一起形成具有 1-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环。

101. 权利要求 100 的化合物，其中 R^1是氟。

102. 权利要求 101 的化合物，其中 R^5是 C_{1-4}脂族基团。

103. 权利要求 102 的化合物，其中 R^5独立地选自甲基或乙基。

104. 权利要求 100 的化合物，其中 R^5是 3-6 元环烷基。

105. 权利要求 104 的化合物，其中 R^5是环丙基。

106. 权利要求 100 的化合物，其中 R^5是具有 1-2 个选自氧或硫的杂原子的 3-6 元杂环基。

107. 权利要求 106 的化合物，其中 R^5是四氢呋喃基或氧杂环丁烷基。

108. 权利要求 100 的化合物，其中 R^5和 R^6与它们所连接的原子一起形成具有 1-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环。

109. 权利要求 108 的化合物，其中由 R^5和 R^6形成的环是 5 元环。

110. 权利要求 108 的化合物，其中由 R^5和 R^6形成的环是 6 元环。

111. 权利要求 68-110 任一项的化合物，其独立地选自：

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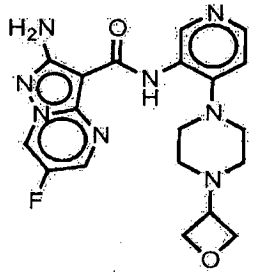

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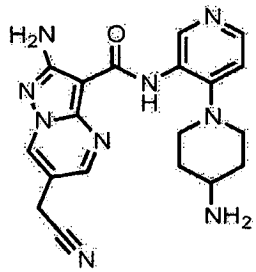

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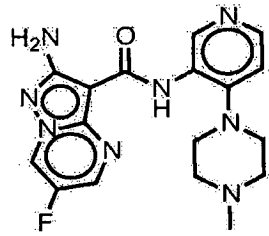

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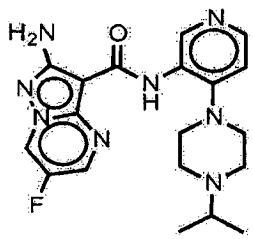

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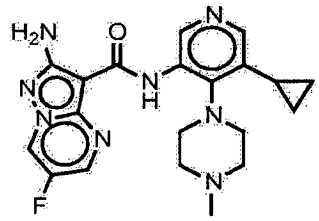

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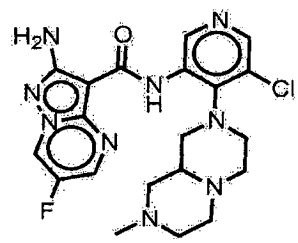

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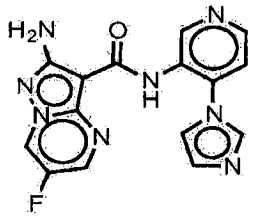

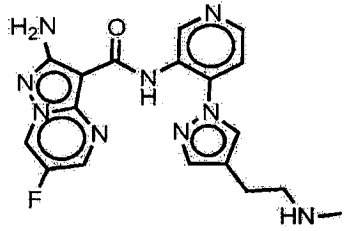

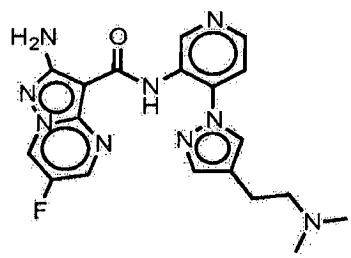

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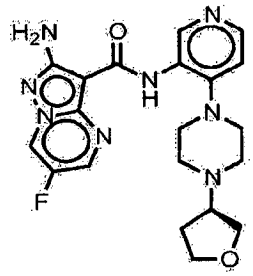
I-N-7



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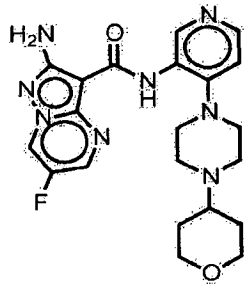

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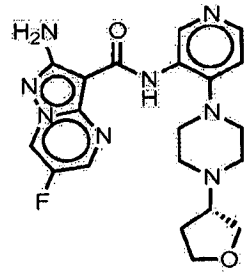

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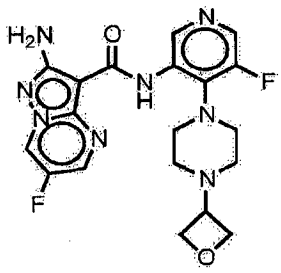

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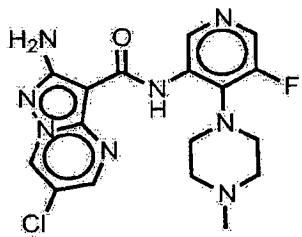

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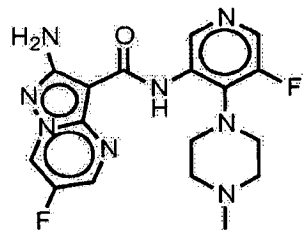

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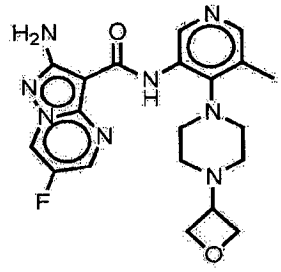

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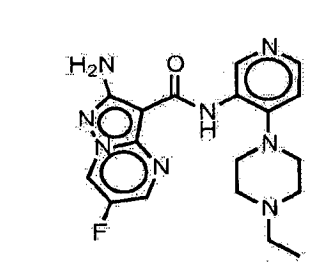

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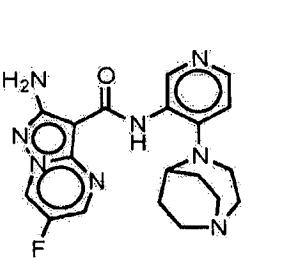

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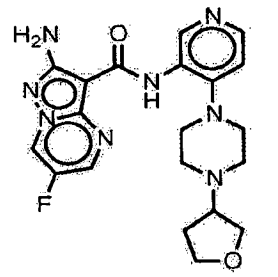

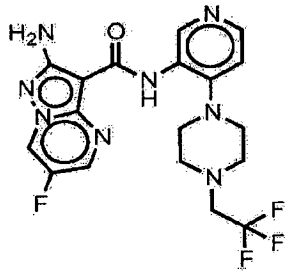

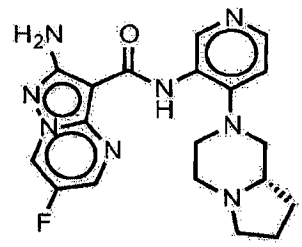

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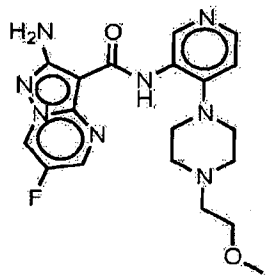

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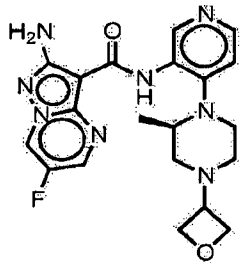

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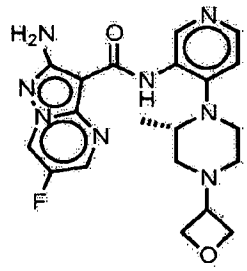

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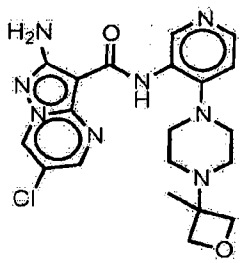

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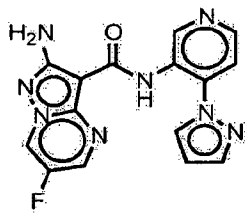

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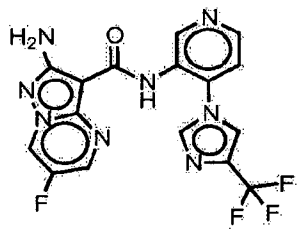

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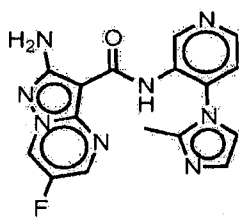

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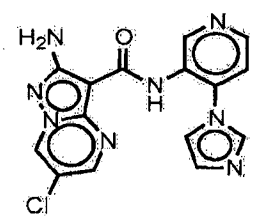

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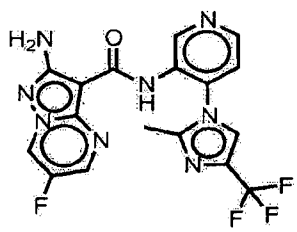
I-N-30



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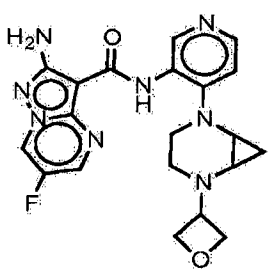

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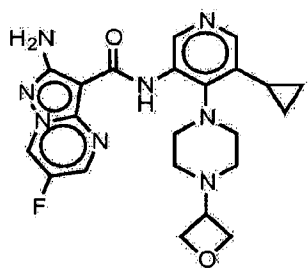
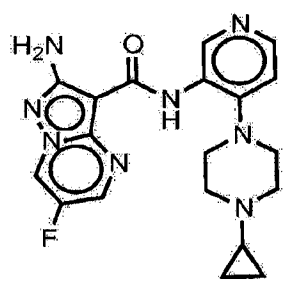
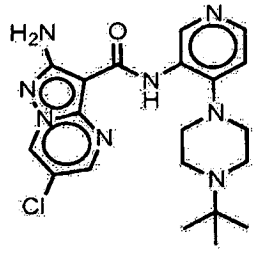
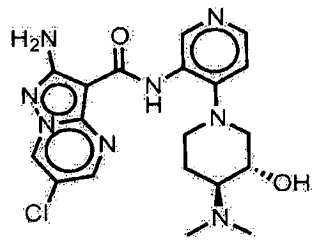


I-N-33





I-N-34



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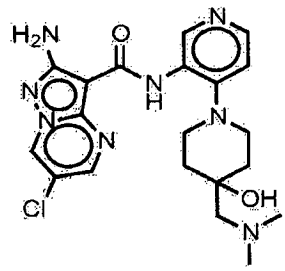

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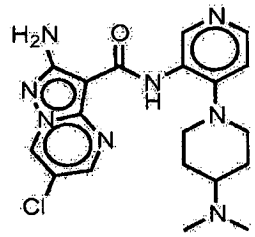

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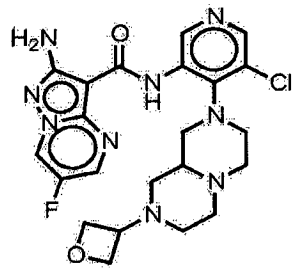

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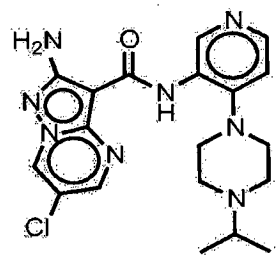

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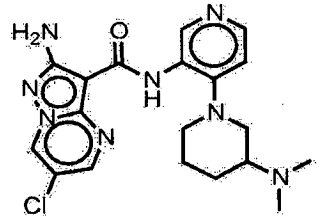

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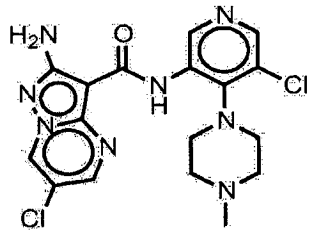

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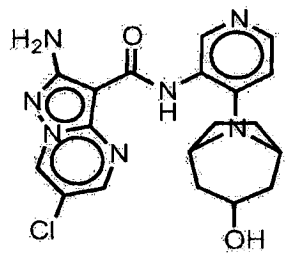

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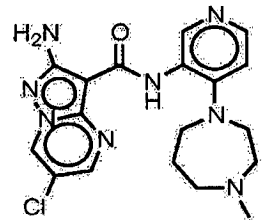

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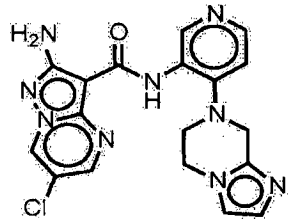

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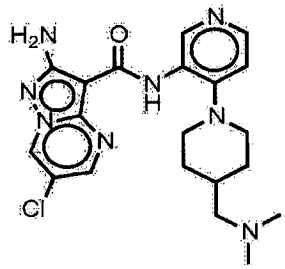
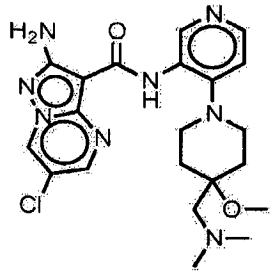
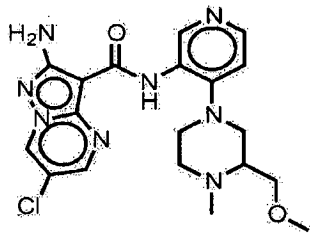


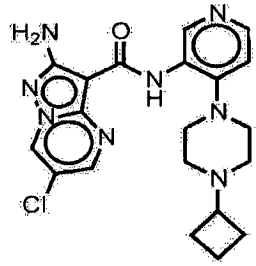
I-N-45



I-N-46



I-N-47



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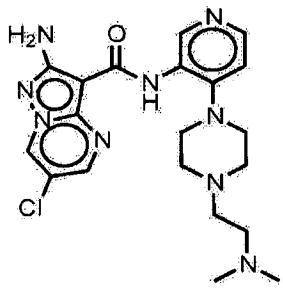
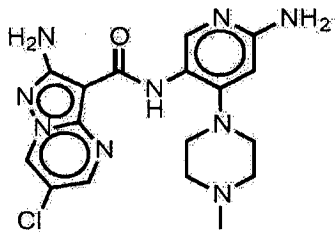


I-N-49



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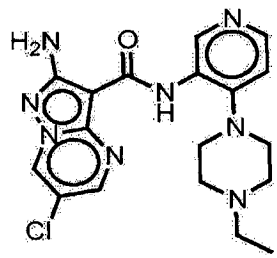

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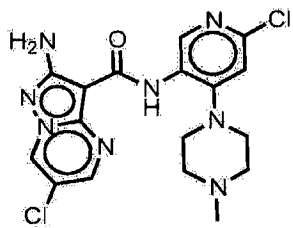

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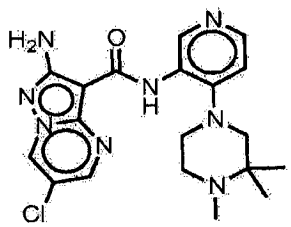

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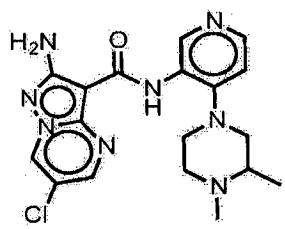

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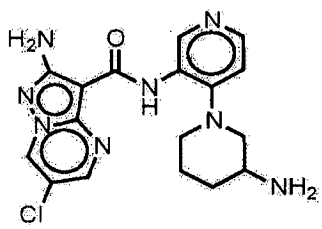

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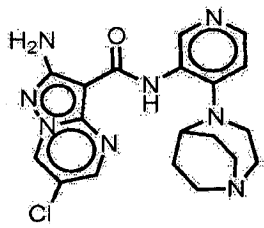

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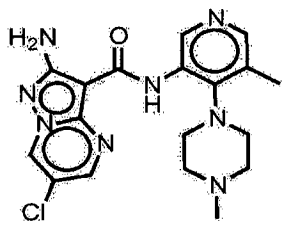

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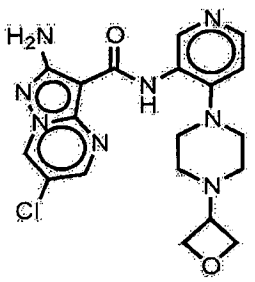

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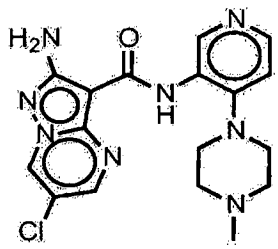

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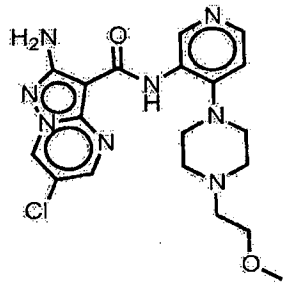

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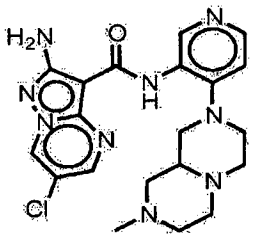

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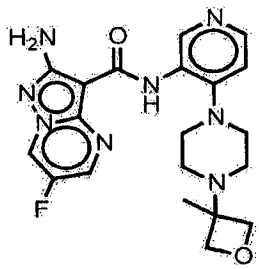

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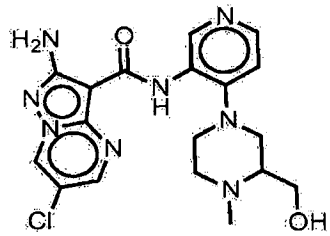

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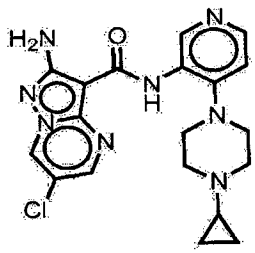

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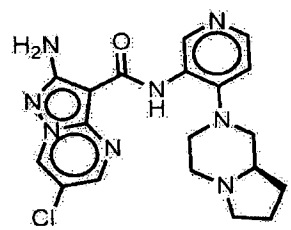

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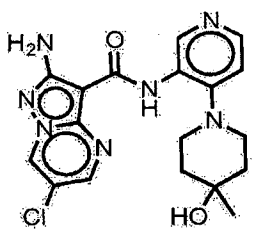
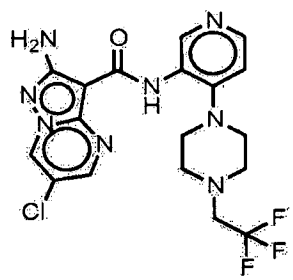
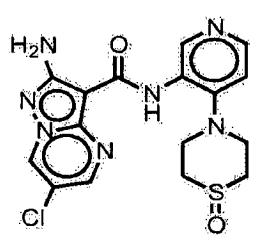


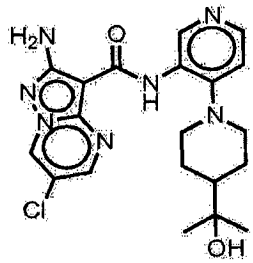
I-N-66



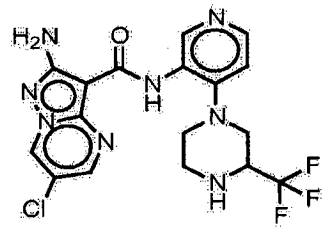
I-N-67



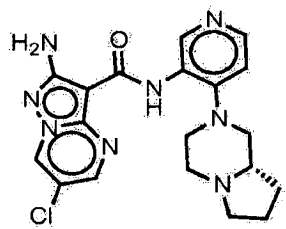
I-N-68



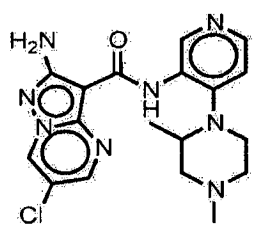
I-N-69



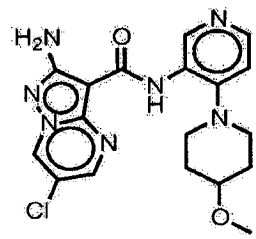
I-N-70



I-N-71



I-N-72



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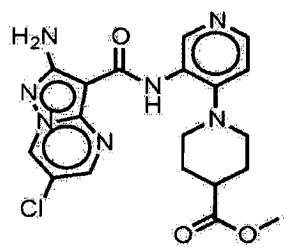

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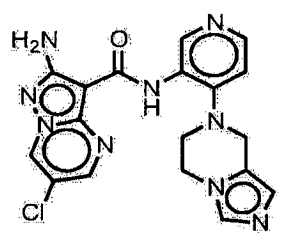
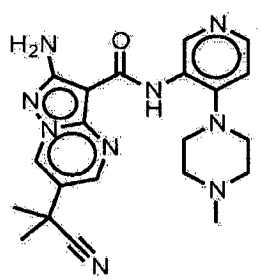
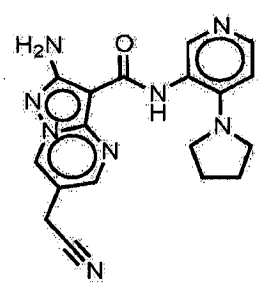


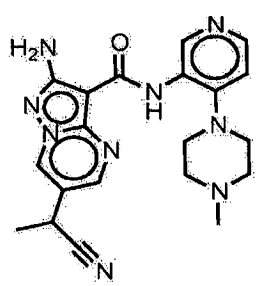
I-N-75



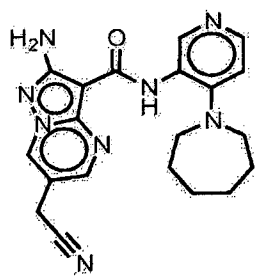
I-N-76



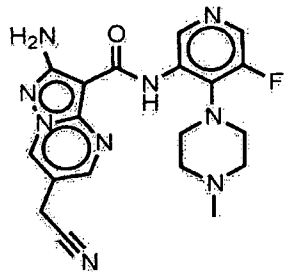
I-N-77



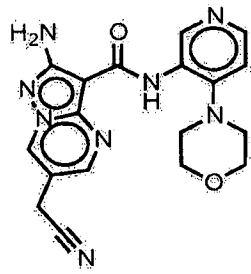
I-N-78



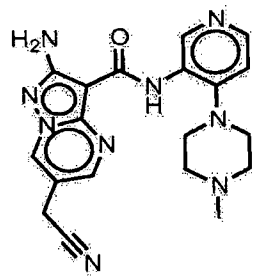
I-N-79



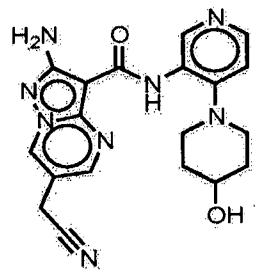
I-N-80



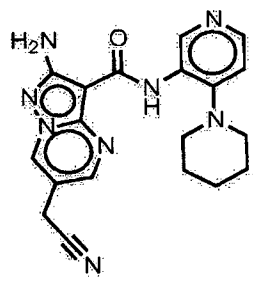
I-N-81



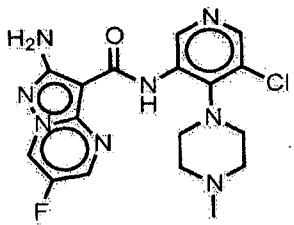
I-N-82



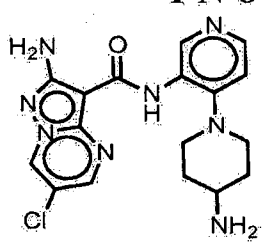
I-N-83



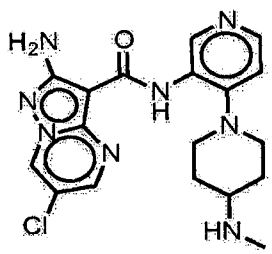
I-N-84



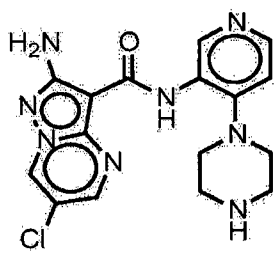
I-N-85



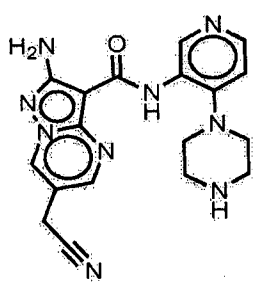
I-N-86



I-N-87



I-N-88



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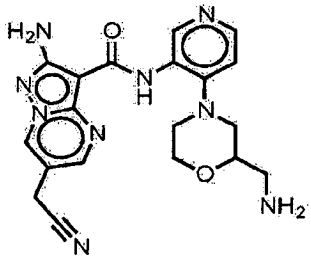

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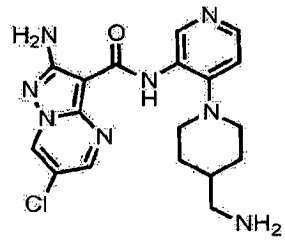

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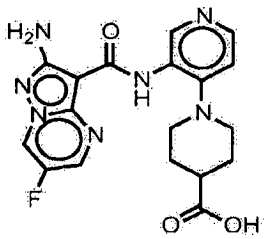

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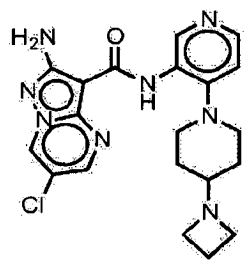

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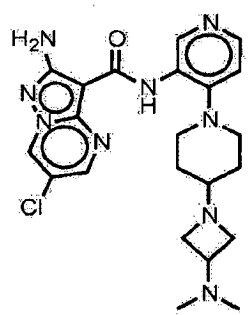

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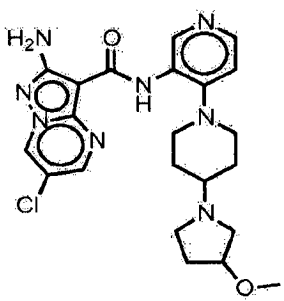

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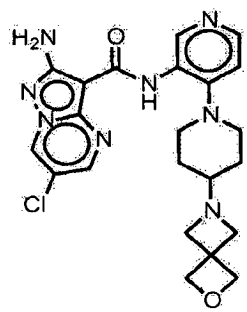

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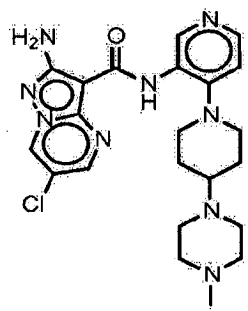

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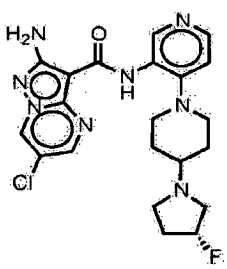

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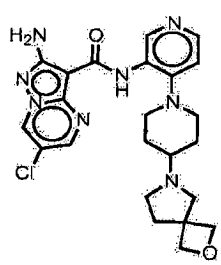

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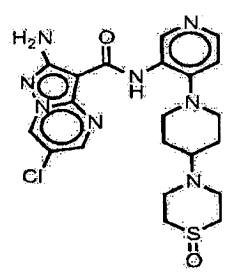

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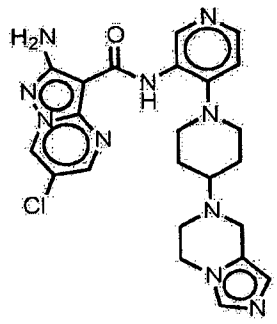

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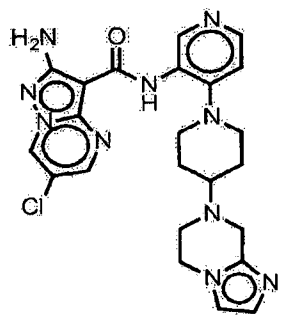

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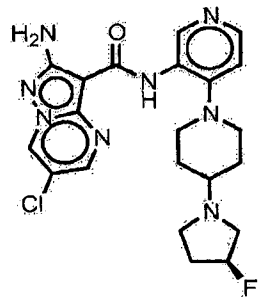

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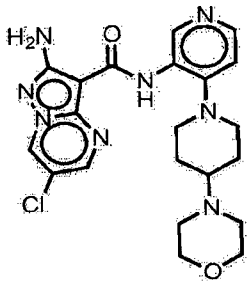

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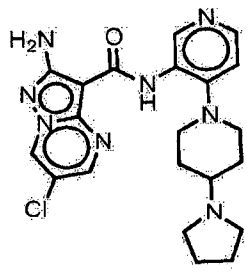

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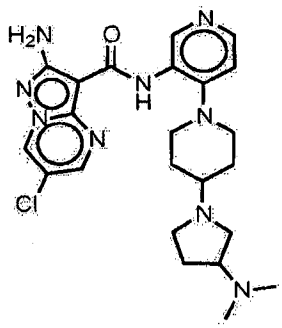

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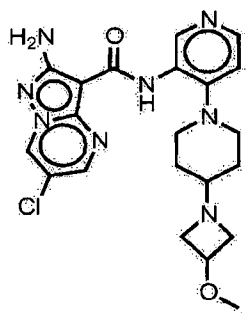

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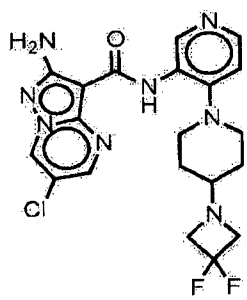

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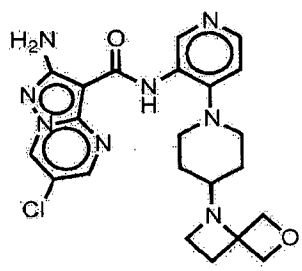

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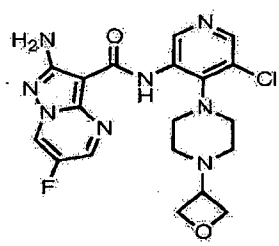

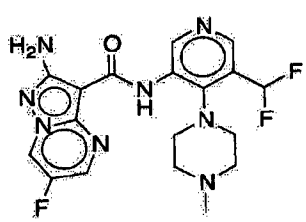

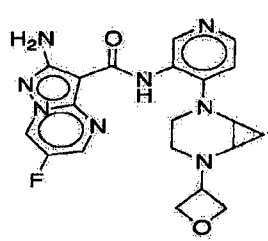

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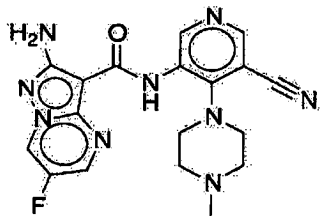

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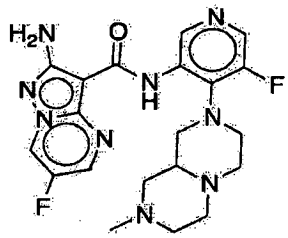

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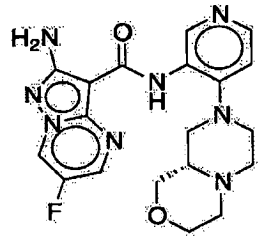

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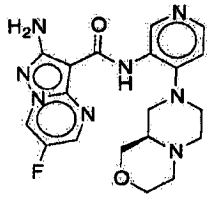

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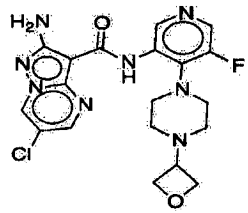

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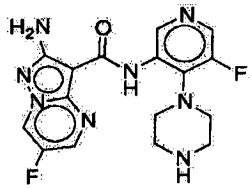

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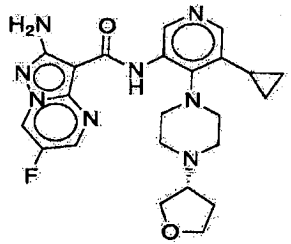

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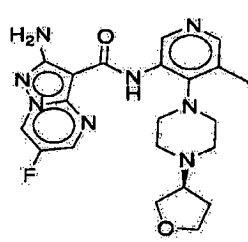
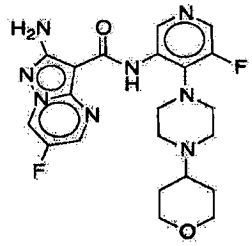


I-N-118

I-N-119

I-N-120

I-N-121



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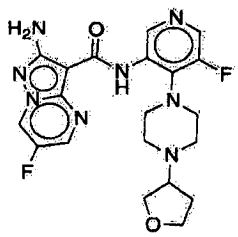

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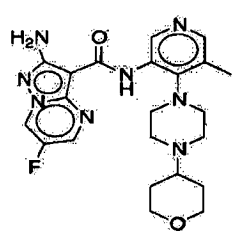

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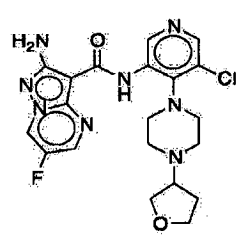

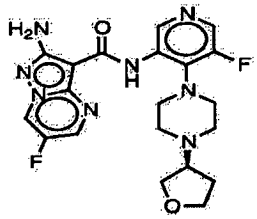

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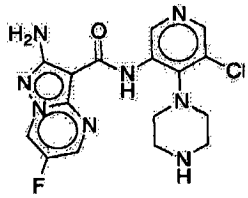

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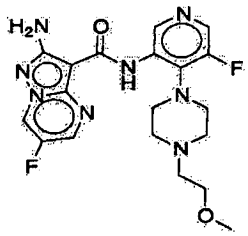

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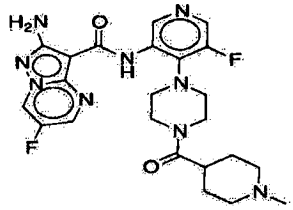

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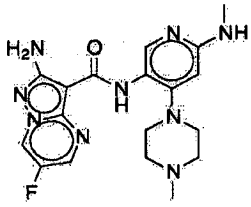

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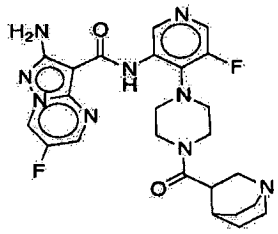

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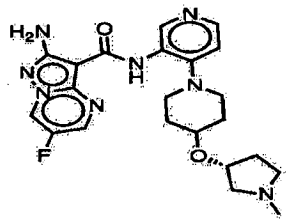

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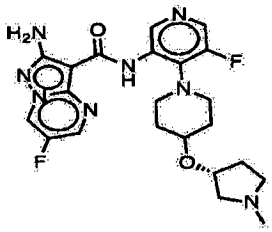

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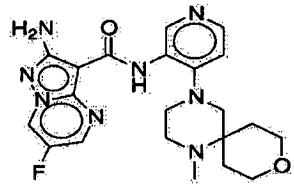

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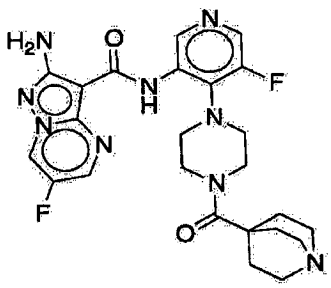

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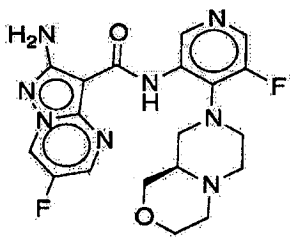

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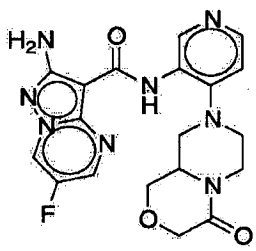

I-N-136

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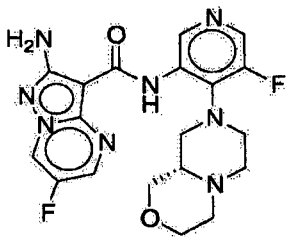

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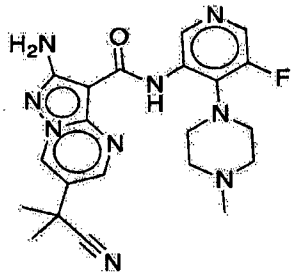

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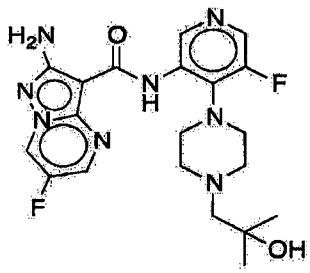

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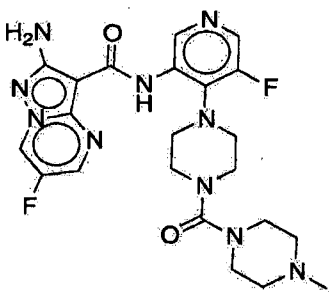

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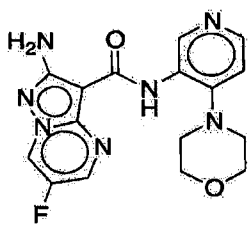
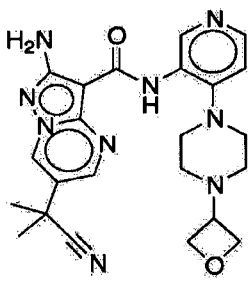


I-N-141



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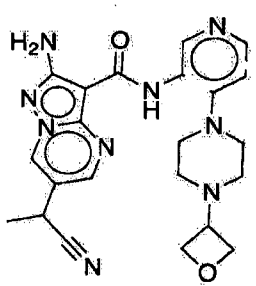

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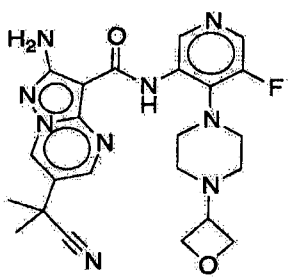

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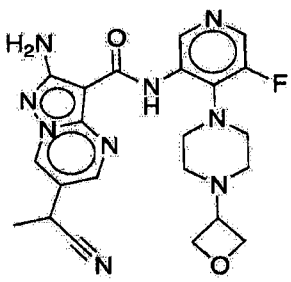

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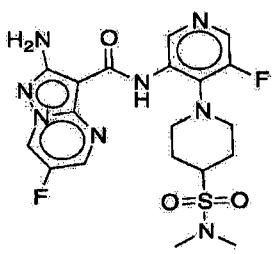

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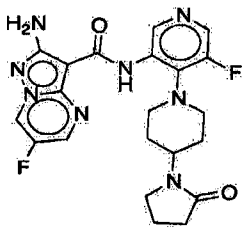

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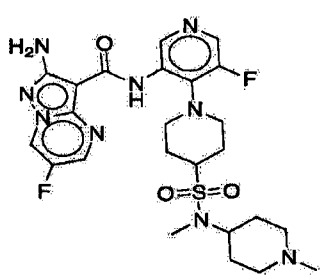

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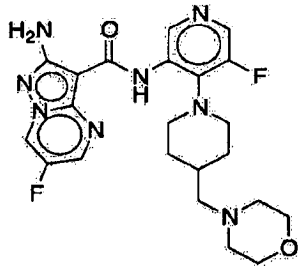

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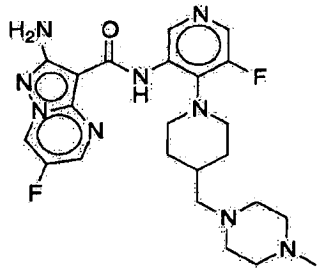

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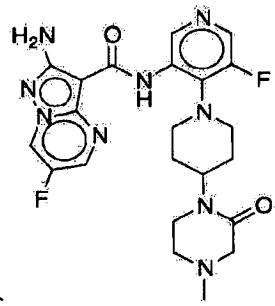

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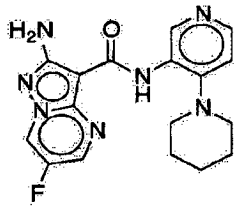

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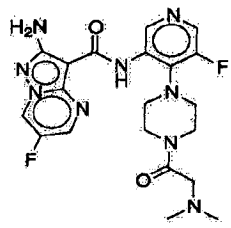

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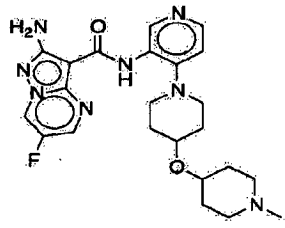

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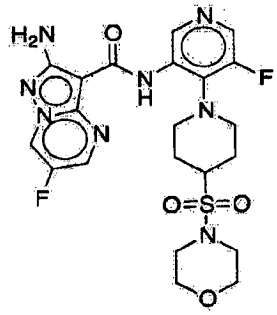

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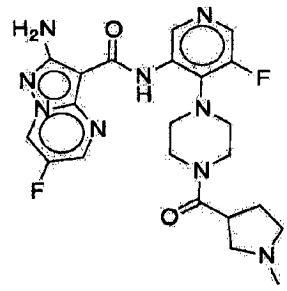

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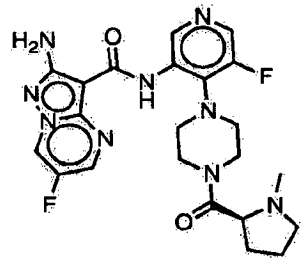

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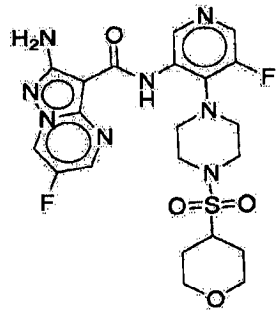

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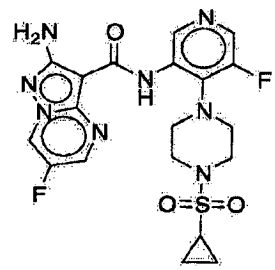

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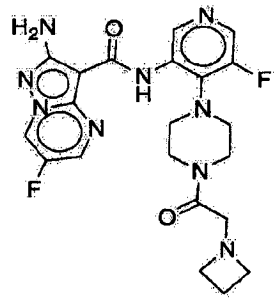

I-N-160

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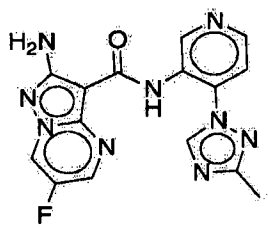

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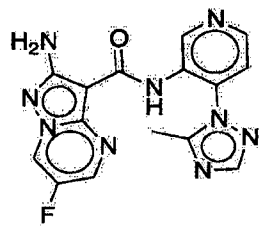

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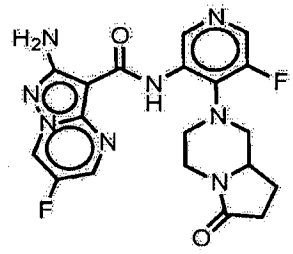

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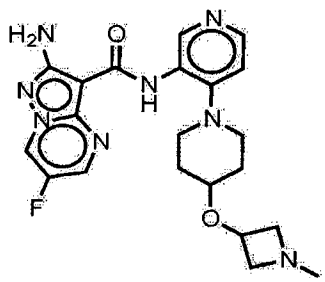

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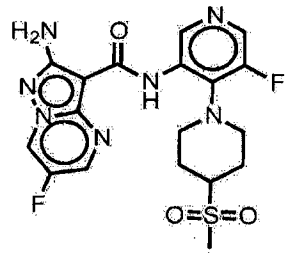

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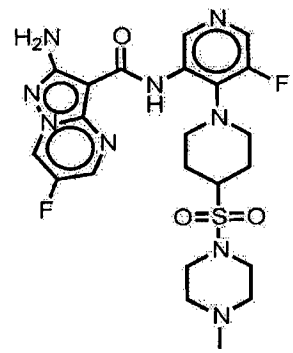

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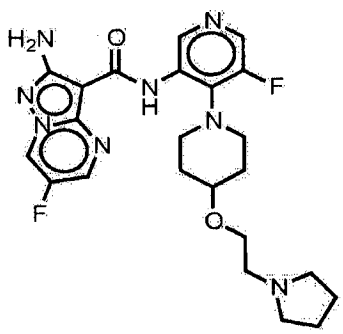

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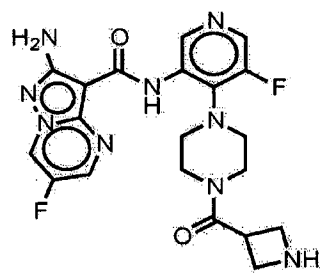

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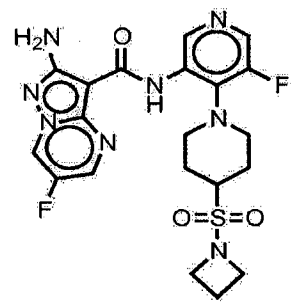

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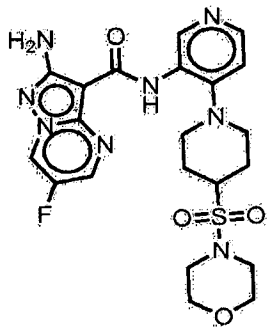

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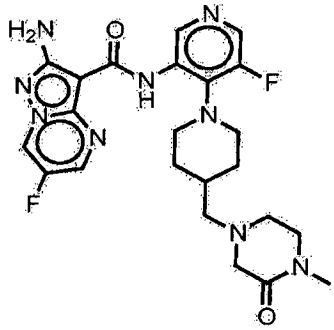

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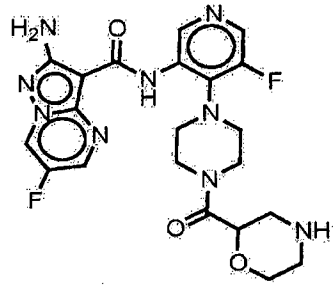

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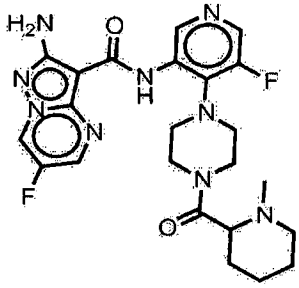

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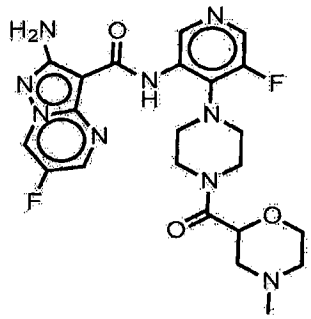

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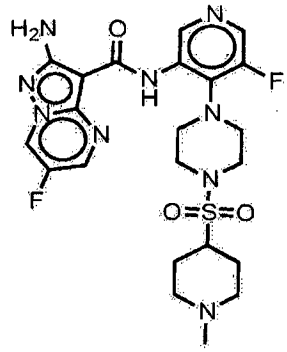

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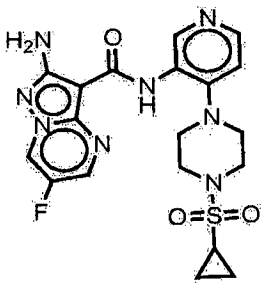

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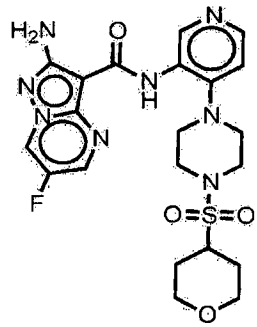

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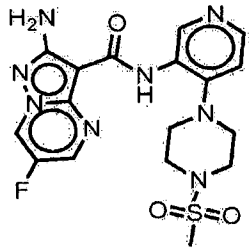

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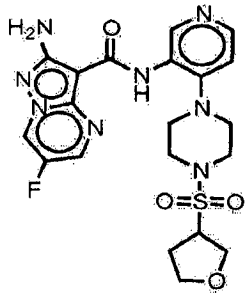

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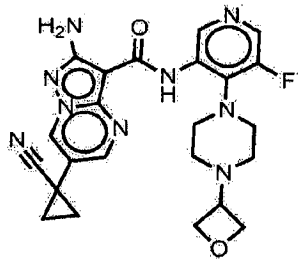

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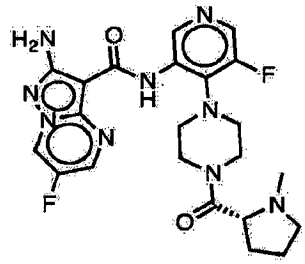

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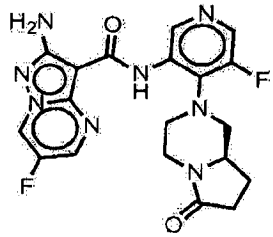

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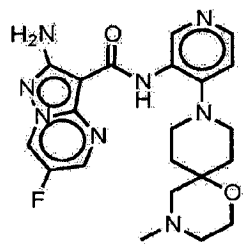

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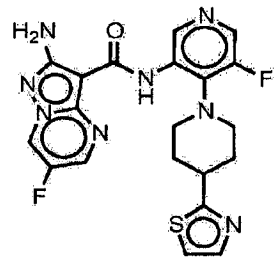

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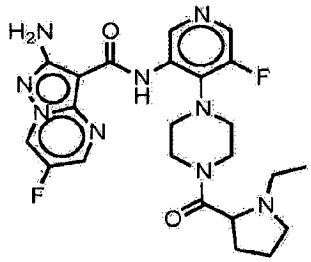

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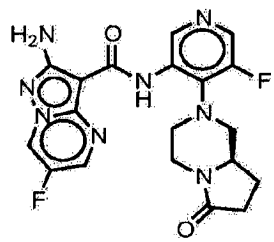

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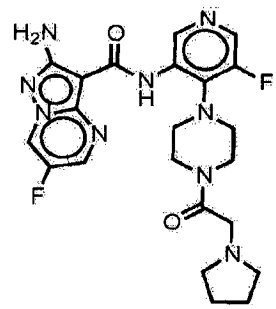

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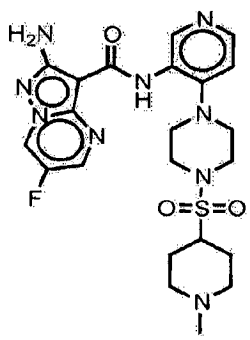

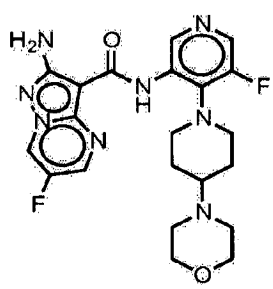

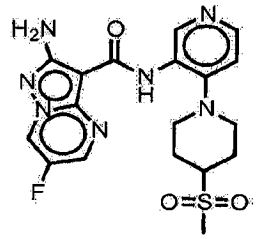

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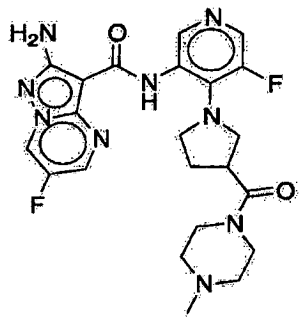

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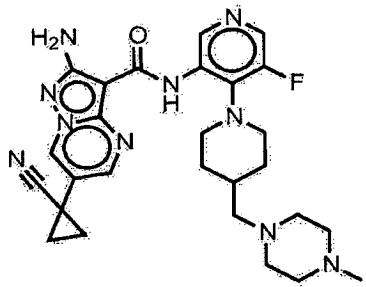

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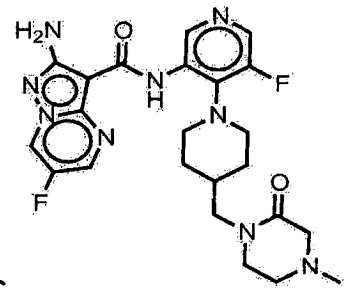

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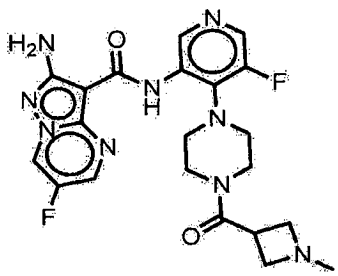

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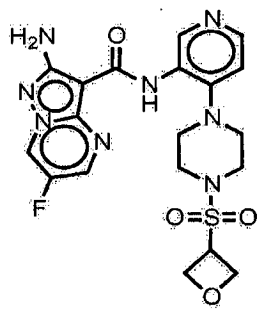
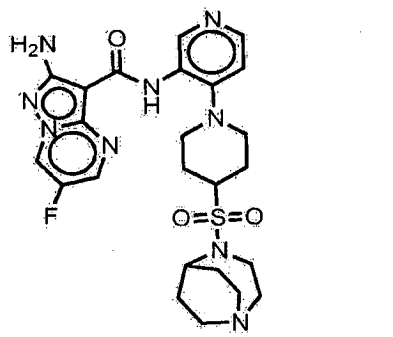


I-N-193



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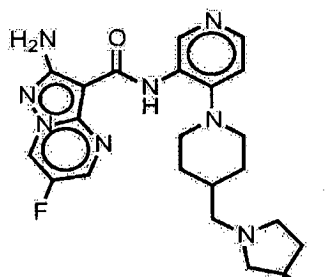

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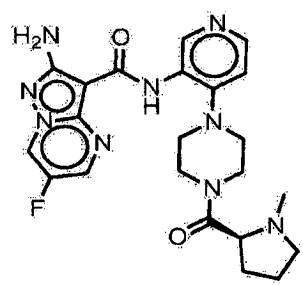
I-N-196

I-N-197

I-N-198



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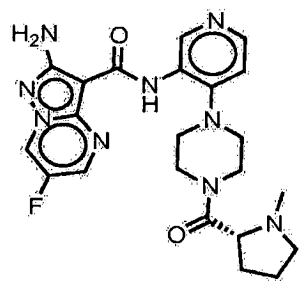

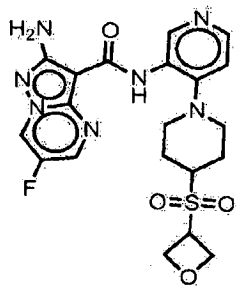

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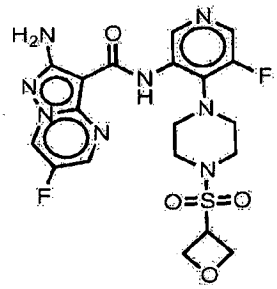

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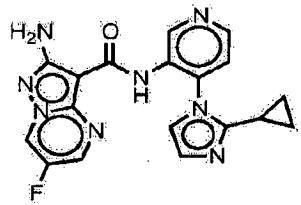

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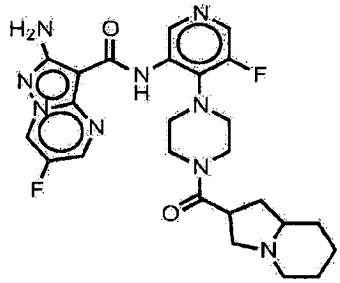

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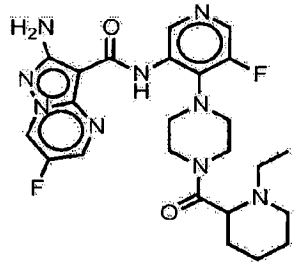

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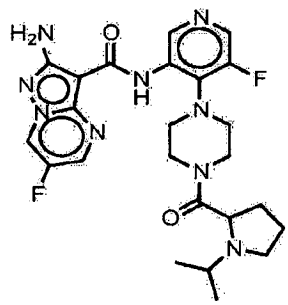

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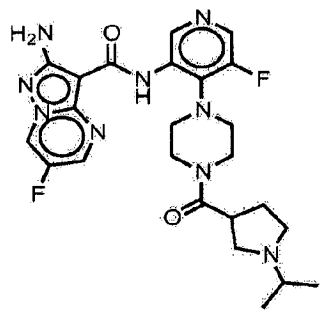

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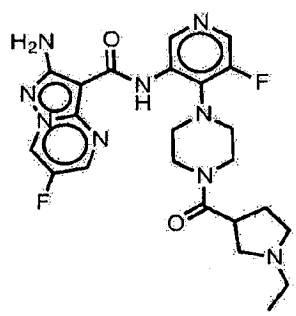

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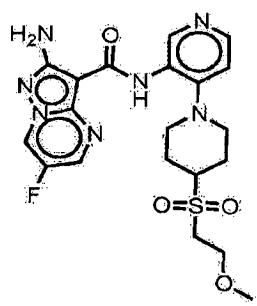

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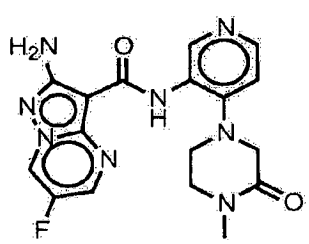

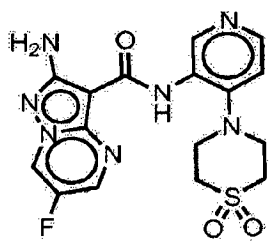

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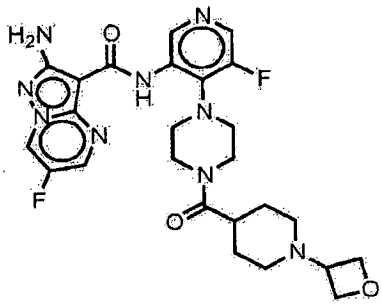

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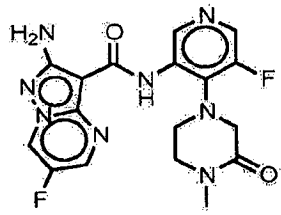

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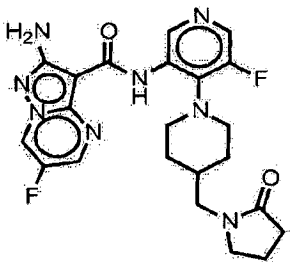

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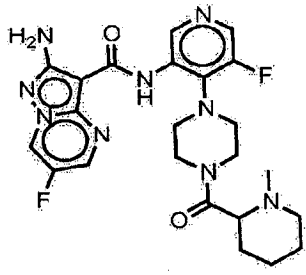

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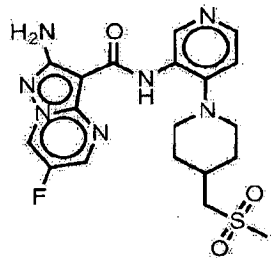

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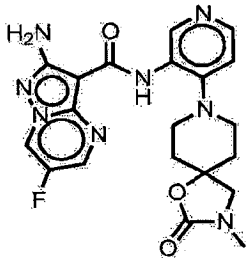

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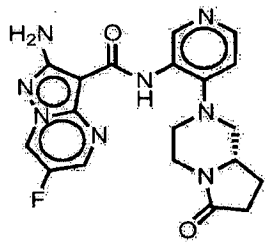

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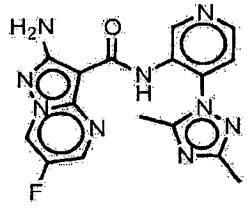

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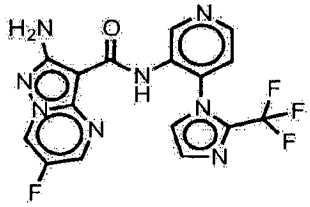

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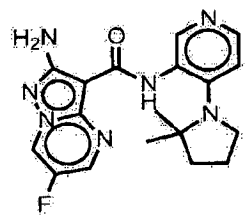

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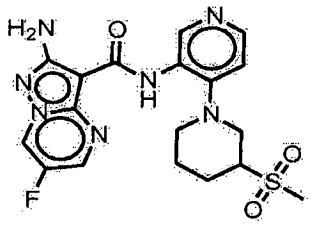

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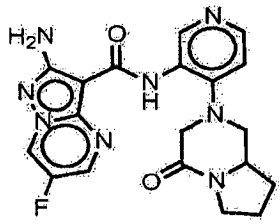

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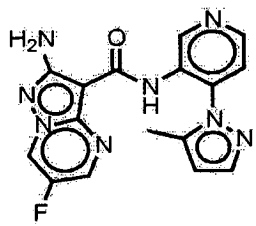

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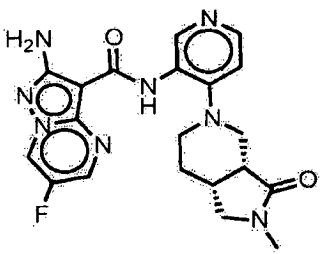

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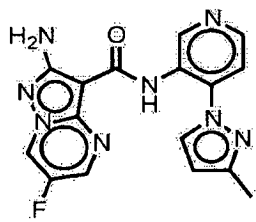

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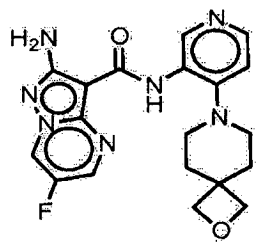

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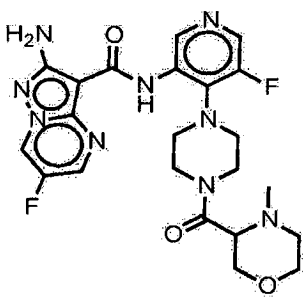

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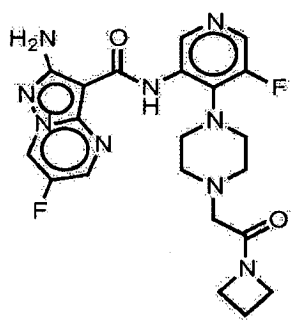

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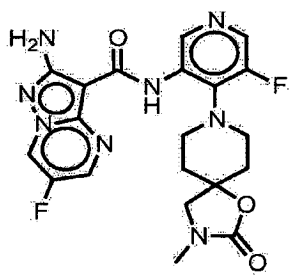

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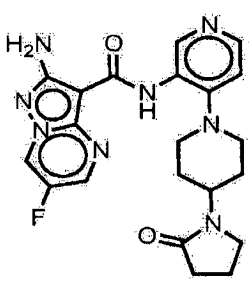

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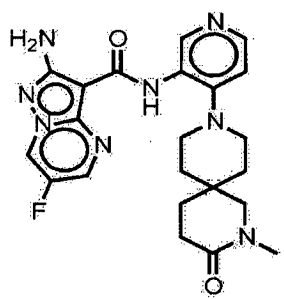

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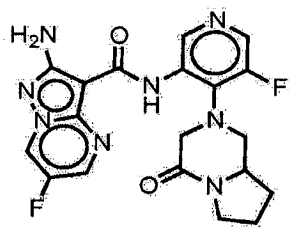

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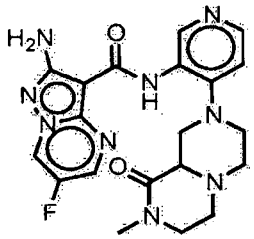

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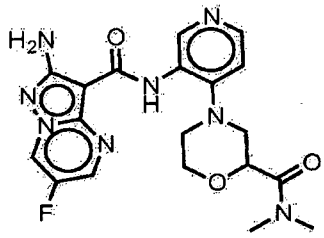

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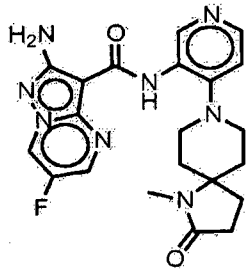

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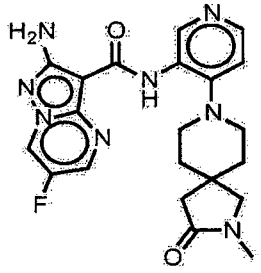

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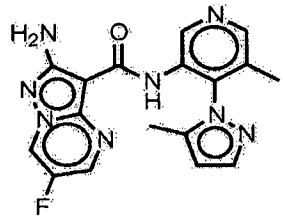

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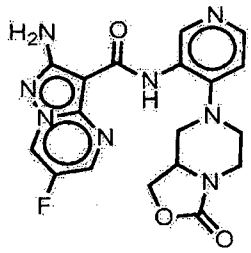

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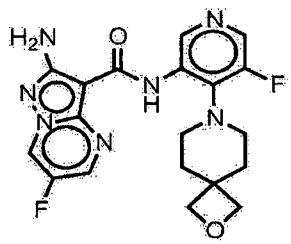

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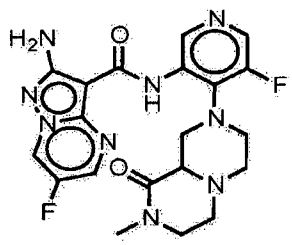

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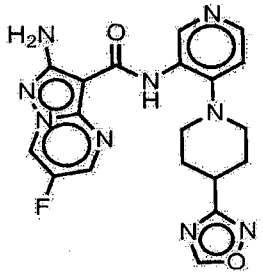

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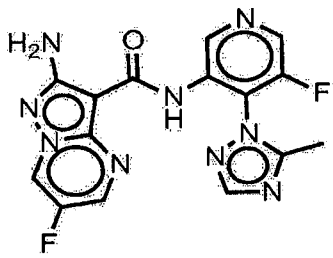
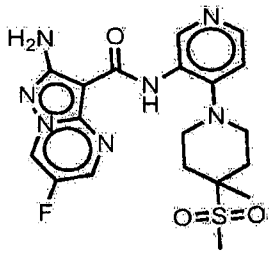


I-N-242

打印ID?619020 Pg 43



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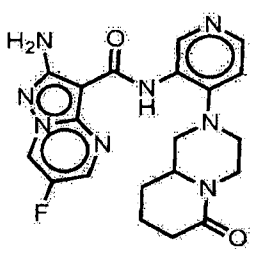

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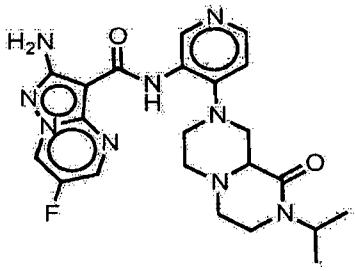

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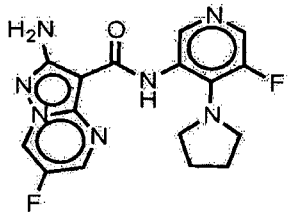

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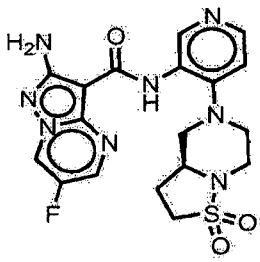

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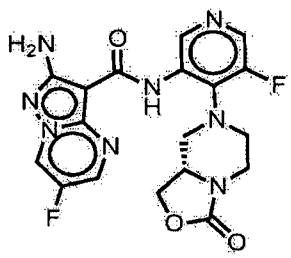

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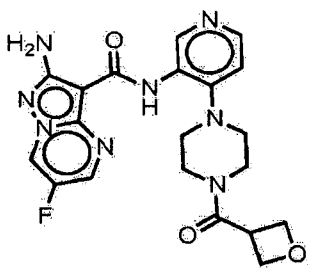
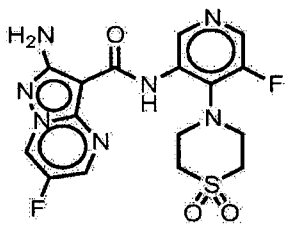
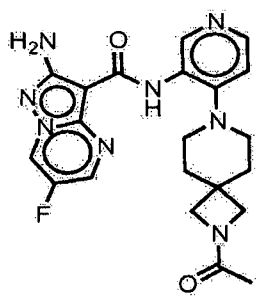


I-N-249



I-N-250



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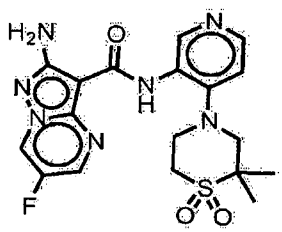

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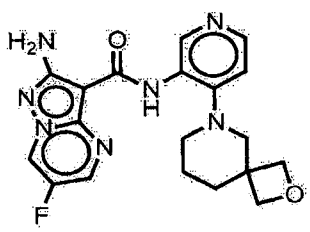

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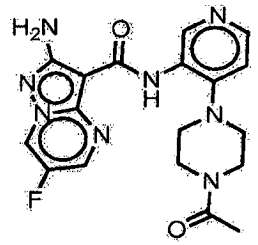

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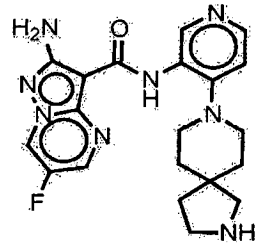

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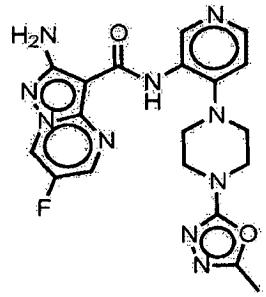

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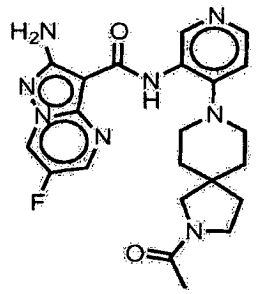

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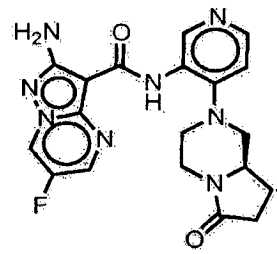

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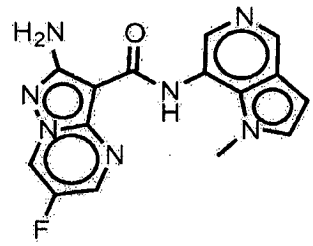

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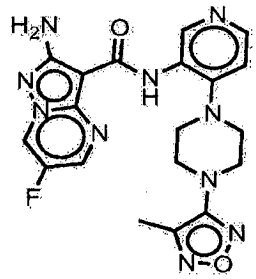

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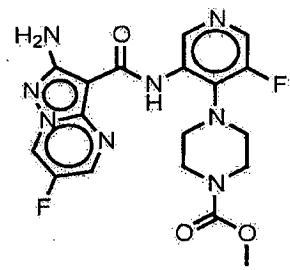

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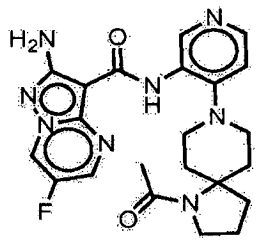

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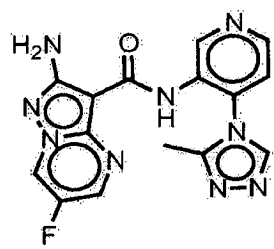

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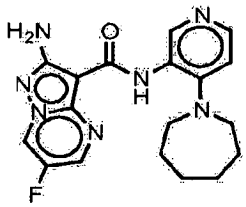

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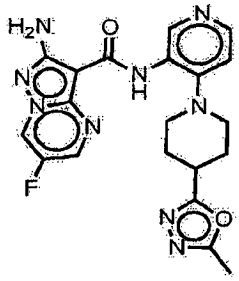

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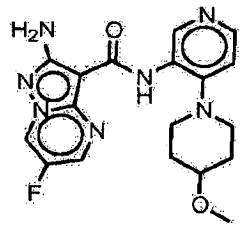

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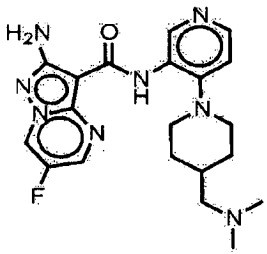

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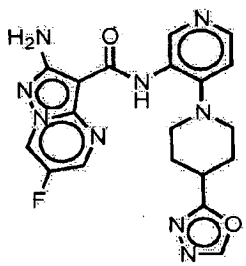

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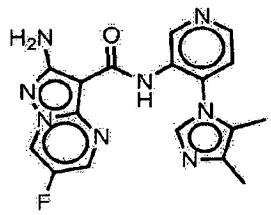

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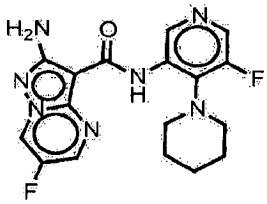

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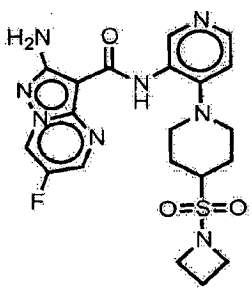

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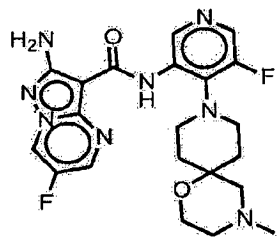

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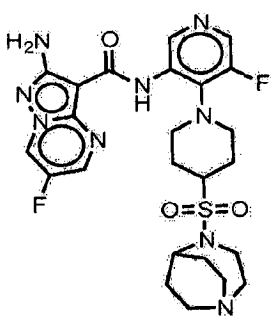

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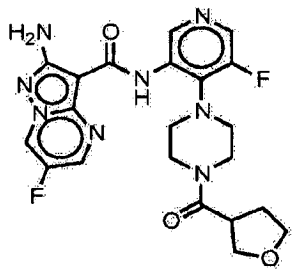

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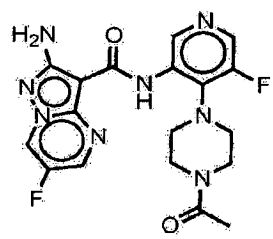

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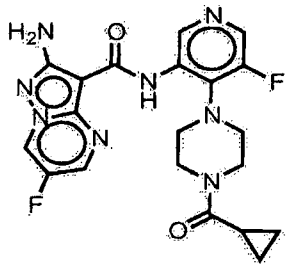
打印ID?619020 Pg 46



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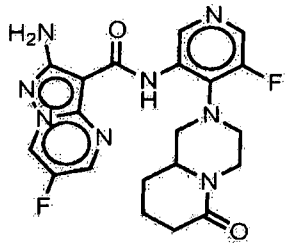

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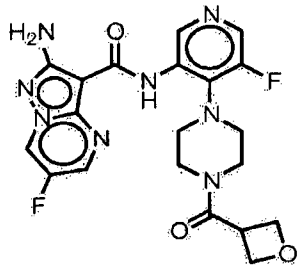

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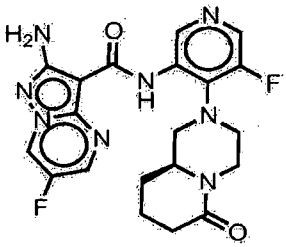

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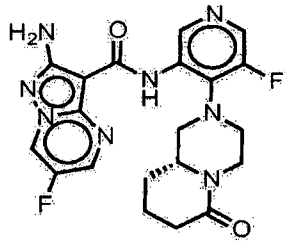

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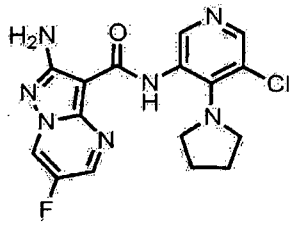

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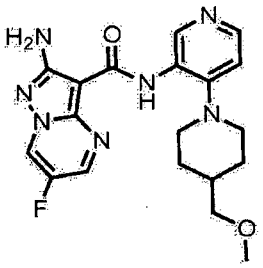

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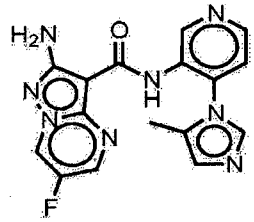

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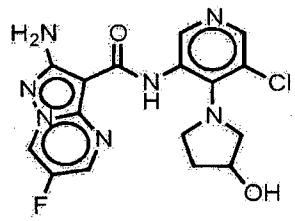

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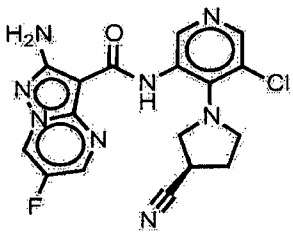

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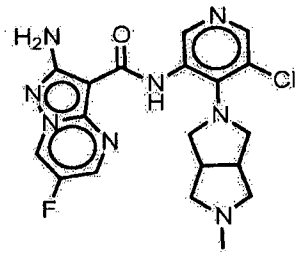
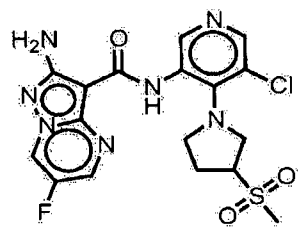
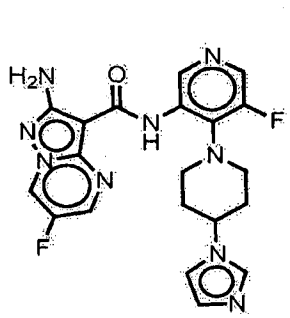


I-N-286

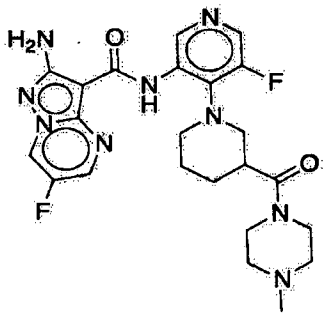


I-N-287

打印ID?619020 Pg 47



I-N-288



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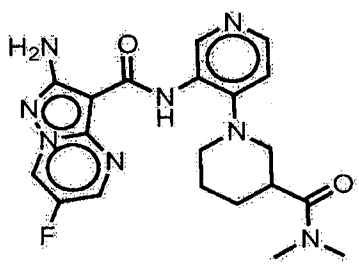
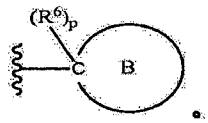


I-N-290。

112. 权利要求 34 的化合物，其中 R^4 是：



113. 权利要求 112 的化合物，其中 p 是 1。

114. 权利要求 113 的化合物，其中环 B 是具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元脂环族环或杂环。

115. 权利要求 114 的化合物，其中环 B 独立地选自环丙基、环丁基、环戊基、环己基、环庚基、吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1, 3-噁嗪烷基、1, 3-噻嗪烷基、二氢吡啶基、二氢咪唑基、1, 3-四氢嘧啶基、二氢嘧啶基、1, 4-二氮杂庚环基、1, 4-氧杂氮杂庚环基、1, 4-硫杂氮杂庚环基、1, 2, 3, 6-四氢吡啶和氮杂环丁烷基。

116. 权利要求 115 的化合物，其中环 B 是哌啶基。

117. 权利要求 112-116 任一项的化合物，其中 J^Q 是 -C(O)- 或 C_{1-4} 烷基。

118. 权利要求 112-116 任一项的化合物，其中 J^Q 是 Q^2。

119. 权利要求 118 的化合物，其中 Q^2 独立地选自氧杂环丁烷基、四氢吡喃基、四氢呋喃基、环丙基、氮杂环丁烷基、吡咯烷基、哌嗪基、哌啶基、环丁基、硫代吗啉基或吗啉基。

120. 权利要求 119 的化合物，其中 Q^2 是氧杂环丁烷基。

121. 权利要求 112 的化合物，其中 p 是 0.

122. 权利要求 121 的化合物，其中环 B 独立地选自苯基、吡啶基、吡嗪基、嘧啶基、四氢吡啶基、哒嗪基或吡唑基。

123. 权利要求 122 的化合物，其中环 B 独立地选自苯基或吡啶基。

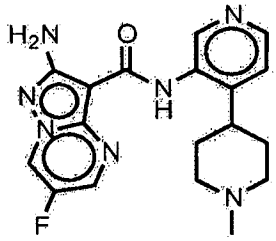
124. 权利要求 34 的化合物，其中 R^4 是 $-CH_2-R^7$。

125. 权利要求 124 的化合物，其中 R^7 是 H。

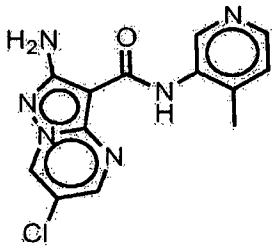
126. 权利要求 22-29 任一项的化合物，其中 R^3 和 R^4 与它们所连接的原子一起形成具有 0-2 个选自氧的杂原子的 5-6 元非芳族环。

127. 权利要求 124 的化合物，其中 J^Z 独立地选自→ O 或 C_{1-4} 烷基。

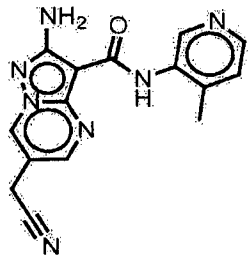
128. 权利要求 112-127 任一项的化合物，其独立地选自：



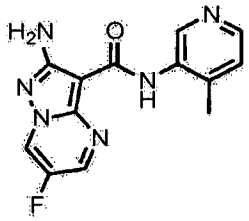
I-C-1



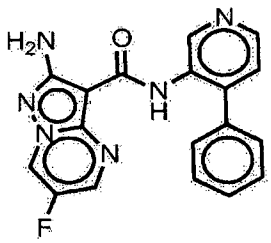
I-C-2



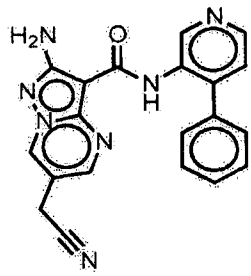
I-C-3



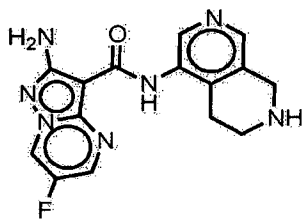
I-C-4



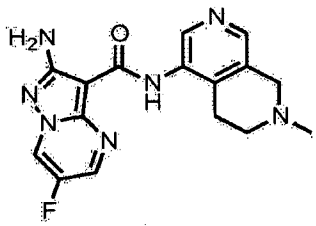
I-C-5



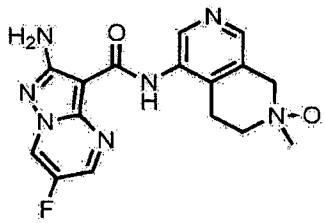
I-C-6



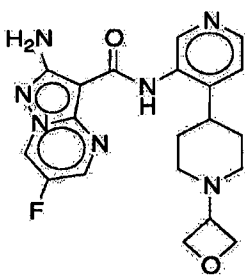
I-C-7



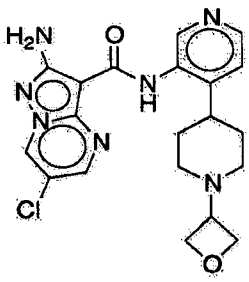
I-C-8



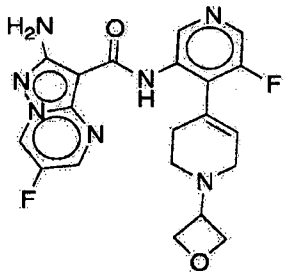
I-C-9



I-C-10

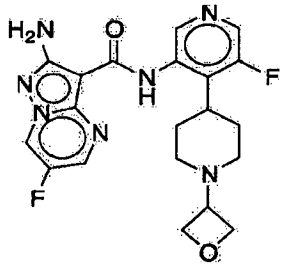


I-C-11

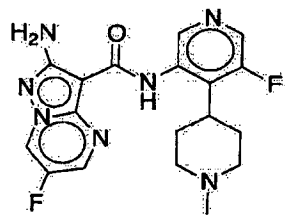


I-C-12

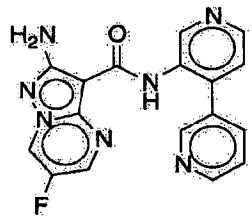
打印ID?619020 Pg 49



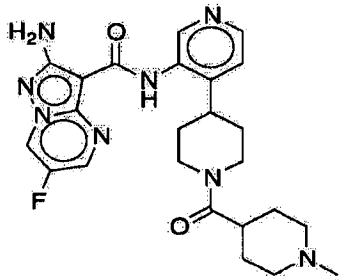
I-C-13



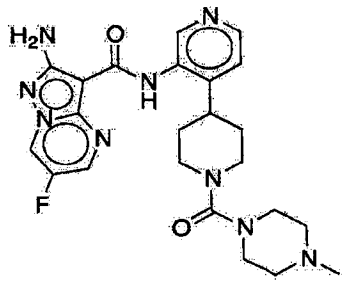
I-C-14



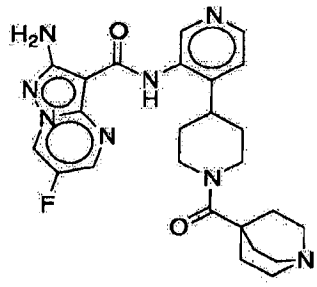
I-C-15



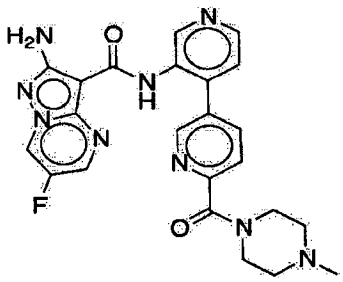
I-C-16



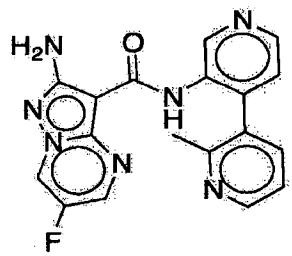
I-C-17



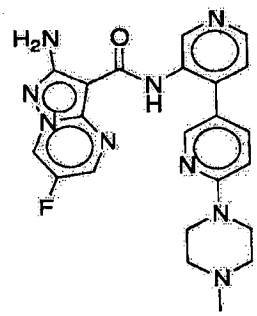
I-C-18



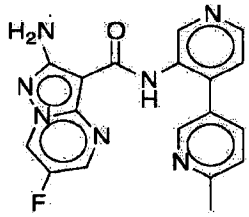
I-C-19



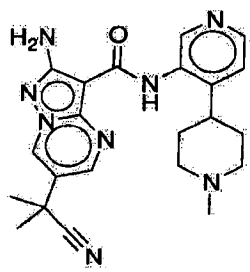
I-C-20



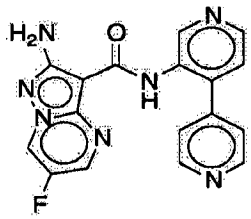
I-C-21



I-C-22

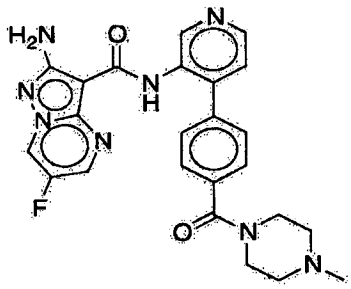


I-C-23

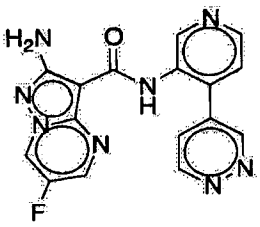


I-C-24

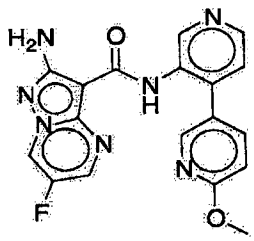
打印ID?619020 Pg 50



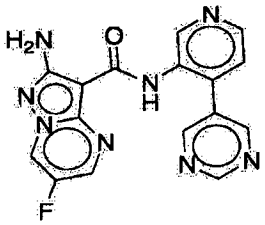
I-C-25



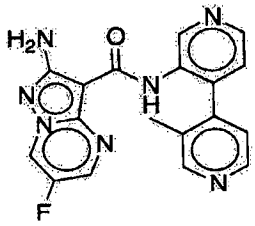
I-C-26



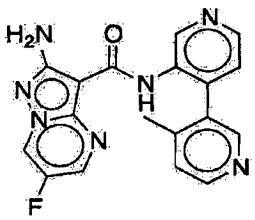
I-C-27



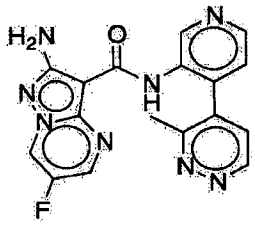
I-C-28



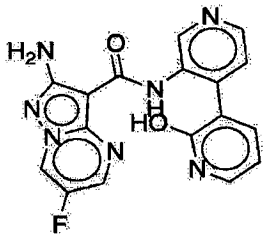
I-C-29



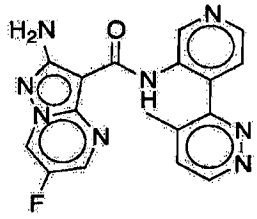
I-C-30



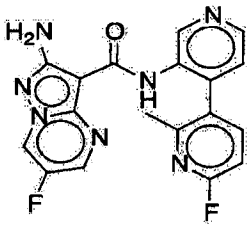
I-C-31



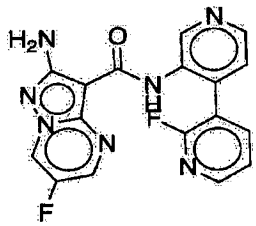
I-C-32



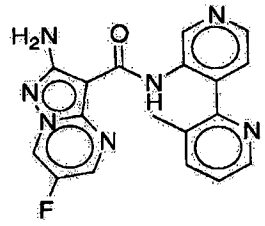
I-C-33



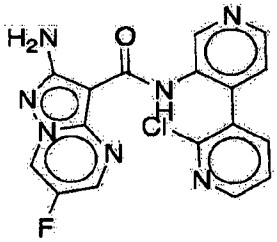
I-C-34



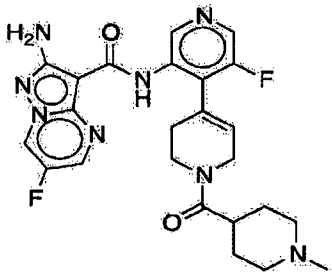
I-C-35



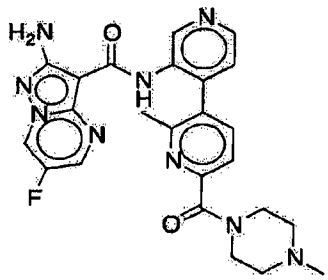
I-C-36



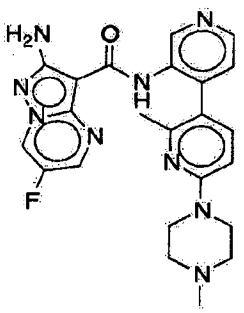
I-C-37



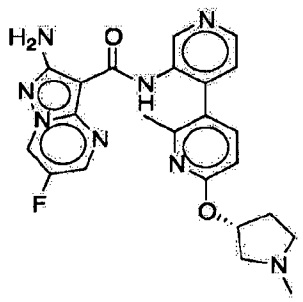
I-C-38



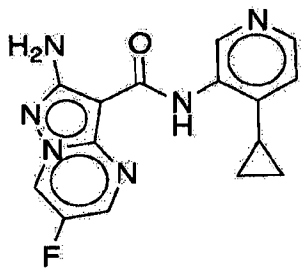
I-C-39



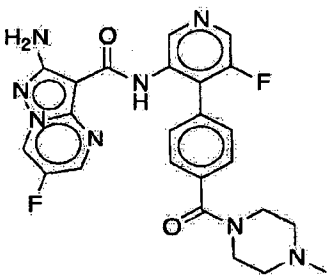
I-C-40



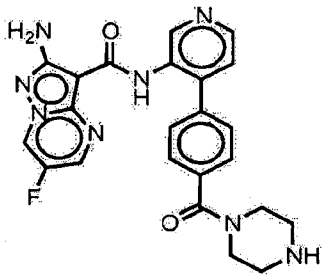
I-C-41



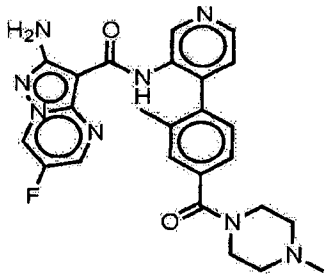
I-C-42



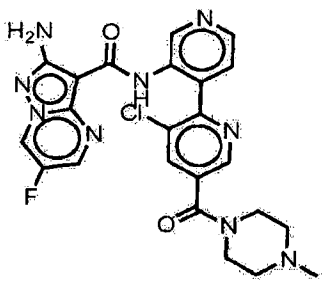
I-C-43



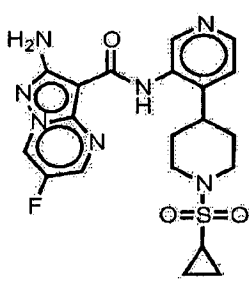
I-C-44



I-C-45

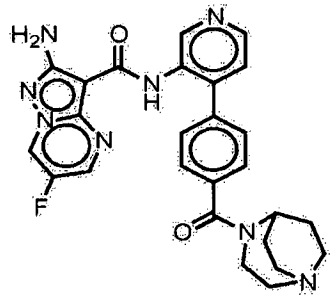


I-C-46

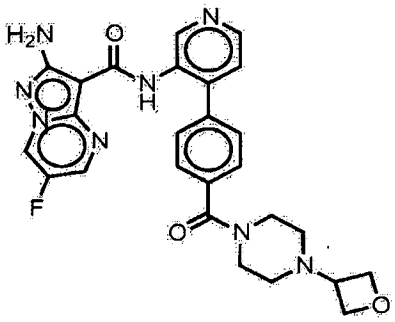


I-C-47

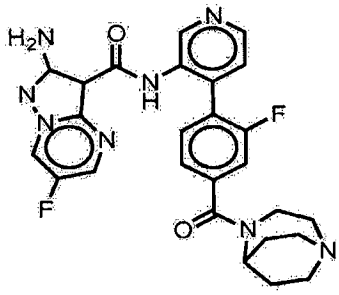
打印ID?619020 Pg 52



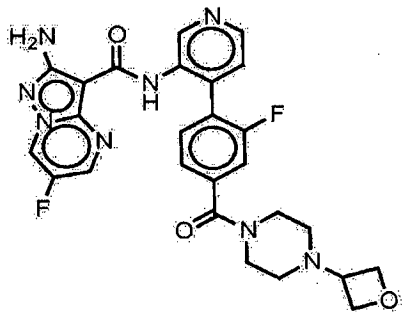
I-C-48



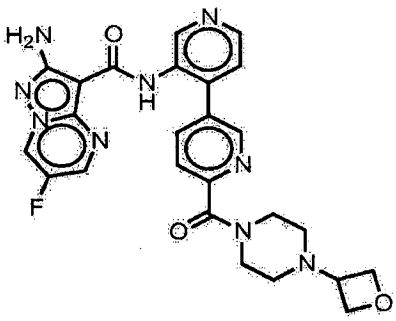
I-C-49



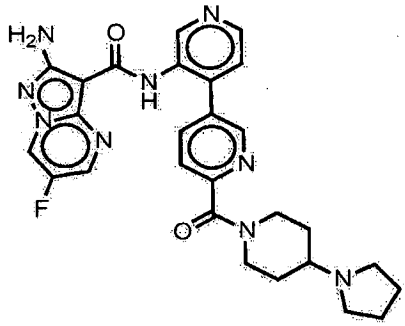
I-C-50



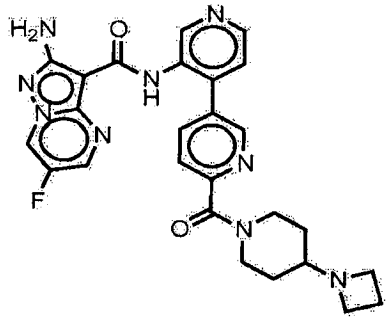
I-C-51



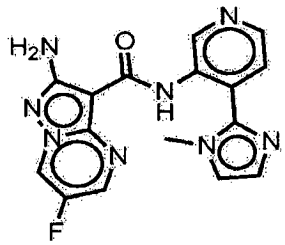
I-C-52



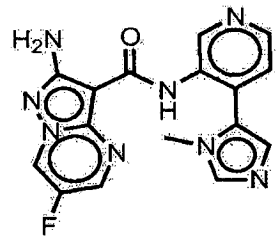
I-C-53



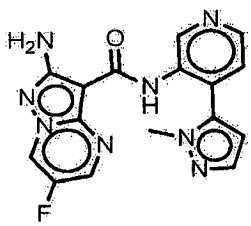
I-C-54



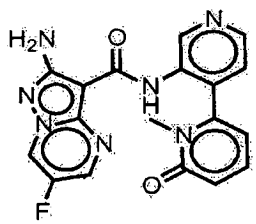
I-C-55



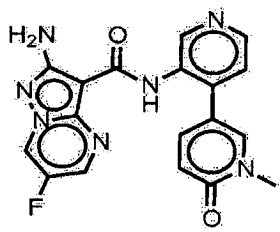
I-C-56



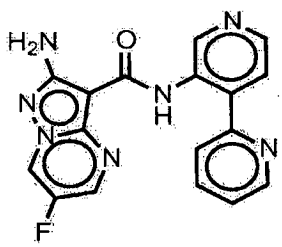
I-C-57



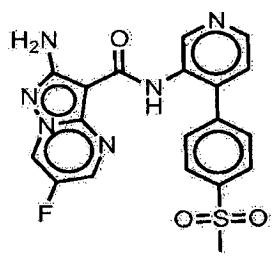
I-C-58



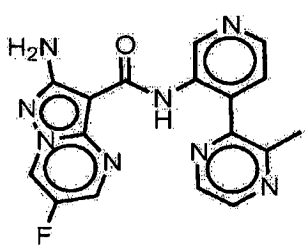
I-C-59



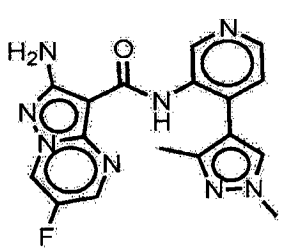
I-C-60



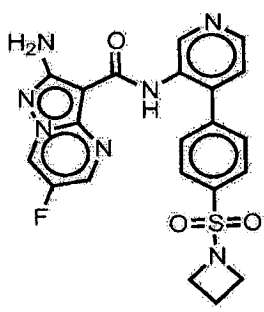
I-C-61



I-C-62

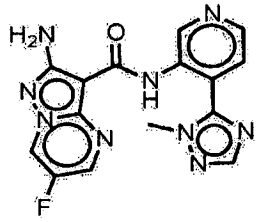


I-C-63



I-C-64

打印ID?619020 Pg 54



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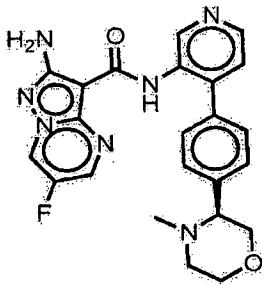
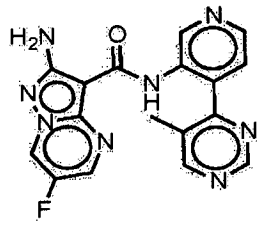
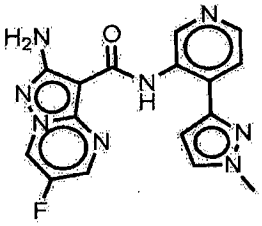


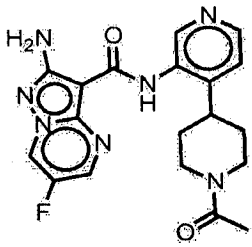
I-C-66



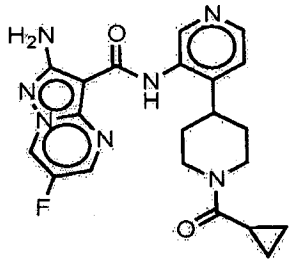
I-C-67



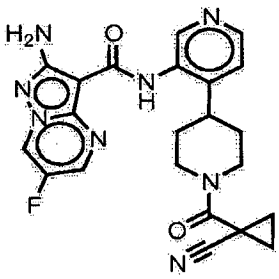
I-C-68



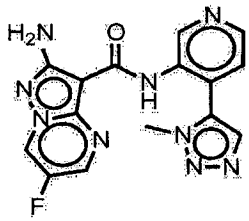
I-C-69



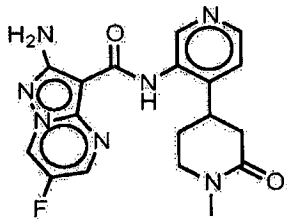
I-C-70



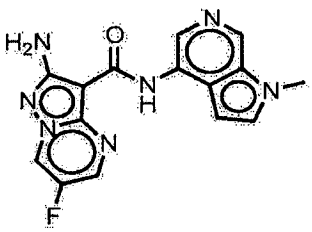
I-C-71



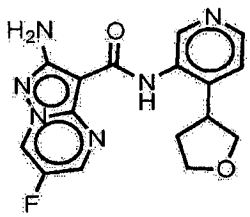
I-C-72



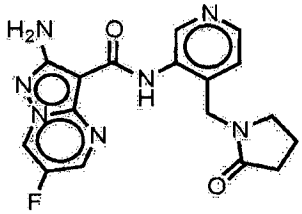
I-C-73



I-C-74

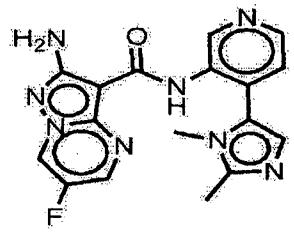


I-C-75

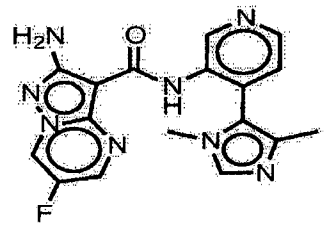


I-C-76

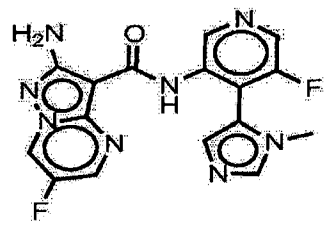
打印ID?619020 Pg 55



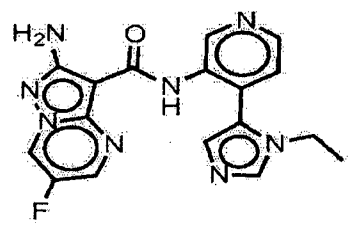
I-C-77



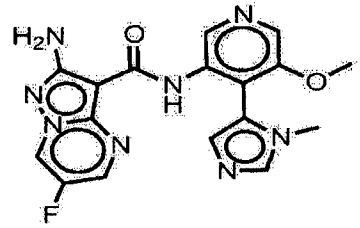
I-C-78



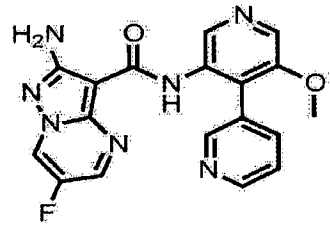
I-C-79



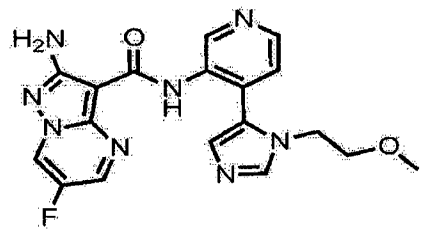
I-C-80



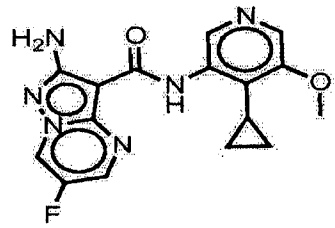
I-C-81



I-C-82

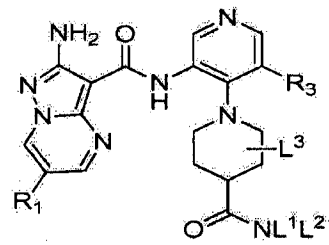


I-C-83



I-C-84。

129. 具有式 I-B 的化合物：



I-B

或其药学上可接受的盐或前药，其中：

R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^3独立地选自 H；氘；氟；任选地被 1-3 次出现的卤素的取代 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

打印ID?619020 Pg 56

L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

J^G独立地选自卤素；$-N(R^\circ)_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；J^G各自任选地被 0-2 次出现的 J^K取代。

同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

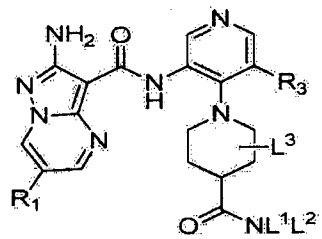
J^K是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

L^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

n 是 0、1 或 2；且

R 和 R° 是 H 或 C_{1-4}烷基。

130. 具有式 I-B 的化合物：



I-B

或其药学上可接受的盐或前药，其中：

R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^1各

打印ID?619020 Pg 57

自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

L^3是 H；C_{1-3}脂族基团；或 CN；

环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

J^G独立地选自卤素；-CN；$-N(R^\circ)_2$；=O；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；J^G各自任选地被 0-2 次出现的 J^K取代。

同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

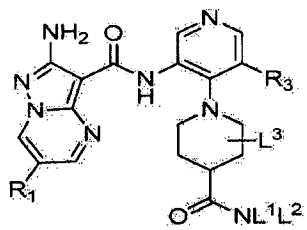
2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^K是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

n 是 0、1 或 2；且

R 和 R° 是 H 或 C_{1-4}烷基。

131. 具有式 I-B 的化合物：



I-B

或其药学上可接受的盐或前药，其中：

R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1独立地选自 H 或 C_{1-2}烷基；或

2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，

打印ID?619020 Pg 58

其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；L^2 各自任选地被 C_{1-4} 脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

L^1 和 L^2 与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G 取代；

环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

J^G 独立地选自卤素；-CN；$-N(R^\circ)_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4} 烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；J^G 各自任选地被 0-2 次出现的 J^K 取代。

同一原子上的 2 次出现的 J^G 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

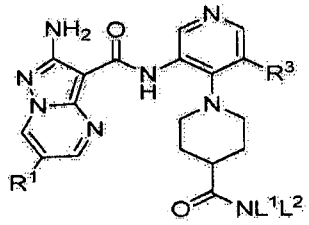
2 次出现的 J^G 与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^K 是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

n 是 0、1 或 2；且

R 和 R° 是 H 或 C_{1-4} 烷基。

132. 式 I-B 的化合物：



I-B

或其药学上可接受的盐或前药，其中：

R^1 独立地选自氟、氯或 $-C(J^1)_2CN$；

J^1 独立地选自 H 或 C_{1-2} 烷基；或

2 次出现的 J^1 与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^3 独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4} 烷基；C_{3-4} 环烷基；-CN；或 C_{1-3} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；

L^1 是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；L^1 各自任选地被 C_{1-4} 脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

L^2 是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$- 替代；L^2 各自任选地被 C_{1-4} 脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

L^1 和 L^2 与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G 取代；

打印ID7619020 Pg 59

环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

J^G 独立地选自卤素；-N(R°)$_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4} 烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$ 替代；J^G 各自任选地被 0-2 次出现的 J^K 取代。

同一原子上的 2 次出现的 J^G 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

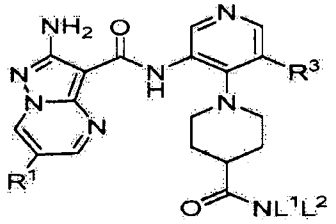
2 次出现的 J^G 与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

J^K 是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

n 是 0、1 或 2；且

R 和 R° 是 H 或 C_{1-4} 烷基。

133. 式 I-B 的化合物：



I-B

或其药学上可接受的盐或前药，其中：

R^1 独立地选自氟、氯或 -C(J^1)$_2$CN；

J^1 独立地选自 H 或 C_{1-2} 烷基；或

2 次出现的 J^1 与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

R^3 独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4} 烷基；C_{3-4} 环烷基；或 -CN；

L^1 是任选取代的 C_{1-6} 脂族基团；

L^2 是任选取代的 C_{1-6} 脂族基团；或

L^1 和 L^2 与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G 取代；

环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和或部分不饱和双环；

J^G 独立地选自 C_{1-4} 烷基、-N(R°)$_2$ 或 3-5 元碳环基；或

2 次出现的 J^G 与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；且

R° 是 H 或 C_{1-4} 烷基。

134. 权利要求 129-132 任一项的化合物，其中 R^1 是氟。

135. 权利要求 129-132 任一项的化合物，其中 R^1 是 $-CH_2CN$。

136. 权利要求 129-132 任一项的化合物，其中 R^1 是氯。

137. 权利要求 129-135 任一项的化合物，其中 R^3 独立地选自 H、氯、氟、环丙基或 C_{1-4} 烷基。

138. 权利要求 137 的化合物，其中 R^3 独立地选自 H、氯或氟。

打印ID?619020 Pg 60

139. 权利要求 137 的化合物，其中 R^3 是 H。

140. 权利要求 137 的化合物，其中 R^3 是氯。

141. 权利要求 137 的化合物，其中 R^3 是氟。

142. 权利要求 138-141 任一项的化合物，其中 L^1 和 L^2 是 H；-(C_{1-3}烷基)O(C_{1-2}烷基)；-(C_{1-3}烷基)N(C_{1-2}烷基)$_2$；C_{1-4}烷基；氮杂环丁烷基；哌啶基；氧杂环丁烷基；或吡咯烷基。

143. 权利要求 134-141 任一项的化合物，其中 L^1 和 L^2 与它们所连接的氮一起形成环 D。

144. 权利要求 143 的化合物，其中环 D 是 3-7 元杂环基环，具有 1-2 个选自氧、氮或硫的杂原子。

145. 权利要求 144 的化合物，其中环 D 独立地选自哌嗪基、哌啶基、吗啉基、四氢吡喃基、氮杂环丁烷基、吡咯烷基或 1,4- 二氮杂庚环基。

146. 权利要求 145 的化合物，其中环 D 是哌嗪基、哌啶基、1,4- 二氮杂庚环基、吡咯烷基或氮杂环丁烷基。

147. 权利要求 146 的化合物，其中环 D 是哌嗪基或哌啶基。

148. 权利要求 144 的化合物，其中环 D 是具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和或部分不饱和双环。

149. 权利要求 148 的化合物，其中环 D 是八氢吡咯并 [1,2-a] 吡嗪或八氢吡咯并 [3,4-c] 吡咯。

150. 权利要求 144-149 任一项的化合物，其中 J^G 是卤素、C_{1-4}烷基、-O(C_{1-3}烷基)、C_{3-6}环烷基、3-6 元杂环基、-NH(C_{1-3}烷基)、-OH 或 -N(C_{1-4}烷基)$_2$。

151. 权利要求 150 的化合物，其中 J^G 是甲基、-N(C_{1-4}烷基)$_2$、乙基、-O(C_{1-3}烷基)、环丙基、氧杂环丁烷基、环丁基、吡咯烷基、哌啶基或氮杂环丁烷基。

152. 权利要求 151 的化合物，其中 J^G 是甲基、-O(C_{1-3}烷基)、氧杂环丁烷基、吡咯烷基、哌啶基或氮杂环丁烷基。

153. 权利要求 152 的化合物，其中 J^G 是甲基。

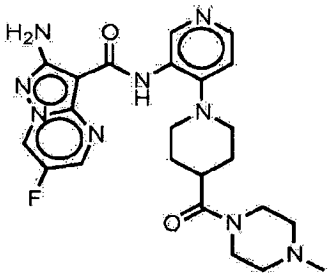
154. 权利要求 145-148 任一项的化合物，其中 2 次出现的 J^G 与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系。

155. 权利要求 154 的化合物，其中所述桥连环系是 1,4- 二氮杂双环 [3.2.2] 壬烷、1,4- 二氮杂双环 [3.2.1] 辛烷或 2,5- 二氮杂双环 [2.2.1] 庚烷。

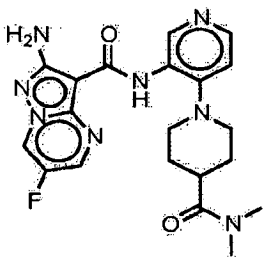
156. 权利要求 144-147 任一项的化合物，其中同一原子上的 2 次出现的 J^G 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环。

157. 权利要求 156 的化合物，其中由同一原子上的 2 次出现的 J^G 形成的环选自氧杂环丁烷基或环丙基。

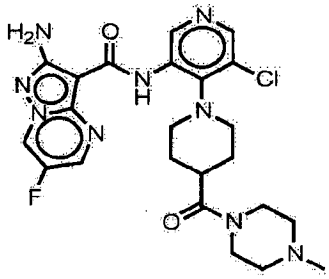
158. 权利要求 129-157 任一项的化合物，其独立地选自：



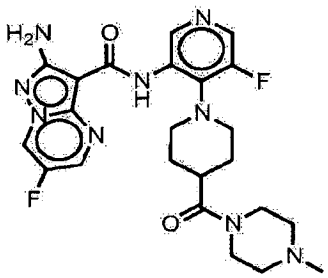
I-G-1



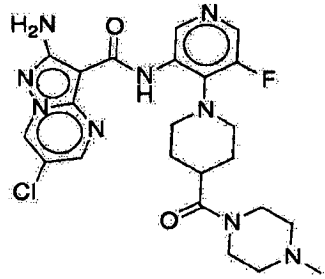
I-G-2



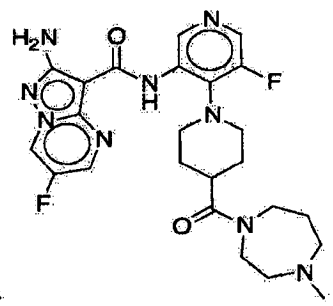
I-G-3



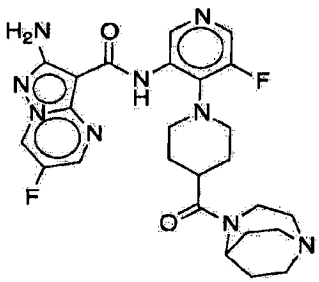
I-G-4



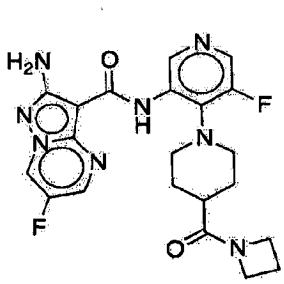
I-G-5



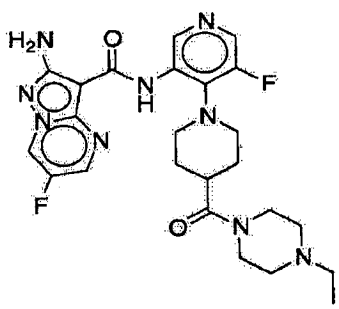
I-G-6



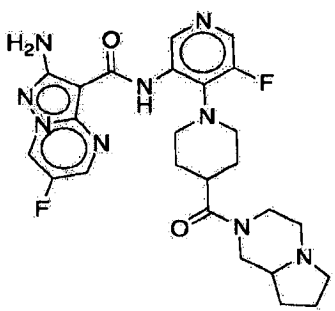
I-G-7

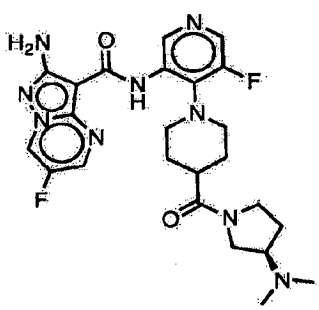


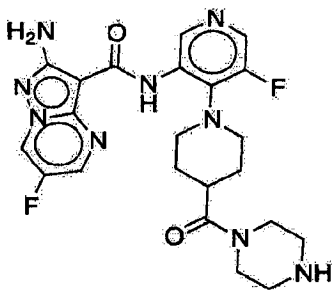
I-G-8



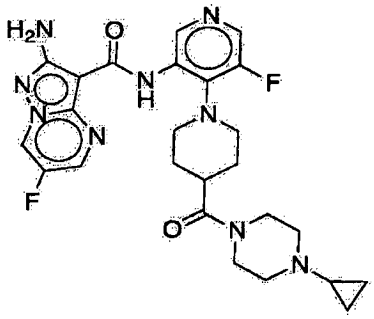
I-G-9



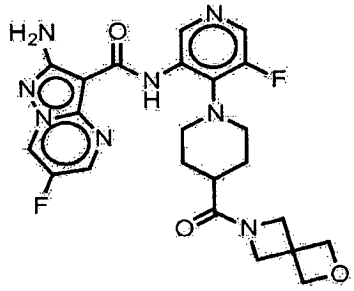




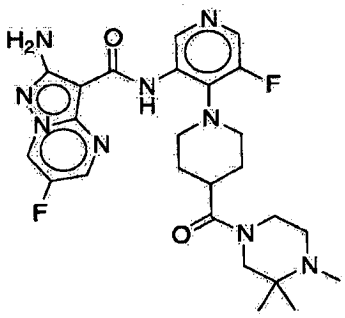
I-G-10



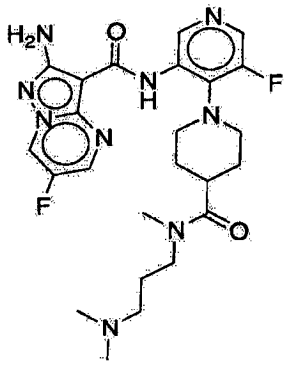
I-G-11



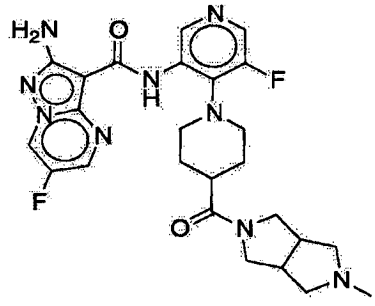
I-G-12



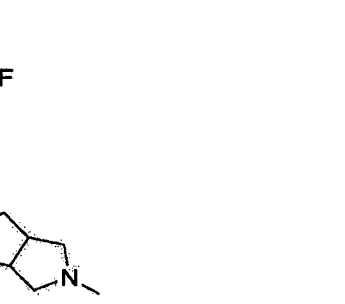
I-G-13



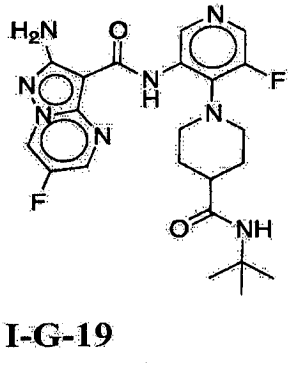
I-G-14



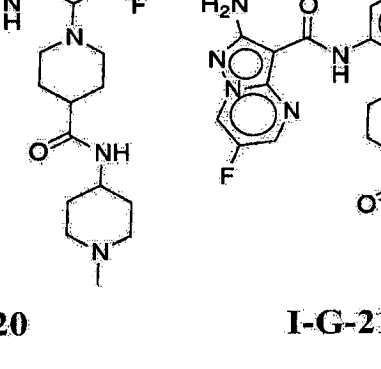
I-G-15



I-G-16

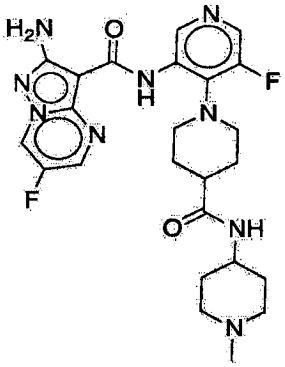


I-G-18

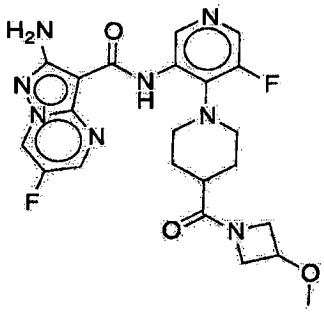


I-G-19

I-G-20



I-G-21



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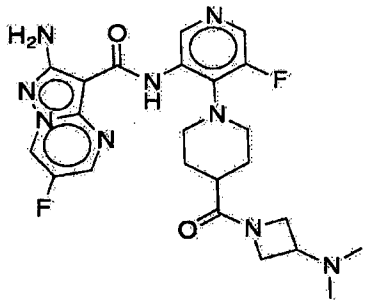
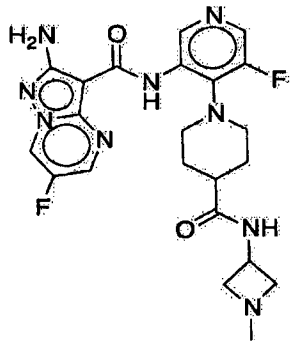
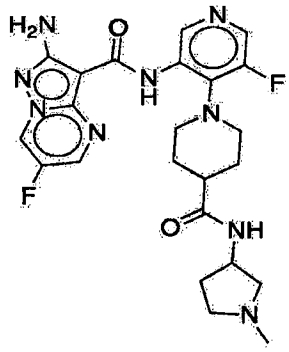


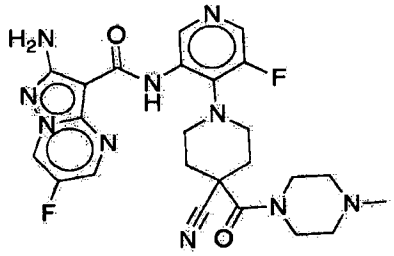
I-G-22



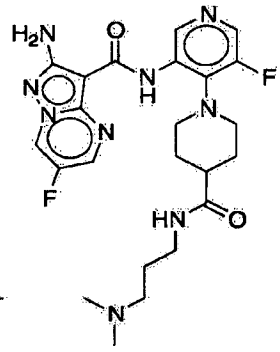
I-G-23



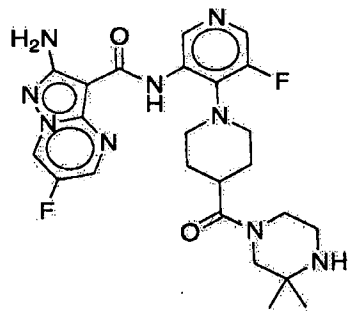
I-G-24



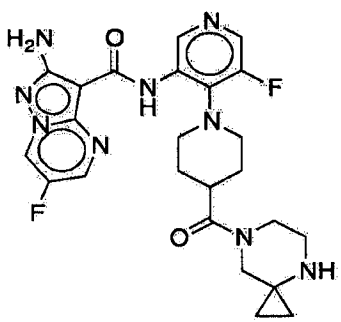
I-G-25



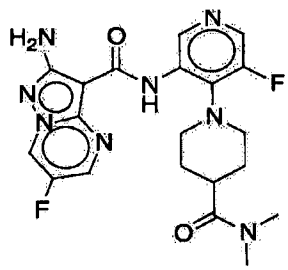
I-G-26



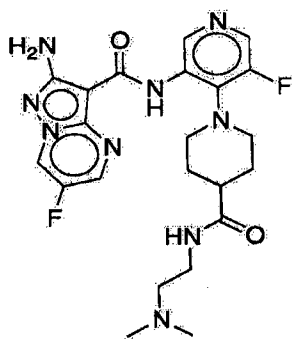
I-G-27



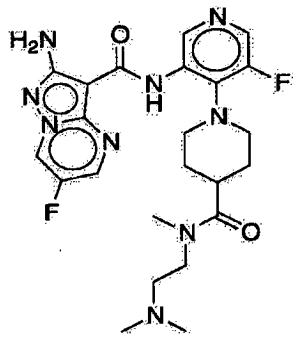
I-G-28



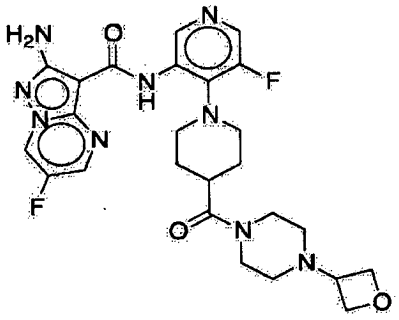
I-G-29



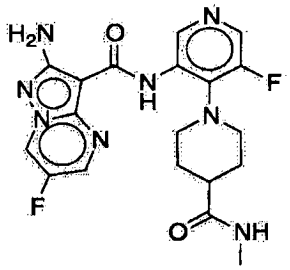
I-G-30



I-G-31



I-G-32



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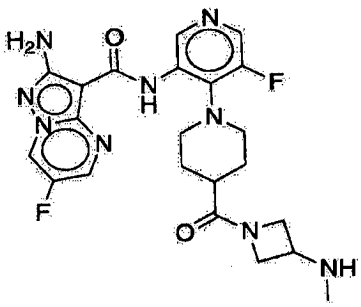

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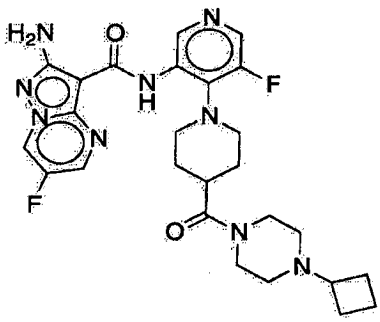

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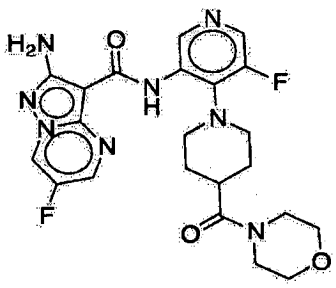

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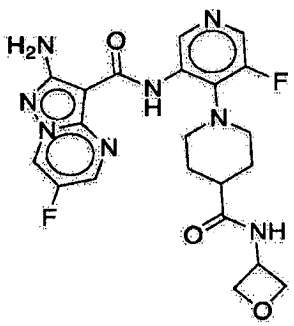

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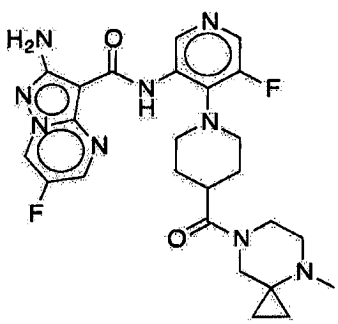
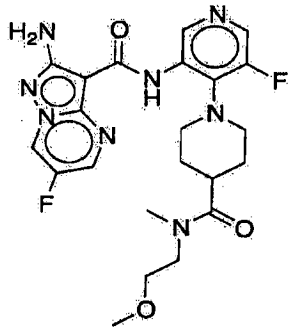


I-G-38

打印ID7619020 Pg 65



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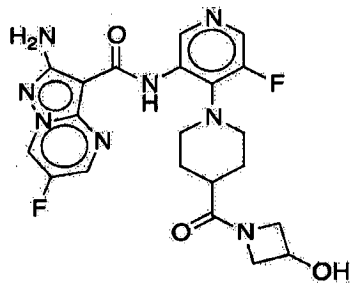

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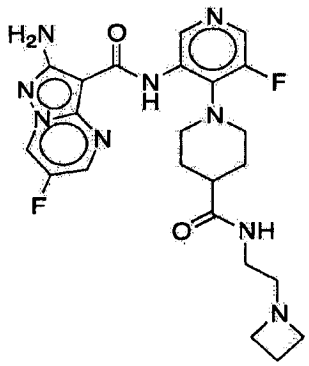

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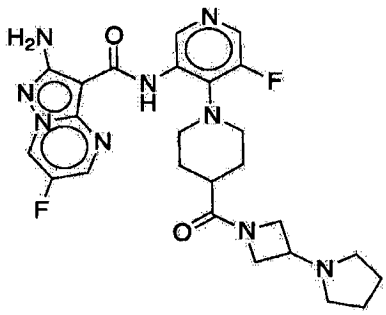

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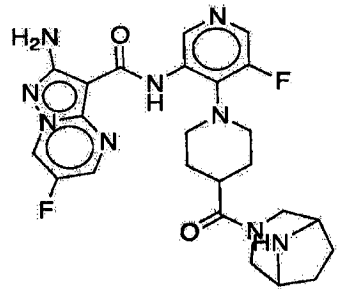

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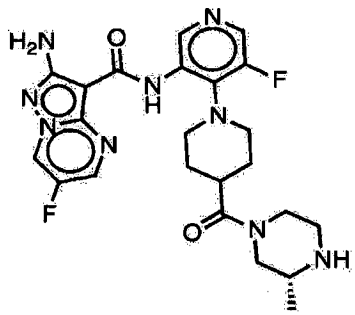

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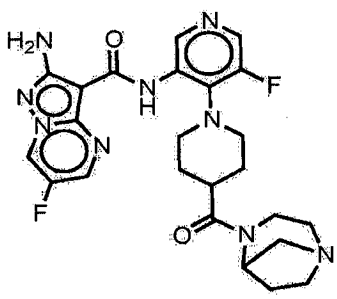

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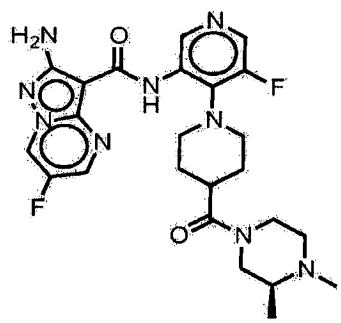

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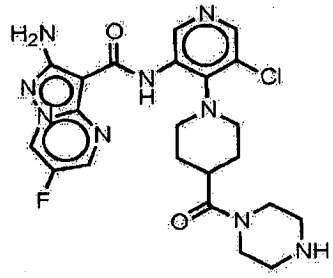

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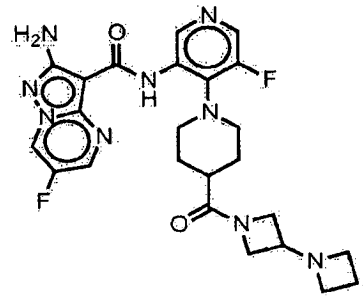

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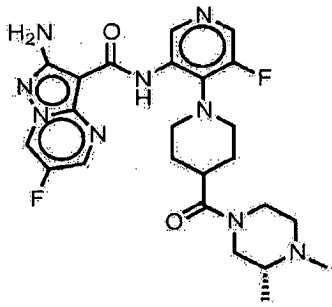

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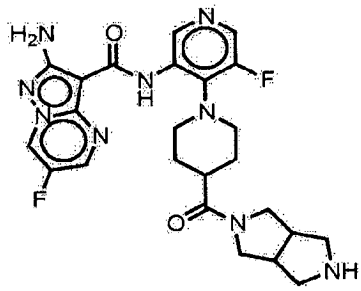

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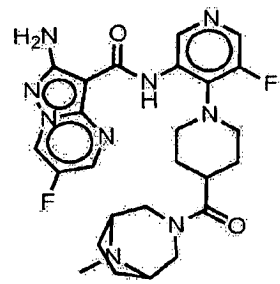

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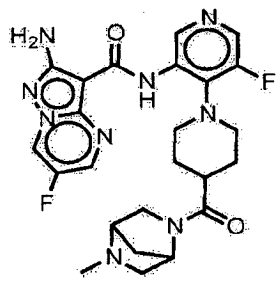

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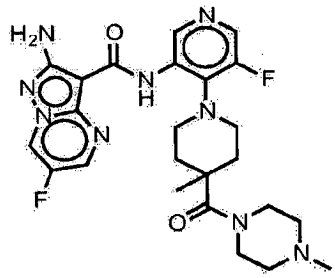

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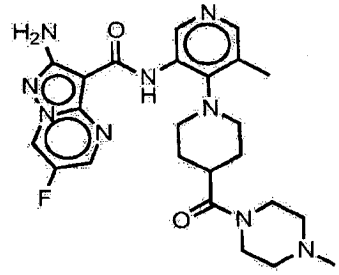

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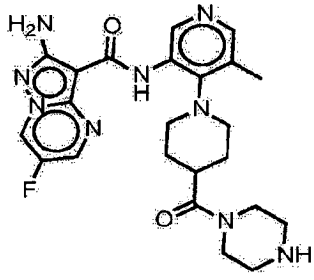

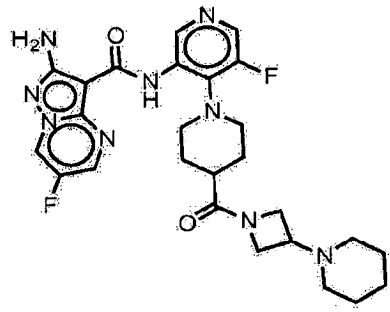

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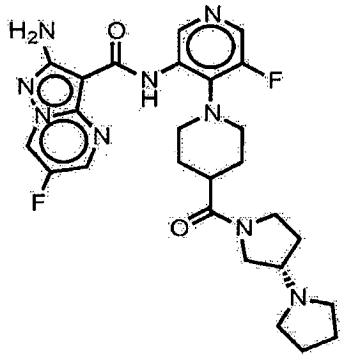

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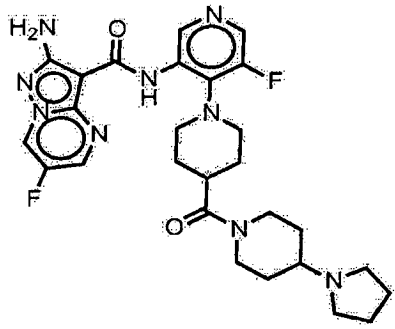

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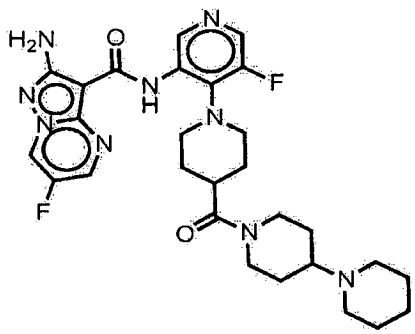

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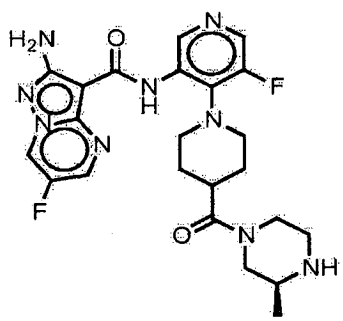
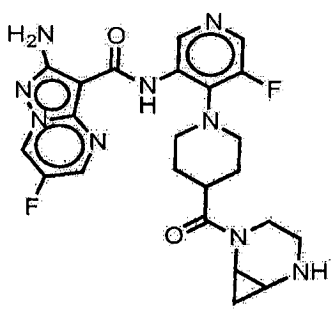


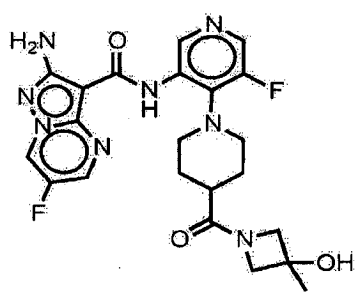
I-G-60

I-G-61

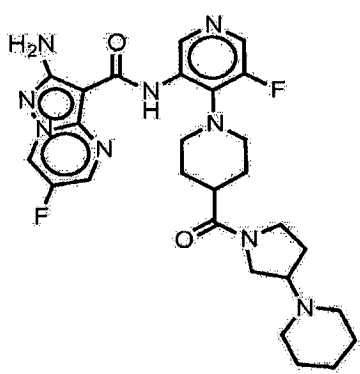
I-G-62



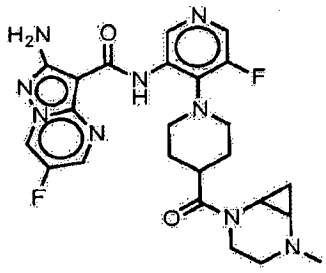
I-G-63



I-G-64



打印ID?619020 Pg 68



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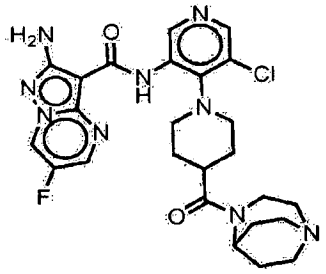

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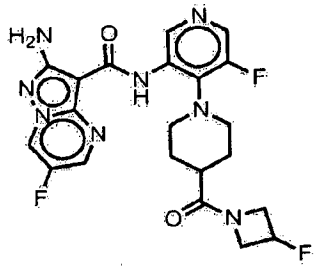

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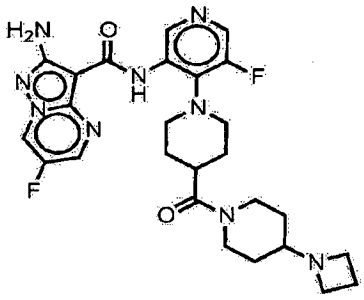

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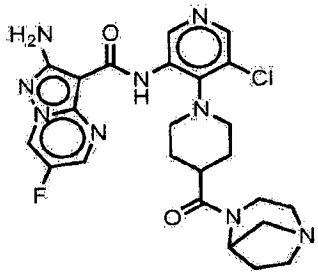

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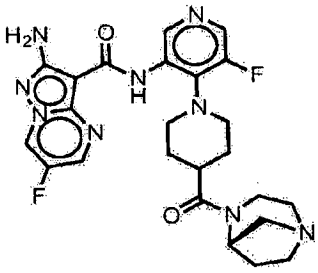

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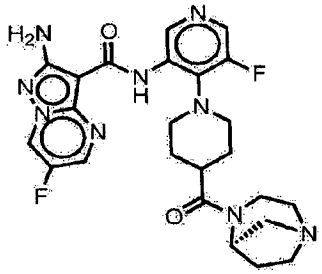
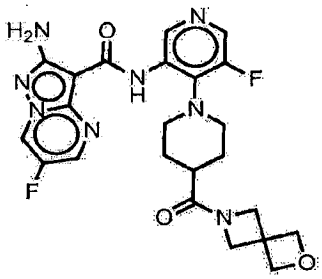
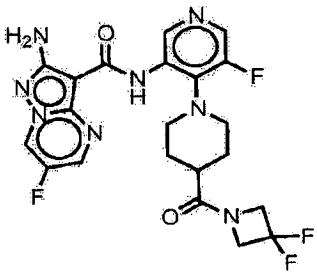


I-G-71



I-G-72



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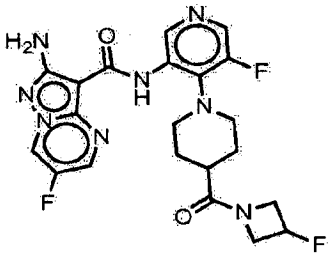

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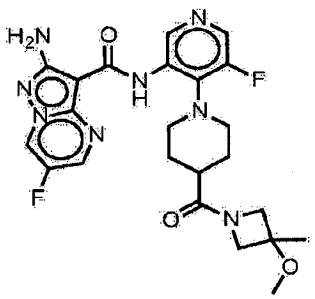

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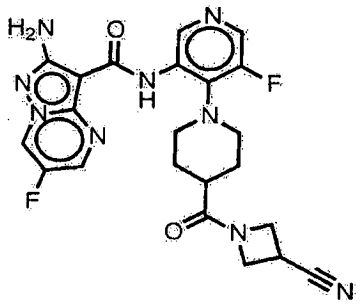

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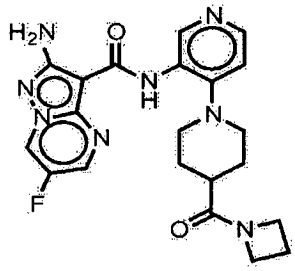

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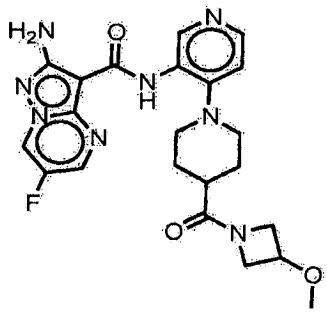
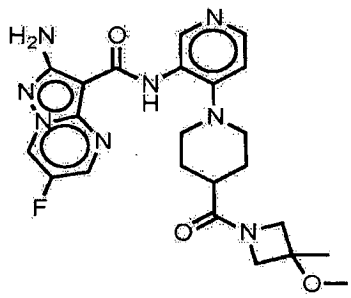
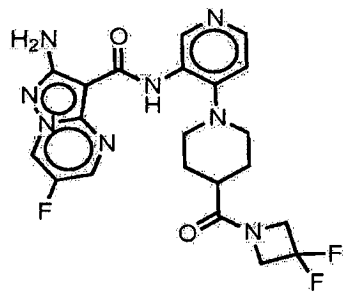


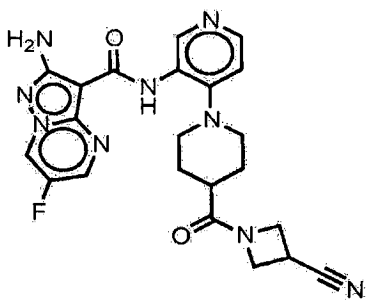
I-G-78



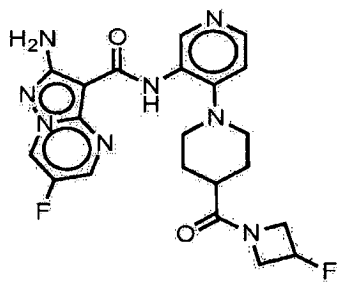
I-G-79



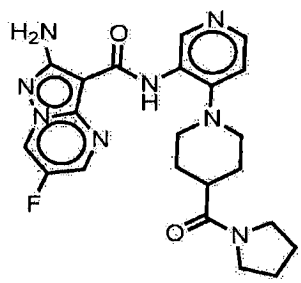
I-G-80



I-G-81

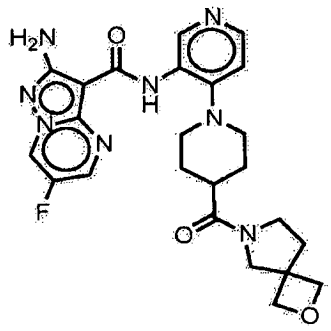


I-G-82

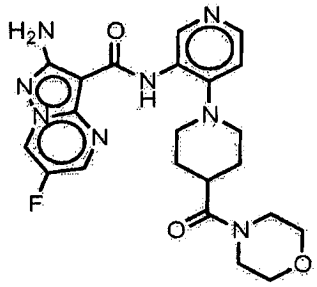


I-G-83

打印ID7619020 Pg 70



I-G-84



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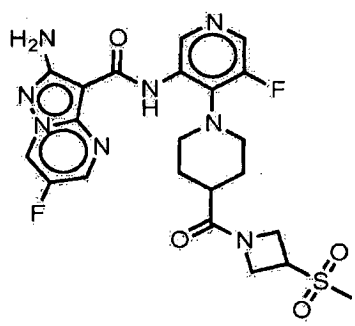

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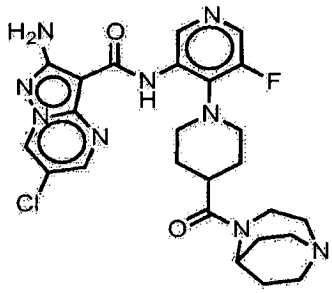

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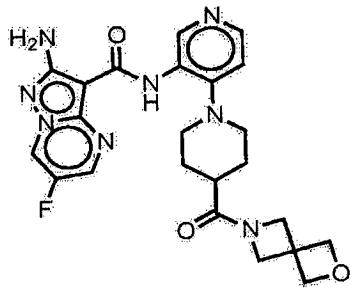

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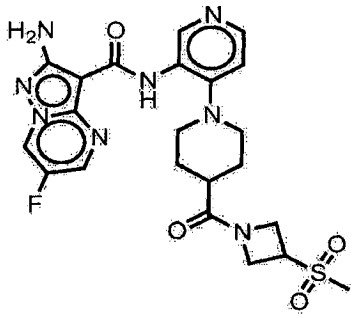

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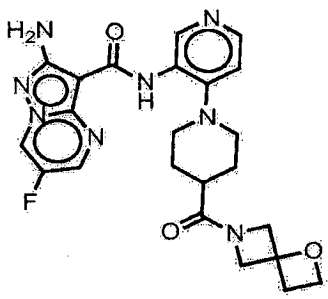

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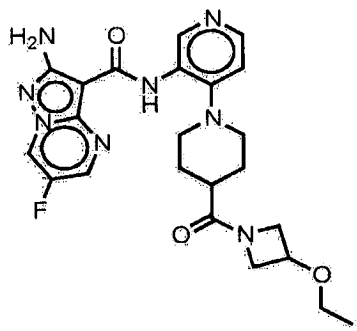

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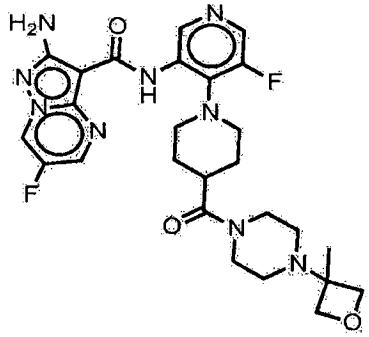
打印ID?619020 Pg 71



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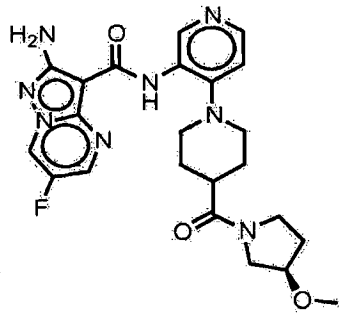

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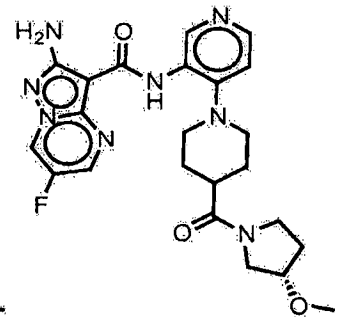

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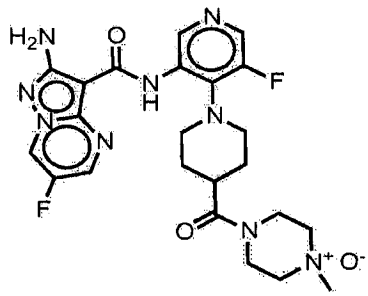

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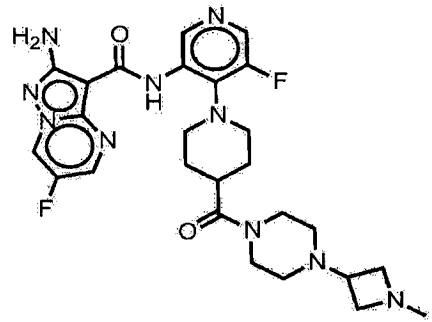

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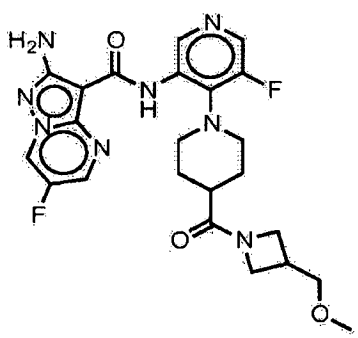

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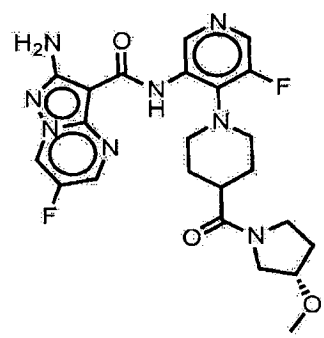


I-G-99。

159. 药物组合物，其包含权利要求 1-158 任一项的化合物和药学上可接受的载体。

160. 治疗患者的癌症的方法，其包括施用权利要求 1-159 任一项的化合物或其药学上可接受的衍生物。

161. 权利要求 160 的方法，其还包括对所述患者施用另外的治疗剂，该另一种治疗剂独立地选自 DNA 损伤剂；其中所述另一种治疗剂适合于所治疗的疾病；且将所述另一种治疗剂与所述化合物作为单个剂型一起施用或作为多种剂型的一部分与所述化合物分别施用。

162. 权利要求 161 的方法，其中所述 DNA 损伤剂选自化疗或放疗。

打印ID?619020 Pg 72

163. 权利要求 161 的方法，其中所述 DNA 损伤剂独立地选自电离辐射、拟辐射新制癌菌素、铂化剂、Topo I 抑制剂、Topo II 抑制剂、抗代谢物、烷化剂、烷基磺酸酯或抗生素。

164. 权利要求 163 的方法，其中所述 DNA 损伤剂独立地选自电离辐射、铂化剂、Topo I 抑制剂、Topo II 抑制剂、抗代谢物、烷化剂或烷基磺酸酯。

165. 权利要求 163 的方法，其中所述 DNA 损伤剂独立地选自电离辐射、铂化剂、Topo I 抑制剂、Topo II 抑制剂或抗生素。

166. 权利要求 164 的方法，其中所述铂化剂独立地选自顺铂、奥沙利铂、卡铂、奈达铂、洛铂、四硝酸三铂、吡铂、沙铂、ProLindac 和 Aroplatin；所述 Topo I 抑制剂选自喜树碱、托泊替康、伊立替康 /SN38、鲁比替康和贝洛替康；所述 Topo II 抑制剂选自依托泊苷、柔红霉素、多柔比星、阿柔比星、表柔比星、伊达比星、氨柔比星、吡柔比星、戊柔比星、佐柔比星和替尼泊苷；所述抗代谢物选自氨蝶呤、甲氨蝶呤、培美曲塞、雷替曲塞、喷司他丁、克拉屈滨、氯法拉滨、氟达拉滨、硫鸟嘌呤、巯嘌呤、氟尿嘧啶、卡培他滨、替加氟、卡莫氟、氟尿苷、阿糖胞苷、吉西他滨、阿扎胞苷和羟基脲；所述烷化剂选自氮芥、环磷酰胺、异环磷酰胺、曲洛磷胺、苯丁酸氮芥、美法仑、泼尼莫司汀、苯达莫司汀、乌拉莫司汀、雌莫司汀、卡莫司汀、洛莫司汀、司莫司汀、福莫司汀、尼莫司汀、雷莫司汀、链佐星、白消安、甘露舒凡、苏消安、卡波醌、噻替哌、三亚胺醌、曲他胺、丙卡巴肼、达卡巴嗪、替莫唑胺、六甲蜜胺、二溴甘露醇、放线菌素、博来霉素、丝裂霉素和普卡霉素。

167. 权利要求 166 的方法，其中所述铂化剂独立地选自顺铂、奥沙利铂、卡铂、奈达铂或沙铂；所述 Topo I 抑制剂选自喜树碱、托泊替康、伊立替康 /SN38、鲁比替康；所述 Topo II 抑制剂选自依托泊苷；所述抗代谢物选自甲氨蝶呤、培美曲塞、硫鸟嘌呤、氟达拉滨、克拉屈滨、阿糖胞苷、吉西他滨、6- 巯嘌呤或 5- 氟尿嘧啶；所述烷化剂选自氮芥类、亚硝基脲类、三氮烯类、烷基磺酸酯类、丙卡巴肼或氮丙啶类；并且所述抗生素选自羟基脲、蒽环类、蒽二酮类或链霉菌科。

168. 权利要求 166 的方法，其中所述 DNA 损伤剂独立地选自铂化剂或电离辐射。

169. 权利要求 164 的方法，其中所述抗代谢物是吉西他滨。

170. 权利要求 164 的方法，其中所述 DNA 损伤剂是电离辐射。

171. 权利要求 164 的方法，其中所述 DNA 损伤剂是铂化剂，其独立地选自顺铂或卡铂。

172. 权利要求 164 的方法，其中所述 DNA 损伤剂是 Topo II 抑制剂，其选自依托泊苷。

173. 权利要求 162 的方法，其中所述 DNA 损伤剂是烷化剂，其选自替莫唑胺。

174. 权利要求 164 的方法，其中所述 DNA 损伤剂独立地选自如下的一种或多种：顺铂、卡铂、吉西他滨、依托泊苷、替莫唑胺或电离辐射。

175. 权利要求 174 的方法，其中所述另外的治疗剂选自如下的一种或多种：吉西他滨、顺铂或卡铂和依托泊苷。

176. 权利要求 160-175 任一项的方法，其中所述癌症为选自如下癌症的实体瘤：口部癌症：口腔癌、唇癌、舌癌、嘴癌、咽癌；心脏癌症：肉瘤（血管肉瘤、纤维肉瘤、横纹肌肉瘤、脂肪肉瘤）、粘液瘤、横纹肌瘤、纤维瘤、脂肪瘤和畸胎瘤；肺部癌症：支气管癌症（鳞状细胞癌或表皮样癌、未分化小细胞癌、未分化大细胞癌、腺癌）、肺泡（细支气管）癌、支气管腺瘤、肉瘤、淋巴瘤、软骨瘤性错构瘤、间皮瘤；胃肠癌症：食道癌症（鳞状细胞癌、喉癌、腺癌、平滑肌肉瘤、淋巴瘤）、胃癌（上皮细胞癌、淋巴瘤、平滑肌肉瘤）、胰腺癌症（导管腺癌、胰

打印ID?619020 Pg 73

岛素瘤、胰高血糖素瘤、胃泌素瘤、类癌瘤、血管活性肠肽瘤）、小肠癌症（腺癌、淋巴瘤、类癌瘤、卡波西氏肉瘤、平滑肌瘤、血管瘤、脂肪瘤、纤维神经瘤、纤维瘤）、大肠癌症（腺癌、管状腺瘤、绒毛状腺瘤、错构瘤、平滑肌瘤）、结肠癌、结肠－直肠癌、结肠直肠癌；直肠癌；泌尿生殖道癌症：肾癌症（腺癌、维耳姆斯瘤［肾胚细胞瘤］、淋巴瘤）、膀胱和尿道癌症（鳞状细胞癌、移行细胞癌、腺癌）、前列腺癌症（腺癌、肉瘤）、睾丸癌症（精原细胞瘤、畸胎瘤、胚胎性癌、畸胎上皮细胞癌、绒毛膜癌、肉瘤、间质细胞癌、纤维瘤、纤维腺瘤、腺瘤样瘤、脂肪瘤）；肝脏癌症：肝细胞瘤（肝细胞癌）、胆管癌、肝胚细胞瘤、血管肉瘤、肝细胞性腺瘤、血管瘤、胆道癌；骨癌症：成骨肉瘤（骨肉瘤）、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤文氏肉瘤、恶性淋巴瘤（网状细胞肉瘤）、多发性骨髓瘤、恶性巨细胞瘤脊索瘤、骨软骨纤维瘤（骨软骨性外生骨疣）、良性软骨瘤、成软骨细胞瘤、软骨粘液纤维瘤、骨样骨瘤和巨细胞瘤；神经系统癌症：颅骨癌症（骨瘤、血管瘤、肉芽肿、黄瘤、畸形性骨炎）、脑膜癌（脑膜瘤、脑膜肉瘤、神经胶质瘤病）、脑癌（星形细胞瘤、成神经管细胞瘤、神经胶质瘤、室管膜瘤、生殖细胞瘤［松果体瘤］、多形性成胶质细胞瘤、少突神经胶质瘤、神经鞘瘤、成视网膜细胞瘤、先天性肿瘤）、脊髓神经纤维瘤、脑膜瘤、神经胶质瘤、肉瘤）；妇科／女性癌症：子宫癌症（子宫内膜癌）、宫颈癌症（宫颈癌、肿瘤前宫颈非典型增生）、卵巢癌症（卵巢癌［浆液性囊腺癌、粘液性囊腺癌、未分类癌瘤］、粒层－卵泡膜细胞瘤、塞－莱二氏细胞瘤、无性细胞瘤、恶性畸胎瘤）、外阴癌症（鳞状细胞癌、上皮内癌、腺癌、纤维肉瘤、黑素瘤）、阴道癌症（透明细胞癌、鳞状细胞癌、葡萄样肉瘤（胚胎性横纹肌肉瘤）、输卵管癌症（癌瘤）、乳腺癌；皮肤癌症：恶性黑素瘤、基底细胞癌、鳞状细胞癌、卡波西氏肉瘤、角化棘皮瘤、发育不良痣、脂肪瘤、血管瘤、皮肤纤维瘤、瘢痕瘤、牛皮癣；甲状腺癌症：乳头状甲状腺癌、滤泡性甲状腺癌；髓样甲状腺癌、2A 型多发性内分泌腺瘤、2B 型多发性内分泌腺瘤、家族性髓样甲状腺癌、嗜铬细胞瘤、副神经节瘤；以及肾上腺癌症：成神经细胞瘤。

177. 权利要求 176 的方法，其中所述癌症选自肺或胰腺的癌症。

178. 权利要求 177 的方法，其中所述癌症是肺癌。

179. 权利要求 178 的方法，其中所述肺癌是非小细胞肺癌或小细胞肺癌。

180. 权利要求 179 的方法，其中所述肺癌是小细胞肺癌且所述另外的治疗剂是顺铂和依托泊苷。

181. 权利要求 179 的方法，其中所述肺癌是非小细胞肺癌且所述另外的治疗剂是吉西他滨和顺铂。

182. 权利要求 181 的方法，其中所述非小细胞肺癌是鳞状非小细胞肺癌。

183. 权利要求 160-175 任一项的方法，其中所述癌症选自肺癌、头颈癌、胰腺癌、胃癌或脑癌。

184. 权利要求 160-175 任一项的方法，其中所述癌症选自非小细胞肺癌、小细胞肺癌、胰腺癌、胆道癌、头颈癌、膀胱癌、结肠直肠癌、胶质母细胞瘤、食道癌、乳腺癌、肝细胞癌或卵巢癌。

185. 权利要求 184 的方法，其中所述癌症是乳腺癌且所述另外的治疗剂是顺铂。

186. 权利要求 185 的方法，其中所述癌症是三阴性乳腺癌。

187. 权利要求 168 的方法，其中所述另外的治疗剂是吉西他滨且所述癌症是胰腺癌。

188. 治疗胰腺癌的方法，其包括对患者施用与另外的治疗剂组合的权利要求 1-158 任

打印ID?619020 Pg 74

一项的化合物，所述另外的治疗剂选自吉西他滨、放射疗法或吉西他滨和放射疗法二者一起。

189. 增加胰腺癌细胞对癌症疗法的敏感性的方法，所述癌症疗法选自化学疗法或放射疗法，该方法通过对患者施用权利要求 1-158 任一项的化合物来进行。

190. 权利要求 189 的方法，其中所述化学疗法是吉西他滨。

191. 权利要求 189 的方法，其中所述癌症疗法是吉西他滨。

192. 权利要求 189 的方法，其中所述癌症疗法是辐射。

193. 权利要求 181 的方法，其中所述癌症疗法是吉西他滨和辐射。

194. 抑制胰腺癌细胞中 Chk1(Ser 345) 磷酸化的方法，其包括施用与吉西他滨 (100nM) 和 / 或辐射 (6Gy) 组合的权利要求 1-159 任一项的化合物。

195. 使胰腺癌细胞对化放疗增敏的方法，其通过施用与化放疗组合的权利要 1-158 求任一项的化合物来进行。

196. 权利要求 166 的方法，其中所述化放疗是吉西他滨和辐射。

197. 使含氧量低的胰腺癌细胞辐射增敏的方法，其通过施用与放射疗法组合的权利要求 1-158 任一项的化合物来进行。

198. 使含氧量低的胰腺癌细胞增敏的方法，其通过施用权利要求 1-158 任一项的化合物与化学疗法的组合来进行。

199. 权利要求 195-198 任一项的方法，其中所述癌细胞是 PSN-1、MiaPaCa-2 或 PancM 癌细胞。

200. 破坏损伤诱导的细胞周期关卡的方法，其通过施用与放射疗法和 / 吉西他滨组合的权利要求 1-158 任一项的化合物来进行。

201. 抑制胰腺癌细胞中同源性重组修复 DNA 损伤的方法，其通过施用与放射疗法和 / 吉西他滨组合的权利要求 1-156 任一项的化合物来进行。

202. 权利要求 195-201 任一项的方法，其中将化合物施用于患者。

203. 权利要求 196-201 任一项的方法，其中将化合物施用于胰腺癌细胞。

204. 权利要求的方法 203，其中所述胰腺癌细胞来源于选自 PSN-1、MiaPaCa-2 或 Panc-1 的胰腺细胞系。

205. 治疗非小细胞肺癌的方法，其包括对患者施用与如下另外的治疗剂中的一种或多种组合的权利要求 1-158 任一项的化合物：顺铂或卡铂、依托泊苷和电离辐射。

206. 促进癌细胞中细胞死亡的方法，其包括对患者施用权利要求 1-158 任一项的化合物。

207. 防止细胞修复 DNA 损伤的方法，其包括对患者施用权利要求 1-158 任一项的化合物。

208. 抑制生物样品中 ATR 的方法，其包括使权利要求任 1-158 一项的化合物接触所述生物样品的的步骤。

209. 权利要求 208 的方法，其中所述生物样品是细胞。

210. 使细胞对 DNA 损伤剂致敏的方法，其包括对患者施用权利要求 1-158 任一项的化合物。

211. 权利要求 161-210 任一项的方法，其中所述细胞是 ATM 信号传导级联中具有缺陷

打印ID?619020 Pg 75

的癌细胞。

212. 权利要求 211 的方法，其中所述缺陷是如下的一种或多种的表达或活性的改变：ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1、H2AX、MCPH1/BRIT1、CTIP 或 SMC1。

213. 权利要求 211 的方法，其中所述缺陷是如下的一种或多种的表达或活性的改变：ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1 或 H2AX。

214. 权利要求 160-210 任一项的方法，其中所述细胞是表达损伤 DNA 的癌基因的癌细胞。

215. 权利要求 214 的方法，其中所述癌细胞具有如下的一种或多种的表达或活性的改变：K-Ras、N-Ras、H-Ras、Raf、Myc、Mos、E2F、Cdc25A、CDC4、CDK2、细胞周期蛋白 E、细胞周期蛋白 A 和 Rb。

216. 权利要求 161-210 任一项的方法，其中所述癌症、癌细胞或细胞具有碱基切除修复蛋白的缺陷。

217. 权利要求 216 的方法，其中所述碱基切除修复蛋白选自 UNG、SMUG1、MBD4、TDG、OGG1、MYH、NTH1、MPG、NEIL1、NEIL2、NEIL3(DNA 糖基化酶）；APE1、APEX2(AP 核酸内切酶）；LIG1、LIG3(DNA 连接酶 I 和 III)；XRCC1(LIG3 辅助因子）；PNK、PNKP(多核苷酸激酶和磷酸酶）；PARP1、PARP2(多聚 (ADP- 核糖）聚合酶）；Pol B、Pol G(聚合酶）；FEN1(核酸内切酶）或 Aprataxin。

218. 权利要求 217 的方法，其中所述碱基切除修复蛋白为 PARP1、PARP2 或 Pol B。

219. 权利要求 218 的方法，其中所述碱基切除修复蛋白为 PARP1 或 PARP2。

220. 权利要求 161-219 任一项的方法，其还包括对所述患者施用另外的治疗剂，其中所述治疗剂抑制或调节碱基切除修复蛋白。

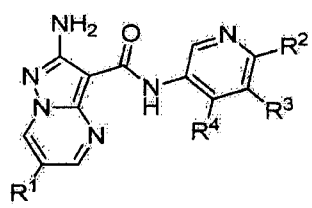
221. 权利要求 220 的方法，其中所述碱基切除修复蛋白选自 UNG、SMUG1、MBD4、TDG、OGG1、MYH、NTH1、MPG、NEIL1、NEIL2、NEIL3(DNA 糖基化酶）；APE1、APEX2(AP 核酸内切酶）；LIG1、LIG3(DNA 连接酶 I 和 III)；XRCC1(LIG3 辅助因子）；PNK、PNKP(多核苷酸激酶和磷酸酶）；PARP1、PARP2(多聚 (ADP- 核糖）聚合酶）；Pol B、Pol G(聚合酶）；FEN1(核酸内切酶）或 Aprataxin。

222. 权利要求 221 的方法，其中所述碱基切除修复蛋白选自 PARP1、PARP2 或 Pol B。

223. 权利要求 222 的方法，其中所述碱基切除修复蛋白选自 PARP1 或 PARP2。

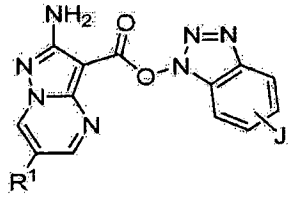
224. 权利要求 213 的方法，其中所述药剂选自奥拉帕尼（也称为 AZD2281 或 KU-0059436）、Iniparib(也称为 BSI-201 或 SAR240550)、Veliparib(也称为 ABT-888)、Rucaparib(也称为 PF-01367338)、CEP-9722、INO-1001、MK-4827、E7016、BMN673 或 AZD2461。

225. 制备式 I-A 的化合物的方法：



I-A

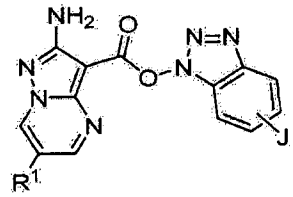
其包括使式 6 的化合物：



6

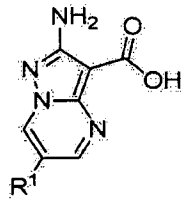
在适合的条件下反应，形成酰胺键，其中 J、R^1、R^2、R^3和 R^4如权利要求 1-158 中所定义。

226. 权利要求 225 的方法，其还包括制备式 6 的化合物的步骤：



6

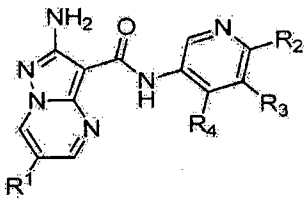
其通过使式 5 的化合物：



5

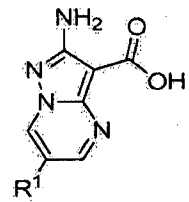
在适合的条件下反应形成活化的酯来制备。

227. 制备式 I-A 的化合物的方法：



I-A

其包括使式 5 的化合物：

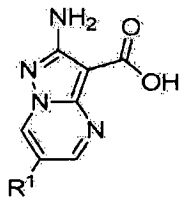


5

打印ID?619020 Pg 77

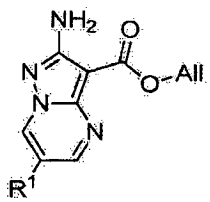
在适合的条件下反应，形成酰胺键，其中 R^1、R^2、R^3和 R^4如权利要求 1-158 中所定义。

228. 权利要求 225-227 任一项的方法，其还包括制备式 5 的化合物的步骤：



5

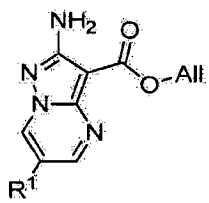
其通过使式 4 的化合物：



4

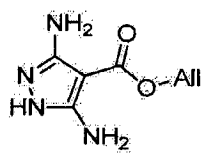
在适合的脱保护条件下反应来制备。

229. 权利要求 228 的方法，其还包括制备式 4 的化合物的步骤：



4

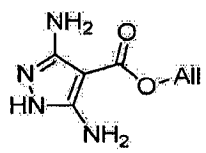
其通过使式 3 的化合物：



3

在适合的缩合条件下反应形成嘧啶环来制备。

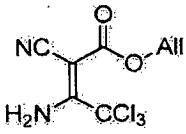
230. 权利要求 229 的方法，其还包括制备式 3 的化合物的步骤：



3

其通过使式 2 的化合物：

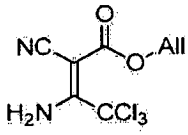
打印ID?619020 Pg 78



2

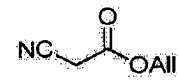
在适合的缩合条件下反应形成吡唑环来制备。

231. 权利要求 230 的方法，其还包括制备式 2 的化合物的步骤：



2

其通过使式 1 的化合物：



1

在适合的缩合条件下反应来制备。

232. 权利要求 225 任一项的方法，其中 R^1 独立地选自卤素或 $-CH_2CN$。

233. 权利要求 232 的方法，其中 R^1 独立地选自氟或氯。

234. 权利要求 225 的方法，其中用于形成酰胺键的适合的条件包括使式 6 的化合物与取代的 3- 氨基吡啶在非质子溶剂中在加热的存在下反应。

235. 权利要求 234 的方法，其中所述非质子溶剂选自 NMP、吡啶或 DMF。

236. 权利要求 234 的方法，其中所述非质子溶剂是任选取代的吡啶。

237. 权利要求 234-236 任一项的方法，其中所述反应在至少 80℃的温度下进行。

238. 权利要求 237 的方法，其中所述反应在至少 100℃的温度下进行。

239. 权利要求 226 任一项的方法，其中用于形成活化的酯的适合的条件包括使式 5 的化合物与酰胺偶合剂在有机碱的存在下反应。

240. 权利要求 239 的方法，其中所述有机碱是脂族胺。

241. 权利要求 240 的方法，其中所述有机碱独立地选自 DIPEA 或三乙胺。

242. 权利要求 239-241 任一项的方法，其中所述酰胺偶合剂独立地选自 EDCI、TBTU、TCTU、HATU、T3P 或 COMU。

243. 权利要求 242 的方法，其中所述酰胺偶合剂独立地选自 TBTU 或 TCTU。

244. 权利要求 243 的方法，其中所述酰胺偶合剂是 TCTU。

245. 权利要求 228 的方法，其中适合的水解条件包括使式 4 的化合物与硅烷在金属催化剂的存在下反应。

246. 权利要求 245 的方法，其中所述硅烷是苯基硅烷。

247. 权利要求 246 的方法，其中所述金属催化剂是钯催化剂。

248. 权利要求 247 的方法，其中所述金属催化剂是 $Pd(PPh_3)_4$。

249. 权利要求 228 的方法，其中适合的水解条件包括使式 4 的化合物与碱金属水溶液

打印ID?619020 Pg 79

反应。

250. 权利要求 249 的方法，其中所述碱金属水溶液独立地选自 LiOH、NaOH 或 KOH。

251. 权利要求 229 的方法，其中用于形成嘧啶环的适合的缩合条件包括使式 3 的化合物与 1,3- 二亲电类物质在溶剂的存在下反应。

252. 权利要求 251 的方法，其中所述 1,3- 二亲电类物质是 1,3- 二醛或 3-(二烷基氨基)- 丙 -2- 烯醛。

253. 权利要求 251 或 252 任一项的方法，其中所述溶剂选自 DMF 或 DMSO。

254. 权利要求 251 的方法，其中所述 1,3- 二亲电类物质由被保护的 1,3- 二亲电类物质在原位生成。

255. 权利要求 254 的方法，其中所述 1,3- 二亲电类物质在磺酸的存在下由缩酮生成。

256. 权利要求 255 的方法，其中所述磺酸是 PTSA。

257. 权利要求 230 的方法，其中用于形成吡唑环的适合的缩合条件包括使式 2 的化合物与肼或水合肼在非质子溶剂的存在下在碱性条件下反应。

258. 权利要求 257 的方法，其中所述非质子溶剂是 DMF。

259. 权利要求 257 的方法，其中所述碱性条件包括使式 2 的化合物在乙酸钾或乙酸钠的存在下反应。

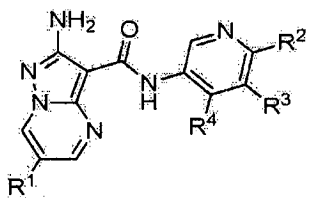
260. 权利要求 231 的方法，其中适合的阴离子缩合条件包 1) 使式 1 的化合物与碱在溶剂的存在下反应，生成式 1 的化合物的阴离子；以及 2) 使式 1 的化合物的阴离子与三氯乙腈反应。

261. 权利要求 260 的方法，其中所述碱是乙酸钾。

262. 权利要求 260 的方法，其中所述溶剂是醇。

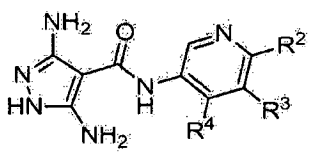
263. 权利要求 262 的方法，其中所述溶剂是异丙醇。

264. 制备式 I-A 的化合物的方法：



I-A

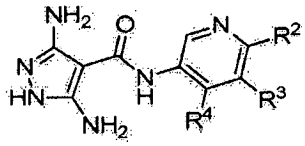
其包括使式 9 的化合物：



9

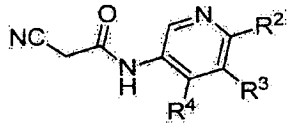
在适合的缩合条件下反应，形成嘧啶环，其中 R^1、R^2、R^3和 R^4如权利要求 1-156 中所定义。

265. 权利要求 264 的方法，其还包括制备式 9 的化合物的步骤：



9

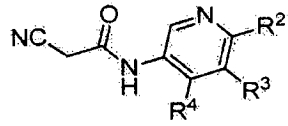
其通过使式 8 的化合物：



8

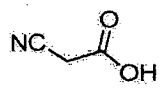
在适合的缩合条件下反应形成吡唑环来制备。

266. 权利要求 265 的方法，其还包括制备式 8 的化合物的步骤：



8

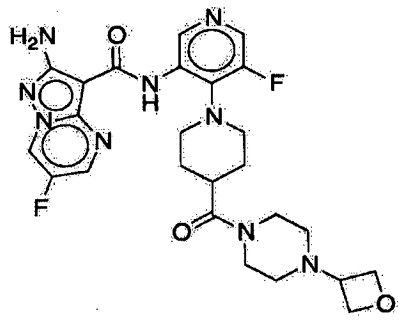
其通过使式 7 的化合物：



7

在适合的条件下反应形成酰胺键来制备。

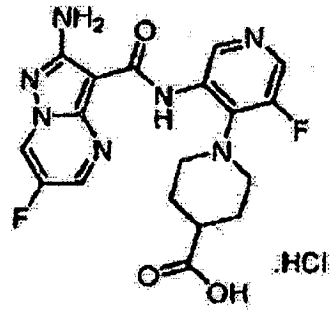
267. 制备式 I-G-32 的化合物的方法：



I-G-32

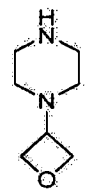
其包括使式 30 的化合物：

打印ID?619020 Pg 81



30

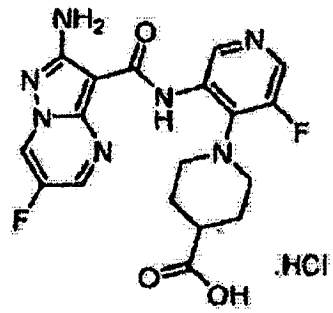
与式 25 的化合物：



25

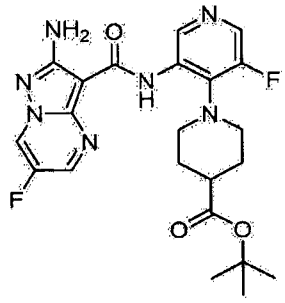
在适合的条件下反应形成酰胺键的步骤。

268. 权利要求 267 的方法，其还包括制备式 30 的化合物的步骤：



30

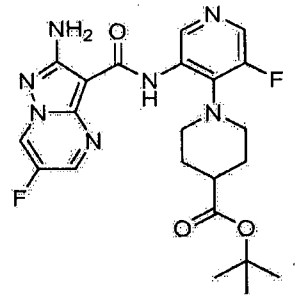
其通过使式 28 的化合物：



28

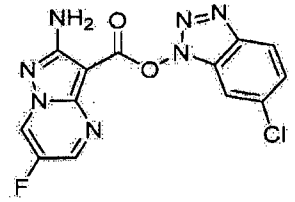
在适合的脱保护条件下反应形成羧酸来制备。

269. 权利要求 268 的方法，其还包括制备式 28 的化合物的步骤：



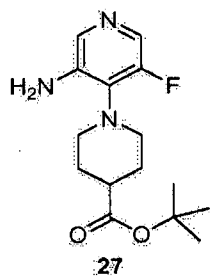
28

通过使式 6a* 的化合物：



6a*

与式 27 的化合物：



27

在适合条件下反应形成酰胺键来制备。

270. 权利要求 267 的化合物，其中用于形成酰胺键的适合的条件包括使式 29 的化合物与式 25 的化合物在酰胺偶合配偶体、非质子溶剂和碱的存在下反应。

打印ID7619020 Pg 83

271. 权利要求 270 的化合物，其中所述非质子溶剂独立地选自 NMP、DMF 或四氢呋喃。

272. 权利要求 271 的方法，其中所述非质子溶剂是四氢呋喃。

273. 权利要求 271 的方法，其中所述碱是脂族胺。

274. 权利要求 273 的方法，其中所述碱是 DIPEA。

275. 权利要求 270-274 任一项的方法，其中所述酰胺偶合配偶体独立地选自 TBTU 或 TCTU。

276. 权利要求 275 的方法，其中所述酰胺偶合配偶体是 TCTU。

277. 权利要求 268 的方法，其中适合的脱保护条件包括使式 28 的化合物与酸在溶剂的存在下反应。

278. 权利要求 277 的方法，其中所述酸是 HCl。

279. 权利要求 278 的方法，其中所述溶剂是 1,4- 二噁烷。

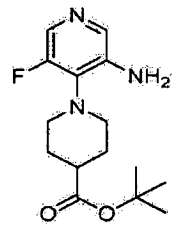
280. 权利要求 269 的方法，其中用于形成酰胺碱的适合的条件包括使式 6a* 的化合物与式 27 的化合物在非质子溶剂的存在下在加热中反应。

281. 权利要求 280 的方法，其中所述非质子溶剂独立地选自 NMP、吡啶或 DMF。

282. 权利要求 281 的方法，其中所述非质子溶剂是吡啶。

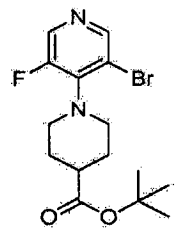
283. 权利要求 280 任一项的方法，其中所述反应在至少 80℃的温度下进行。

284. 制备式 27 的化合物的方法：



27

其括含使式 26 的化合物：

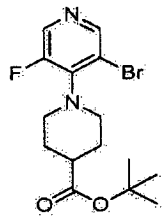


26

在适合的条件下反应形成胺的步骤。

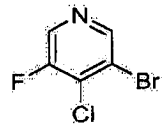
285. 权利要求 284 的方法，其还包括制备式 26 的化合物的步骤：

打印ID?619020 Pg 84



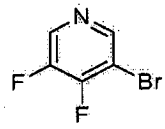
26

其通过如下步骤制备 :1) 使式 18 的化合物 :



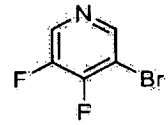
18

在适合的卤素交换条件下反应,生成式 32 的化合物



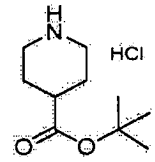
32, 以及

2) 使式 32 的化合物 :



32

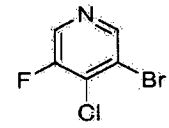
与式 22 的化合物 :



22

在适合的置换条件下反应。

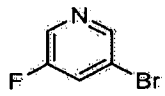
286. 权利要求 284 的方法,其还包括制备式 18 的化合物的步骤 :



18

其通过使式 31 的化合物 :

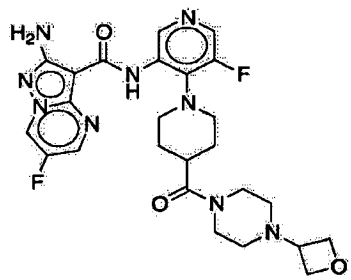
打印ID?619020 Pg 85



31

在适合的卤化条件下反应来制备。

287. 具有结构 I-G-32 的化合物：

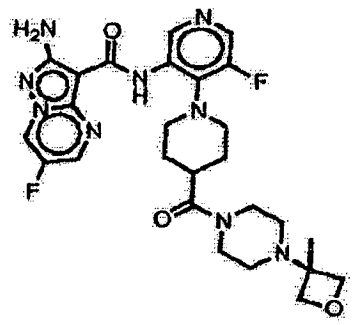


I-G-32

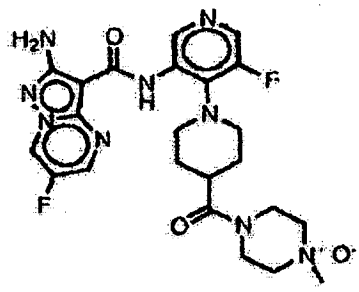
或其药学上可接受的盐。

288. 化合物，其选自

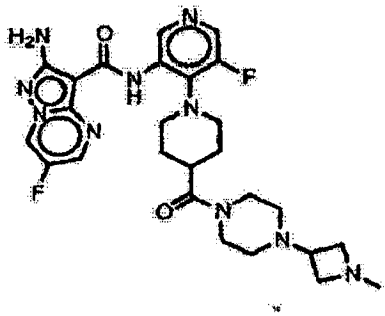
打印ID?619020 Pg 86



I-G-92



I-G-95



I-G-96

或其药学上可接受的盐。

可用作 ATR 激酶抑制剂的化合物

[0001] 发明背景

[0002] ATR(“ATM 和 Rad3 相关的”)激酶是涉及对 DNA 损伤的一些形式(例如双链断裂和复制应激)的细胞应答的蛋白激酶。ATR 激酶与 ATM(“共济失调毛细血管扩张突变”)激酶和许多其它蛋白质一起起作用以调节对双链 DNA 断裂和复制应激的细胞应答,通常称为 DNA 损伤应答(“DDR”)。DDR 刺激 DNA 修复,促进存活和通过激活细胞周期关卡而阻碍细胞周期进程,这提为修复供了时间。没有 DDR,则细胞对 DNA 损伤更敏感得多,并且易死于由内源性细胞过程例如 DNA 复制或癌症疗法中常用的外源性 DNA 损伤剂诱导的 DNA 损害。

[0003] 健康细胞可以依赖于许多用于 DNA 修复的不同蛋白质,包括 DDR 激酶 ATR 和 ATM。在一些情况中,这些蛋白质可以通过激活功能性丰余的 DNA 修复过程彼此补偿。相反,许多癌细胞在其一些 DNA 修复过程(例如 ATM 信号传导)中隐藏缺陷,从而对其剩余的完整 DNA 修复蛋白(其包括 ATR)表现出更大依赖性。

[0004] 此外,许多癌细胞表达激活的致癌基因或缺乏关键肿瘤抑制基因,这可以使得这些癌细胞易处于 DNA 复制的失调期,这继而引起 DNA 损伤。ATR 作为受破坏 DNA 复制的应答中的 DDR 的关键成分而被牵涉。因此,这些癌细胞比健康细胞更依赖于 ATR 活性以用于存活。因此,ATR 抑制剂可以单独使用或与 DNA 损伤剂联用适用于癌症治疗,因为它们切断了 DNA 修复机制,而该修复机制对许多癌细胞的细胞存活而言比健康正常细胞的细胞存活更重要。

[0005] 实际上,已显示 ATR 功能的破坏(例如通过基因缺失)在无论有无 DNA 损伤剂的存在下都促进癌细胞死亡。这表明 ATR 抑制剂作为单一药剂和作为对放疗或遗传毒性化疗的有效增敏剂二者都可能是有效的。

[0006] 可以使用文献中已知的各种方法表达和分离 ATR 肽(参见例如,**Ünsal-Kaçmaz** 等人 PNAS 99:10, pp6673-6678, May 14,2002;还可参见 Kumagai 等人 Cell 124, pp943-955, March 10,2006;Unsal-Kacmaz 等人 Molecular 和 Cellular Biology,Feb 2004,p1292-1300;以及 Hall-Jackson 等人 Oncogene 1999,18,6707-6713)。

[0007] 由于所有这些原因,对于开发作为单一药剂或作为与放疗或遗传毒性化疗的联合疗法用于治疗癌症的有效和选择性的 ATR 抑制剂存在需求。

[0008] 发明概述

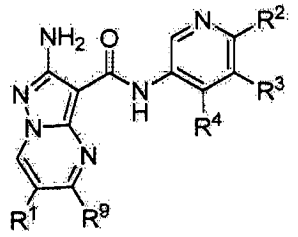
[0009] 本发明涉及可用作 ATR 蛋白激酶抑制剂的化合物。本发明还涉及包含本发明所述化合物的药学上可接受的组合物;使用本发明所述化合物治疗不同疾病、障碍和病症的方法;用于制备本发明本发明化合物的方法;用于制备本发明所述化合物的中间体;以及在体外应用中使用所述化合物的方法,所述体外应用为例如对生物学和病理学现象中的激酶的研究;对这类激酶介导的胞内信号转导途径的研究;以及对新激酶抑制剂的对比评价。

[0010] 本发明的化合物是极为有效的 ATR 抑制剂。在联合疗法中,这些化合物还显示与其它癌症药剂例如顺铂和吉西他滨具有令人意外的协同作用。

[0011] 发明详述

[0012] 本发明的一个方面提供式 I 的化合物:

[0013]



I

[0014] 或其药学上可接受的盐或前药，其中：

[0015] R^1独立地选自 $-C(J^1)_2CN$、卤素、$-(L)_k-W$ 或 M；

[0016] R^9独立地选自 H、$-C(J^1)_2CN$、卤素、$-(L)_k-W$ 或 M；

[0017] J^1独立地选自 H 或 C_{1-2}烷基；或

[0018] 2 次出现的 J^1与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

[0019] k 是 0 或 1；

[0020] M 和 L 是 C_{1-8}脂族基团，其中至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代，M 和 L^1各自任选地被 0-3 次出现的 J^{LM}取代；

[0021] J^{LM}独立地选自卤素、-CN 或 C_{1-4}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

[0022] W 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；其中 W 任选地被 0-5 次出现的 J^W取代；

[0023] J^W独立地选自 -CN、卤素、$-CF_3$；C_{1-4}脂族基团，其中至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；

[0024] 同一原子上的 2 次出现的 J^W与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；或

[0025] 2 次出现的 J^W与 W 一起形成 6-10 元饱和或部分不饱和桥连环系；

[0026] R^2独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2}烷基；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0027] R^3独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；3-4 元杂环基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0028] R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

[0029] R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元芳族或非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

[0030] Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不

饱和或芳族双环；

[0031] J^z独立地选自 C_{1-6}脂族基团、=O、卤素或→O；

[0032] J^Q独立地选自 -CN；卤素；=O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多3个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被0-3次出现的 J^R取代；或

[0033] 同一原子上的2次出现的 J^Q与它们所连接的原子一起形成具有0-2个选自氧、氮或硫的杂原子的3-6元环；其中由2次出现的 J^Q形成的环任选地被0-3次出现的 J^X取代；或

[0034] 2次出现的 J^Q与 Q^1一起形成6-10元饱和或部分不饱和桥连环系；

[0035] Q^2独立地选自具有0-3个选自氧、氮或硫的杂原子的3-7元完全饱和、部分不饱和或芳族单环；或具有0-5个选自氧、氮或硫的杂原子的7-12元完全饱和、部分不饱和或芳族双环；

[0036] J^R独立地选自 -CN；卤素；=O；→O；Q^3；或 C_{1-6}脂族链，其中所述脂族链的至多3个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；J^R各自任选地被0-3次出现的 J^T取代；或

[0037] 同一原子上的2次出现的 J^R与它们所连接的原子一起形成具有0-2个选自氧、氮或硫的杂原子的3-6元环；其中由2次出现的 J^R形成的环任选地被0-3次出现的 J^X取代；或

[0038] 2次出现的 J^R与 Q^2一起形成6-10元饱和或部分不饱和桥连环系；

[0039] Q^3是具有0-3个选自氧、氮或硫的杂原子的3-7元完全饱和、部分不饱和或芳族单环；或具有0-5个选自氧、氮或硫的杂原子的7-12元完全饱和、部分不饱和或芳族双环；

[0040] J^X独立地选自 -CN；=O；卤素；或 C_{1-4}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

[0041] J^T独立地选自卤素、-CN；→O；=O；-OH；C_{1-6}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有0-2个选自氧、氮或硫的杂原子的3-6元非芳族环；每次出现的 J^T任选地被0-3次出现的 J^M取代；或

[0042] 同一原子上的2次出现的 J^T与它们所连接的原子一起形成具有0-2个选自氧、氮或硫的杂原子的3-6元环；或

[0043] 2次出现的 J^T与 Q^3一起形成6-10元饱和或部分不饱和桥连环系；

[0044] J^M独立地选自卤素或 C_{1-6}脂族基团；

[0045] n是0、1或2；且

[0046] R独立地选自H或 C_{1-4}脂族基团。

[0047] 在另一个实施方案中，本发明是式I的化合物，其中 R^9是H。

[0048] 在一个或多个方面，本发明是式I的化合物，其中 R^9是M。在另一个方面，本发明是式I的化合物，其中M是 C_{1-8}脂族基团，其中至多3个亚甲基单元任选地被 -O- 或 -NR- 替代。在一些方面，本发明是式I的化合物，其中M是 C_{1-4}烷基、$-(C_{1-4}$烷基$)O(C_{1-3}$脂族基团$)$、$-(C_{1-3}$烷基$)OH$、$-O(C_{1-4}$烷基$)N(C_{1-2}$烷基$)_2$、$-NH(C_{1-4}$烷基$)$ 或 $-(C_{1-4}$烷基$)NH(C_{1-4}$烷基$)$。在另一个方面，本发明是式I的化合物，其中M是 C_{1-4}烷基。

[0049] 在一个或多个实施方案中，本发明是式I的化合物，其中 J^{LM}是卤素。

[0050] 在一些实施方案中，本发明是式 I 的化合物，其中 R^9 是 $-(L)_k-W$。

[0051] 在另一个实例中，本发明是式 I 的化合物，其中 k 是 1。在其它实例中，本发明是式 I 的化合物，其中 k 是 0。

[0052] 在一个或多个方面，本发明是式 I 的化合物，其中 L 是 C_{1-8} 脂族基团，其中至多 3 个亚甲基单元任选地被 -O- 或 -NR- 替代。在本发明的其它方面，本发明是式 I 的化合物，其中 L 是 -O-、$-O(C_{1-4}$ 脂族基团 $)-$ 或 $-NR(C_{1-3}$ 烷基 $)-$。

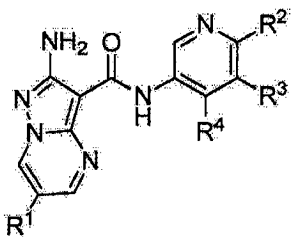
[0053] 在一个或多个实施方案中，本发明是式 I 的化合物，其中 W 是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。在一些实施方案中，本发明是式 I 的化合物，其中 W 是 3-7 元杂环基。在另一个实施方案中，本发明是式 I 的化合物，其中 W 独立地选自吡咯烷基、哌啶基、哌嗪基、氧杂环丁烷基或氮杂环丁烷基。

[0054] 在其它实施方案中，本发明是式 I 的化合物，其中 W 是具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。在另一个实施方案中，本发明是式 I 的化合物，其中 W 是八氢吡咯并 [1,2-a] 吡嗪。

[0055] 在一些方面，本发明是式 I 的化合物，其中 J^W 选自 C_{1-3} 烷基或 CF_3。在其它方面，本发明是式 I 的化合物，其中同一原子上的 2 次出现的 J^W 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环。在另一个方面，本发明是式 I 的化合物，其中由同一原子上 2 次出现的 J^W 形成的环是氧杂环丁烷基。

[0056] 本发明的另一个方面提供式 I-A 的化合物：

[0057]



I-A

[0058] 或其药学上可接受的盐或前药，其中：

[0059] R^1 独立地选自氟、氯或 $-C(J^1)_2CN$；

[0060] J^1 独立地选自 H 或 C_{1-2} 烷基；或

[0061] 2 次出现的 J^1 与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

[0062] R^2 独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2} 烷基；或 C_{1-3} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$ 替代；

[0063] R^3 独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4} 烷基；C_{3-4} 环烷基；-CN；或 C_{1-3} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$ 替代；

[0064] R^4 独立地选自 Q^1 或 C_{1-10} 脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；R^4 各自任选地被 0-5 次出现的 J^Q 取代；或

[0065] R^3 和 R^4 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6

元芳族或非芳族环；由 R^3和 R^4形成的环任选地被 0-3 次出现的 J^Z取代；

[0066] Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0067] J^z独立地选自 C_{1-6}脂族基团、=O、卤素或→O；

[0068] J^Q独立地选自 -CN；卤素；=O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被 0-3 次出现的 J^R取代；或

[0069] 同一原子上的 2 次出现的 J^Q与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^Q形成的环任选地被 0-3 次出现的 J^X取代；或

[0070] 2 次出现的 J^Q与 Q^1一起形成 6-10 元饱和或部分不饱和桥连环系；

[0071] Q^2独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0072] J^R独立地选自 -CN；卤素；=O；→O；Q^3；或 C_{1-6}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；J^R各自任选地被 0-3 次出现的 J^T取代；或

[0073] 同一原子上的 2 次出现的 J^R与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由 2 次出现的 J^R形成的环任选地被 0-3 次出现的 J^X取代；或

[0074] 2 次出现的 J^R与 Q^2一起形成 6-10 元饱和或部分不饱和桥连环系；

[0075] Q^3是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0076] J^X独立地选自 -CN；=O；卤素；或 C_{1-4}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；

[0077] J^T独立地选自卤素、-CN；→O；=O；-OH；C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T任选地被 0-3 次出现的 J^M取代；或

[0078] 同一原子上的 2 次出现的 J^T与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；或

[0079] 2 次出现的 J^T与 Q^3一起形成 6-10 元饱和或部分不饱和桥连环系；

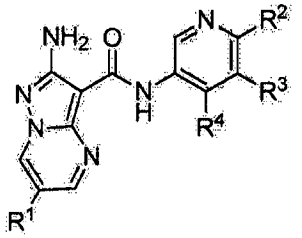
[0080] J^M独立地选自卤素或 C_{1-6}脂族基团；

[0081] n 是 0、1 或 2；且

[0082] R 独立地选自 H 或 C_{1-4}脂族基团。

[0083] 本发明的另一个方面提供式 I-A 的化合物：

[0084]



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[0085] 或其药学上可接受的盐或前药，其中：

[0086] R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

[0087] J^1独立地选自 H 或 C_{1-2}烷基；或

[0088] 2 次出现的 J^1与它们所连接的碳原子一起形成 3-4 元任选取代的碳环；

[0089] R^2独立地选自 H；卤素；-CN；NH_2；任选地被 0-3 次出现的氟取代的 C_{1-2}烷基；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0090] R^3独立地选自 H；卤素；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0091] R^4独立地选自 Q^1或 C_{1-10}脂族链，其中所述脂族链的至多 4 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；R^4各自任选地被 0-5 次出现的 J^Q取代；或

[0092] R^3和 R^4与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环；由形成 R^3和 R^4的环任选地被 0-3 次出现的 J^Z取代；

[0093] Q^1独立地选自 3-7 元完全饱和、部分不饱和或芳族单环，该 3-7 元环具有 0-3 个选自氧、氮或硫的杂原子；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0094] J^Z独立地选自 C_{1-6}脂族基团、= O、卤素或→ O；

[0095] J^Q独立地选自 -CN；卤素；= O；Q^2；或 C_{1-8}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；每次出现的 J^Q任选地被 0-3 次出现的 J^R取代；或

[0096] 同一原子上的 2 次出现的 J^Q与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；其中由环 2 次出现的 J^Q形成的任选地被 0-3 次出现的 J^X取代；或

[0097] 2 次出现的 J^Q与一起 Q^1形成 6-10 元饱和或部分不饱和桥连环系；

[0098] Q^2独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0099] J^R独立地选自 -CN；卤素；= O；→ O；Q^3；或 C_{1-6}脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被替代 -O-、-NR-、-C(O)- 或 $-S(O)_n-$；J^R各自任选地被 0-3 次出现的 J^T取代；或

[0100] 同一原子上的 2 次出现的 J^R与所连接的原子一起具有 0-2 个选自氧、氮或硫的杂

原子的形成 3-6 元环；其中由 2 次出现的 J^R 形成的环任选地被 0-3 次出现的 J^X 取代；或

[0101] 2 次出现的 J^R 与 Q^2 一起形成 6-10 元饱和或部分不饱和桥连环系；

[0102] Q^3 是具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0103] J^X 独立地选自 -CN；卤素；或 C_{1-4} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被替代 -O-、-NR-、-C(O)- 或 $-S(O)_n-$；

[0104] J^T 独立地选自 -CN；=O；-OH；C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n-$ 替代；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环；每次出现的 J^T 任选地被 0-3 次出现的 J^M 取代；或

[0105] 同一原子上的 2 次出现的 J^T 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；或

[0106] 2 次出现的 J^T 与一起 Q^3 形成 6-10 元饱和或部分不饱和桥连环系；

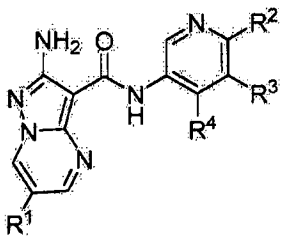
[0107] J^M 独立地选自卤素或 C_{1-6} 脂族基团；

[0108] n 是 0、1 或 2；且

[0109] R 独立地选自 H 或 C_{1-4} 脂族基团。

[0110] 本发明的另一个方面提供式 I-A 的化合物：

[0111]



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[0112] 或其药学上可接受的盐或前药，其中：

[0113] R^1 独立地选自氟、氯或 $-C(J^1)_2CN$；

[0114] J^1 独立地选自 H 或 C_{1-2} 烷基；或

[0115] 2 次出现的 J^1 与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0116] R^2 独立地选自 H；氯；NH_2；或任选地被氟取代的 C_{1-2} 烷基；

[0117] R^3 独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4} 烷基；C_{3-4} 环烷基；或 -CN；

[0118] R^4 独立地选自 Q^1 或 C_{1-10} 脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR- 或 -S- 替代；R^4 各自任选地被 0-5 次出现的 J^Q 取代；或

[0119] R^3 和 R^4 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环；由 R^3 和 R^4 形成的环任选地被 0-3 次出现的 J^Z 取代；

[0120] Q^1 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0121] J^Z 独立地选自 C_{1-6} 脂族基团、=O、卤素或→O；

[0122] J^Q独立地选自卤素；＝O；Q^2；或C_{1-8}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被-O-、-NR-、-S-、-C(O)-或$-S(O)_n-$替代；每次出现的J^Q任选地被0-3次出现的J^R取代；或

[0123] 同一原子上的2次出现的J^Q与它们所连接的原子一起形成具有0-2个选自氧、氮或硫的杂原子的3-6元环；其中由2次出现的J^Q形成的环任选地被0-3次出现的J^X取代；或

[0124] 2次出现的J^Q与Q^1一起形成6-10元饱和或部分不饱和桥连环系；

[0125] Q^2独立地选自具有0-3个选自氧、氮或硫的杂原子的3-7元完全饱和、部分不饱和或芳族单环；或具有0-5个选自氧、氮或硫的杂原子的8-12元完全饱和、部分不饱和或芳族双环；

[0126] J^R独立地选自卤素；＝O；→O；具有0-3个选自氧、氮或硫的杂原子的3-7元完全饱和、部分不饱和或芳族单环；或C_{1-4}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被-O-、-NR-、-S-、-C(O)-或$-S(O)_n-$替代；J^R各自任选地被0-3次出现的J^T取代；或

[0127] 同一原子上的2次出现的J^R与它们所连接的原子一起形成具有0-2个选自氧、氮或硫的杂原子的3-6元环；其中由2次出现的J^R形成的环任选地被0-3次出现的J^X取代；或

[0128] 2次出现的J^R与Q^2一起形成6-10元饱和或部分不饱和桥连环系；

[0129] J^X独立地选自卤素或C_{1-4}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被-O-、-NR-、-S-、-C(O)-或$-S(O)_n-$替代；或

[0130] J^T独立地选自C_{1-6}脂族基团或具有0-2个选自氧、氮或硫的杂原子的3-6元非芳族环；每次出现的J^T任选地被0-3次出现的J^M取代；

[0131] J^M独立地选自卤素或C_{1-6}脂族基团；

[0132] n是1或2；且

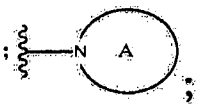
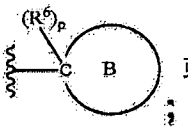
[0133] R独立地选自H或C_{1-4}脂族基团。

[0134] 在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^1是氟。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^1是$-CH_2CN$。在另一个实施方案中，R^1是$-CH(C_{1-2}$烷基$)CN$。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^1是$C(CH_3)_2CN$。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^1是氯。

[0135] 在一个实例中，本发明是由结构式I或I-A表示的化合物，其中R^2独立地选自$-CF_3$、$-NH(C_{1-2}$烷基$)$、氯或H。在另一个实例中，本发明是由结构式I或I-A表示的化合物，其中R^2是H。在其它实例中，本发明是由结构式I或I-A表示的化合物，其中R^2是-氯。

[0136] 在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3独立地选自H、氯、氟、CHF_2、-CN、环丙基或C_{1-4}烷基。在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3独立地选自H、氯或氟。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3是H。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3是$-O(C_{1-2}$烷基$)$。在其它实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3是氯。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中R^3是氟。

[0137] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^4 独立地选自：

[0138] -O-；  ；  ；或 $-CH_2-R^7$，其中：-O- 被 1 个 J^Q 取代；

[0139] 环 A 独立地选自具有 1-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0140] 环 B 独立地选自具有 0-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环；或具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环；

[0141] R^6 是 H；

[0142] R^7 独立地选自 H 或 C_{1-8} 脂族链，其中所述脂族链的至多 3 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代；且

[0143] p 是 0 或 1。

[0144] 在一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^4 是 -O-。在一些实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^Q 独立地选自 $-(C_{1-4}$ 烷基)、$-(C_{1-4}$ 烷基)$N(C_{1-4}$ 烷基$)_2$、$-(C_{1-3}$ 烷基)$O(C_{1-2}$ 烷基)$N(C_{1-3}$ 烷基$)_2$、$(C_{1-4}$ 烷基)OH、$-(C_{1-4}$ 烷基)NH_2 或 $-(C_{1-4}$ 烷基)$O(C_{1-4}$ 烷基)。

[0145] 在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^Q 是 Q^2。在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是具有 0-3 个选自氧、硫或氮的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。

[0146] 在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 独立地选自 5-6 元芳基、5-6 元杂芳基、4-6 元脂环族基团或 4-7 元杂环基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是 4-7 元杂环基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时、Q^2 独立地选自吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1,3-噁嗪烷基、1,3-噻嗪烷基、二氢吡啶基、二氢咪唑基、1,3-四氢嘧啶基、二氢嘧啶基、1,4-二氮杂庚环基、1,4-氧杂氮杂庚环基、1,4-硫杂氮杂庚环基、四氢噻喃基、四氢呋喃基、四氢吡喃基、氮杂环丁烷基和氧杂环丁烷基。在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 独立地选自四氢噻喃基、吡咯烷基、哌啶基、哌嗪基、四氢呋喃基、四氢吡喃基或氮杂环丁烷基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是哌啶基。

[0147] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是 5-6 元杂芳基。在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 独立地选自咪唑基、吡咯基、吡啶基、吡嗪基、嘧啶基、吡唑基、1,2,3-三唑基或 1,2,4-三唑基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的

化合物，其中当 R^4 是 -O- 时，Q^2 是吡啶基。

[0148] 在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是 4-6 元脂环族基团。在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 独立地选自环丁基或环己基。在其它实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是苯基。

[0149] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和、部分不饱和或芳族双环。在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是具有 0-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^2 是 6,7- 二氢 -5H- 吡咯并 [1,2-a] 咪唑。

[0150] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是 C_{1-6} 脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-S-、-C(O)- 或 $-S(O)_n-$ 替代。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 独立地选自 C_{1-4} 烷基、$-N(C_{1-4}烷基)_2$、-C(O)OH、$-C(O)O(C_{1-4}烷基)$、$-C(O)N(C_{1-4}烷基)_2$、$-(C_{1-4}烷基)O(C_{1-4}烷基)$ 或 -C(O)-。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是 C_{1-4} 烷基。

[0151] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是具有 0-3 个选自氧、硫或氮的杂原子的 3-6 元完全饱和、部分不饱和或芳族单环。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是具有 1-3 个选自氧、氮或硫的杂原子的 3-6 元杂环基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 独立地选自氧杂环丁烷基、哌啶基、氮杂环丁烷基、哌嗪基、吡咯烷基、吗啉基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是氧杂环丁烷基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是环丙基。

[0152] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是 Q^3。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 Q^3 是具有 0-3 个选自氧、硫或氮的杂原子的 3-6 元完全饱和、部分不饱和或芳族单环。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^3 是具有 1-3 个选自氧、氮或硫的杂原子的 3-6 元杂环基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^3 独立地选自氧杂环丁烷基、哌啶基、氮杂环丁烷基、哌嗪基、吡咯烷基、吗啉基。在其它实施方案中，当 R^4 是 -O- 时，Q^3 是氧杂环丁烷基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，Q^3 是环丙基。

[0153] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^R 是 = O 或卤素。

[0154] 在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环。在另一个实施方案中，本发明是由结构式 I 或 I-A 表

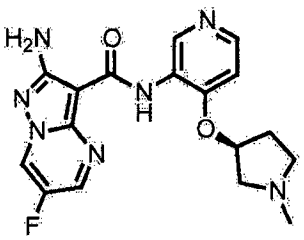
示的化合物，其中当 R^4 是 -O- 时，由同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成的环选自氧杂环丁烷基、环丁基或氮杂环丁烷基。

[0155] 在其它实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^T 是具有 1-2 个选自氧、氮或硫的杂原子的 4-6 元杂环。在一些实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是 -O- 时，J^T 是哌嗪基。

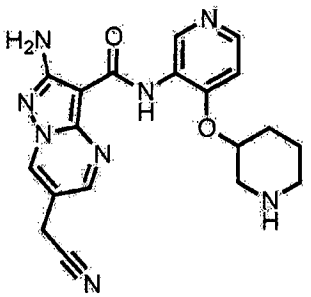
[0156] 在另一个实例中，本发明的式 I 和 I-A 的化合物呈现在表 1 中。本领域技术人员可以理解，本发明的化合物可以以不同的互变体形式呈现。

[0157] 表 1

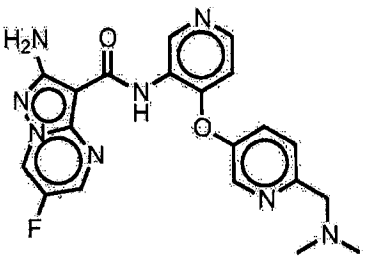
[0158]



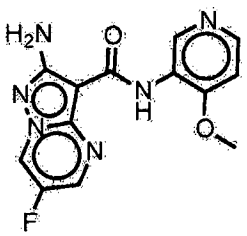
I-O-1



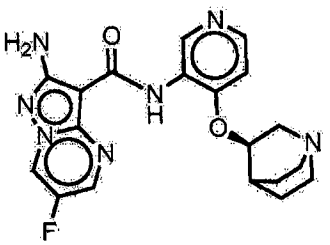
I-O-2



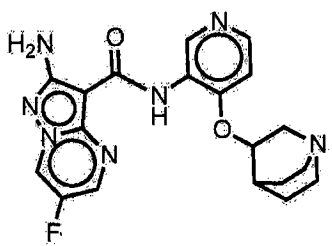
I-O-3



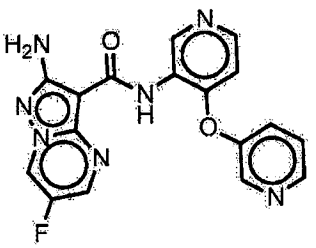
I-O-4



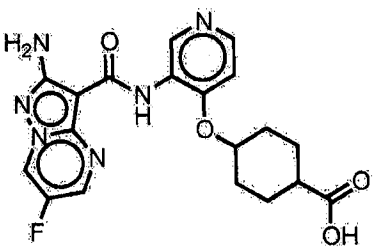
I-O-5



I-O-6

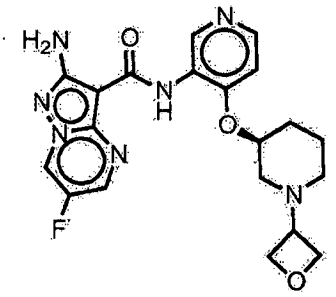


I-O-7

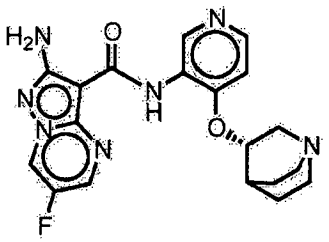


I-O-8

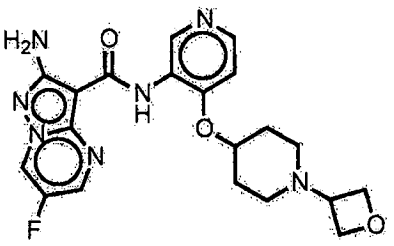
[0159]



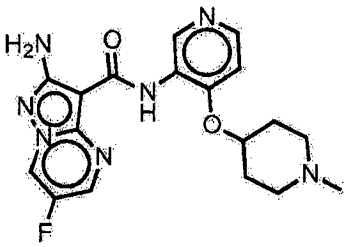
I-O-9



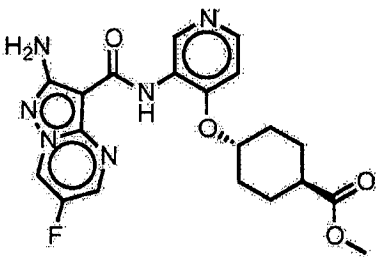
I-O-10



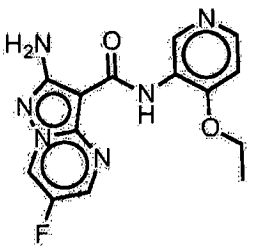
I-O-11



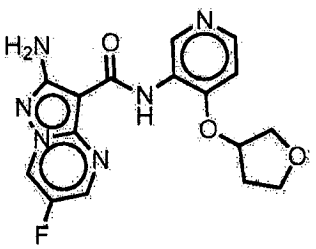
I-O-12



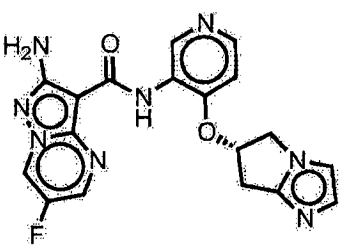
I-O-13



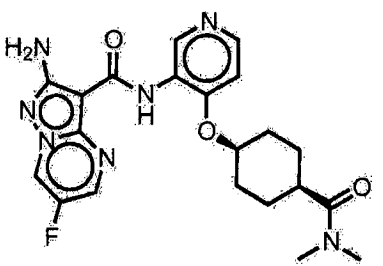
I-O-14



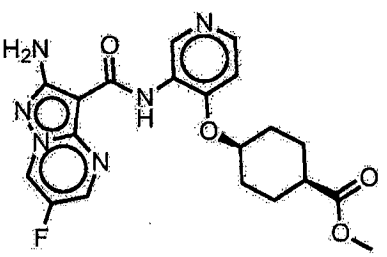
I-O-15



I-O-16

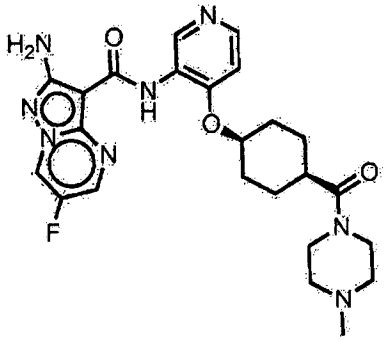


I-O-17

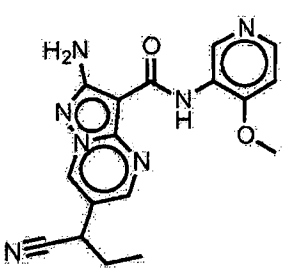


I-O-18

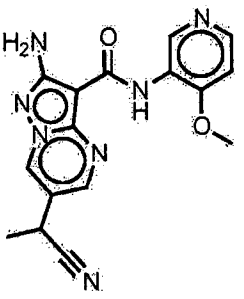
[0160]



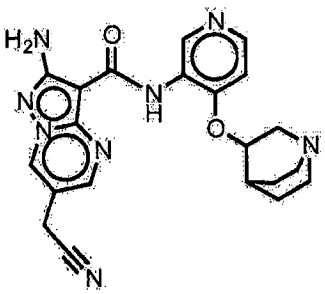
I-O-19



I-O-20



I-O-21



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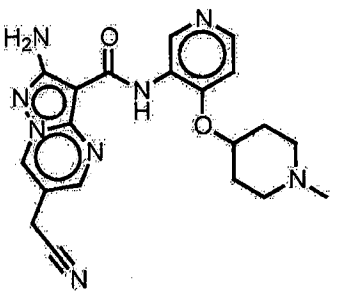

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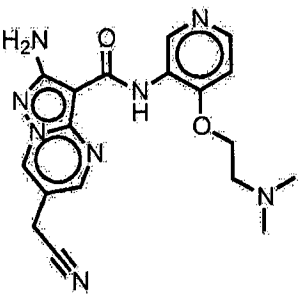
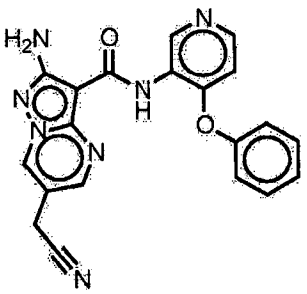


I-O-24



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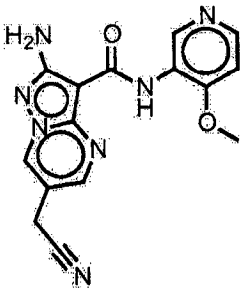

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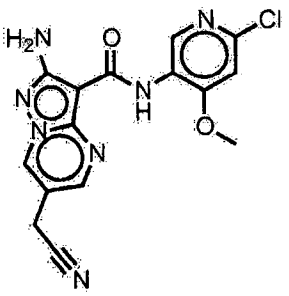

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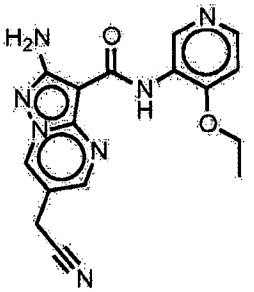

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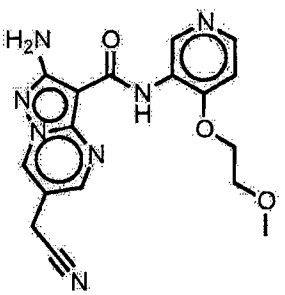

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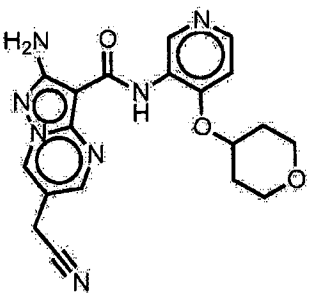

I-O-30

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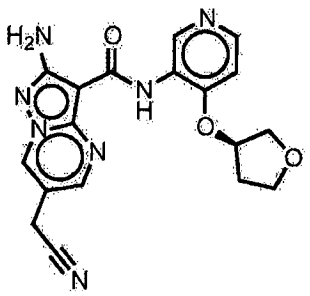
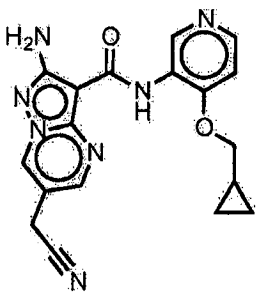


I-O-31



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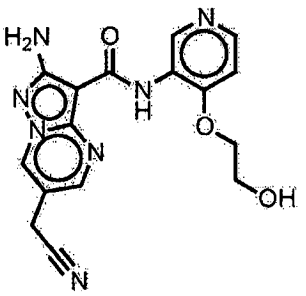

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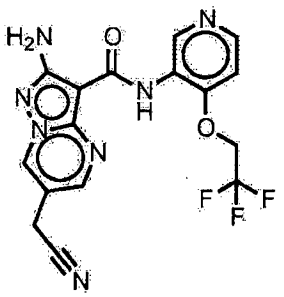
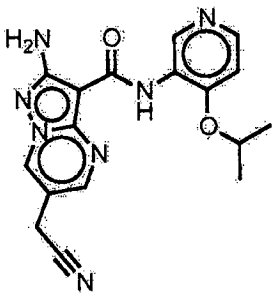
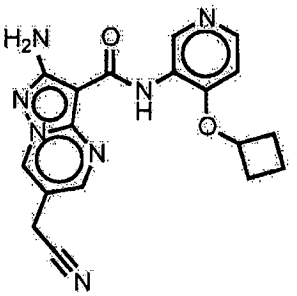


I-O-34



I-O-35



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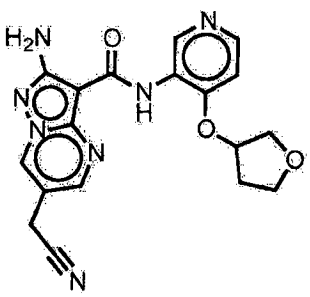

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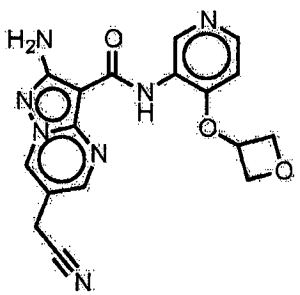
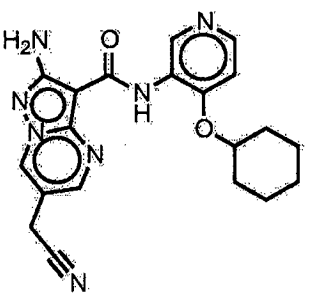


I-O-38



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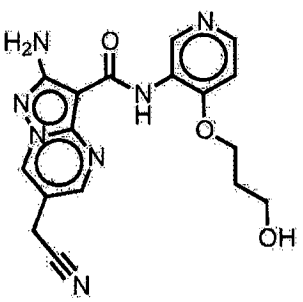

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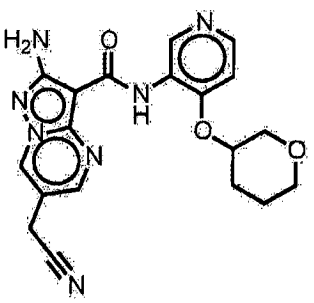

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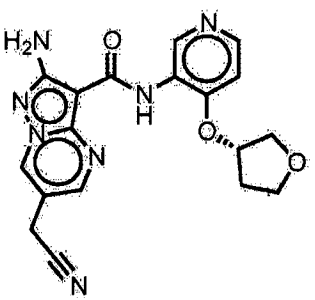
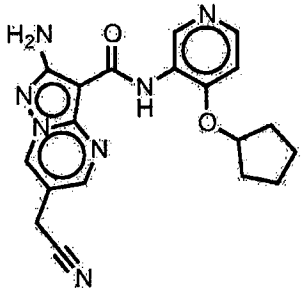
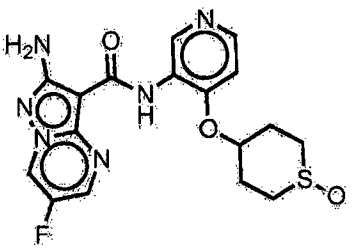


I-O-42

[0162]



I-O-43



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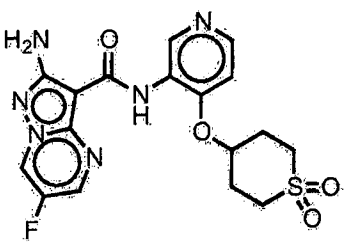
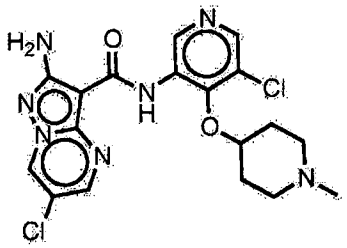
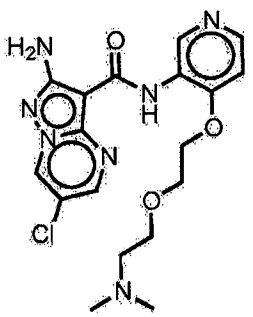


I-O-45



I-O-46



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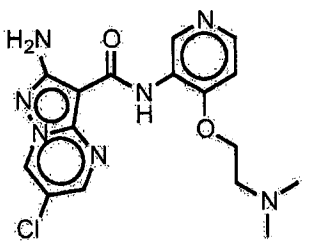

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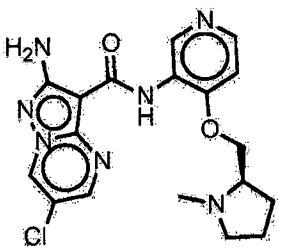

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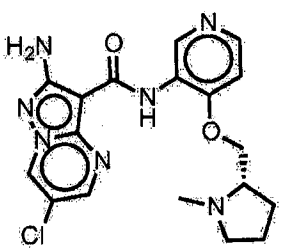
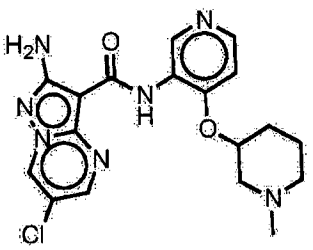
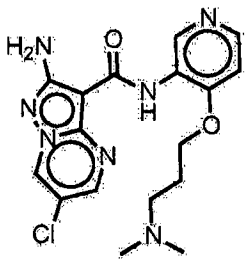


I-O-50



I-O-51



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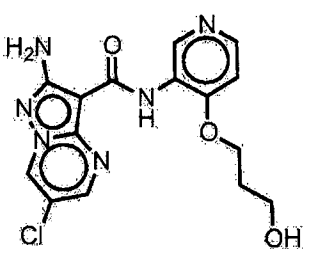
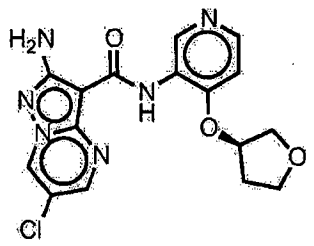


I-O-53

[0163]



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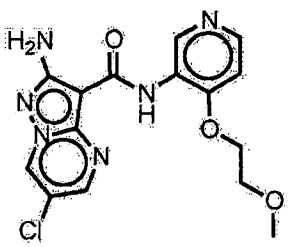

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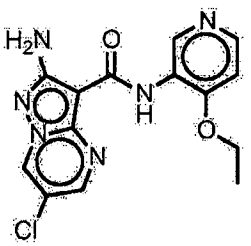
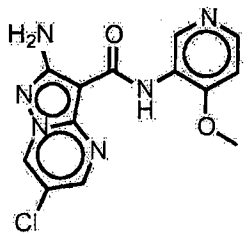


I-O-56



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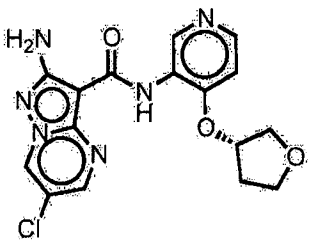
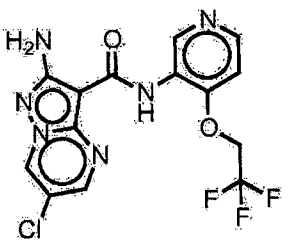
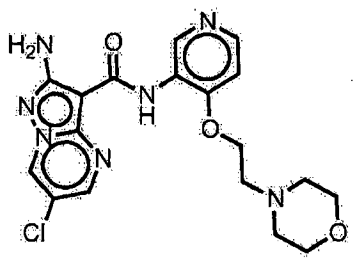


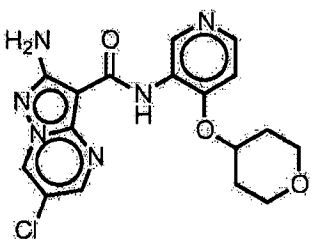
I-O-58



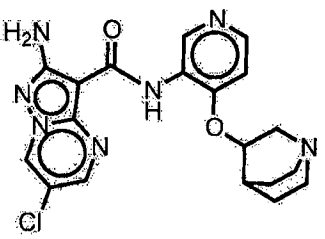
I-O-59



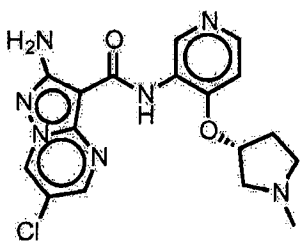
I-O-60



I-O-61



I-O-62



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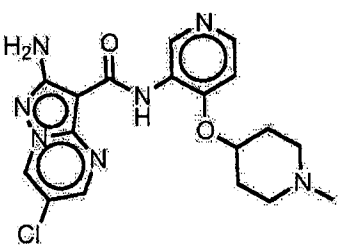
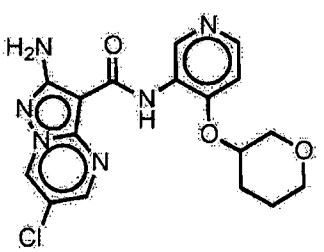


I-O-64



I-O-65

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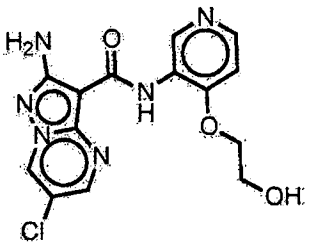
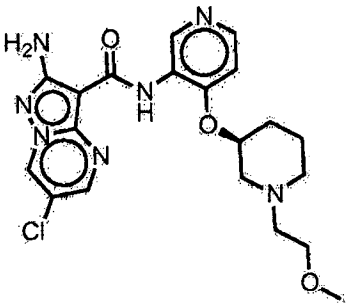
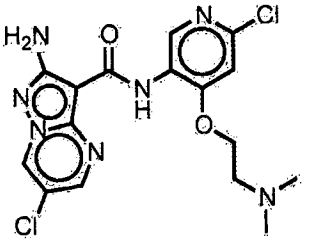


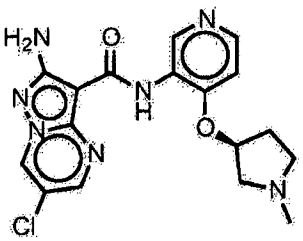
I-O-66



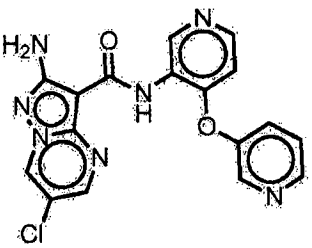
I-O-67



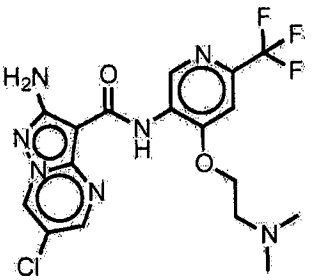
I-O-68



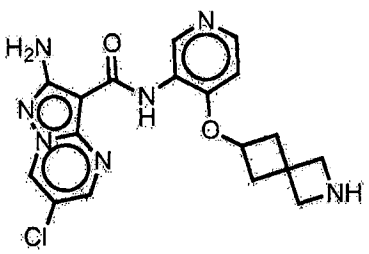
I-O-69



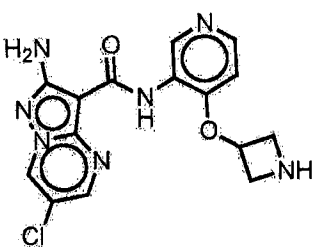
I-O-70



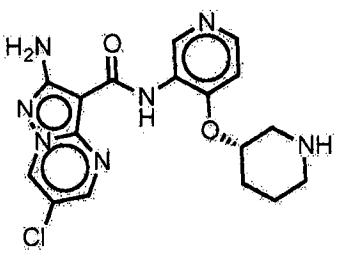
I-O-71



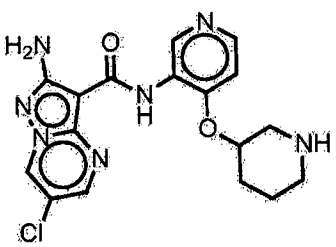
I-O-72



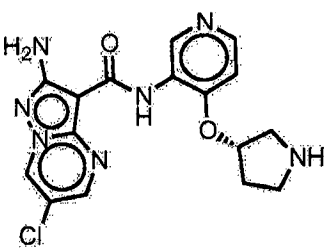
I-O-73



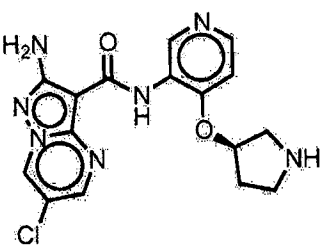
I-O74



I-O-75

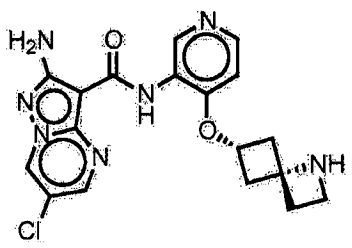


I-O-76

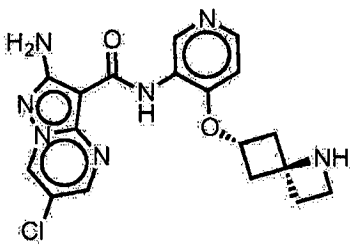


I-O-77

[0165]



I-O-78



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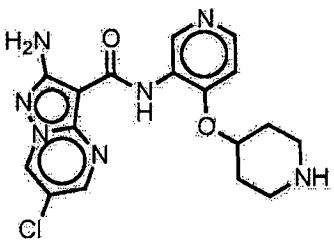

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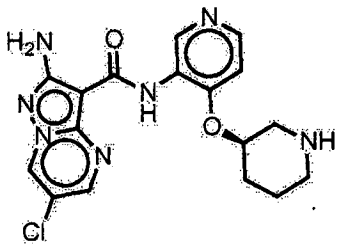
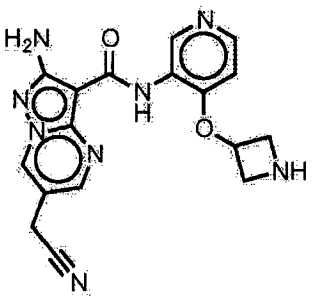
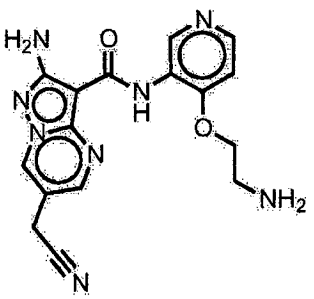


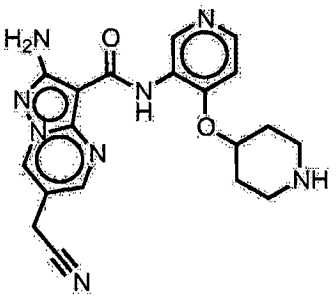
I-O-81



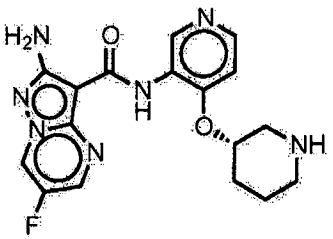
I-O-82



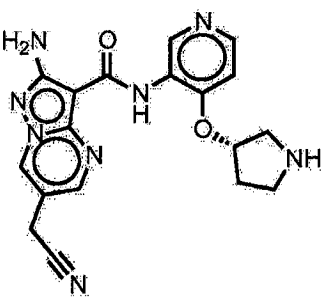
I-O-83



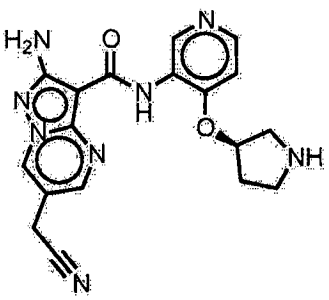
I-O-84



I-O-85

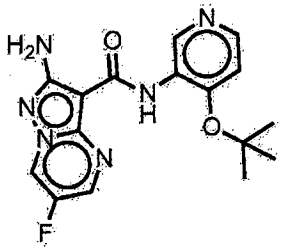


I-O-86

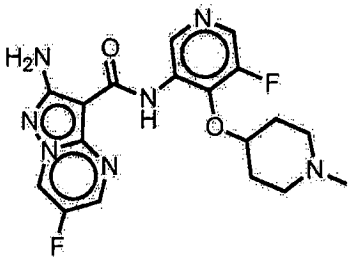


I-O-87

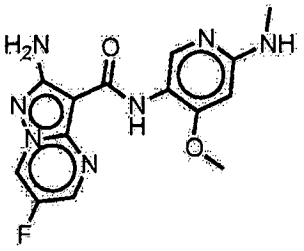
[0166]



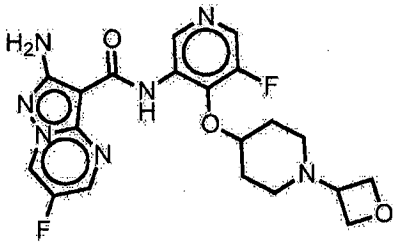
I-O-88



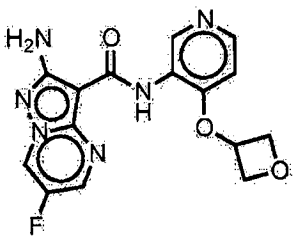
I-O-89



I-O-90



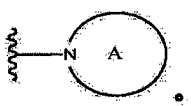
I-O-91



I-O-92。

[0167] 在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^4 是环 A，其以如下结构表示：

[0168]



[0169] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 是具有 1-3 个选自氧、氮或硫的杂原子的 3-7 元完全饱和、部分不饱和或芳族单环。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 是 4-6 元杂环基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 是 3-7 元杂环基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1,3- 噁嗪烷基、1,3- 噻嗪烷基、二氢吡啶基、二氢咪唑基、1,3- 四氢嘧啶基、二氢嘧啶基、1,4- 二氮杂庚环基、1,4- 氧杂氮杂庚环基、1,4- 硫杂氮杂庚环基和氮杂环丁烷基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自哌啶基、哌嗪基、1,4- 二氮杂庚环基、硫代吗啉基、吡咯烷基、氮杂庚环基和吗啉基。在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自哌嗪基或哌啶基。

[0170] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 是 5 元杂芳基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自吡咯基、咪唑基、吡唑基、1,2,3- 三唑基或 1,2,4- 三唑基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自吡唑基或咪唑基。

[0171] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 是具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和、部分不饱和或芳族双环。在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 A 独立地选自八氢吡咯并 [1,2-a] 吡

嗪基、5,6,7,8-四氢咪唑并[1,2-a]吡啶基、八氢-1H-吡嗪并[1,2-a]吡嗪基、5,6,7,8-四氢咪唑并[1,5-a]吡嗪基、2,5-二氮杂双环[4.1.0]或八氢吡嗪并[2,1-c][1,4]噁嗪基。

[0172] 在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q是C_{1-8}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被-O-、-NR-或-C(O)-替代。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q是C_{1-6}脂族链，其中所述脂族链的至多2个亚甲基单元任选地被-O-、-NR-或-C(O)-替代。在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q独立地选自-O-、-C(O)-、-S(O)$_2$-、C_{1-4}烷基、-(C_{0-4}烷基)NH_2、-(C_{0-4}烷基)NH(C_{1-4}烷基)、-(C_{0-4}烷基)N(C_{1-4}烷基)$_2$、-(C_{0-4}烷基)OH、-(C_{0-4}烷基)O(C_{1-4}烷基)、-C(O)OH、-S(O)$_2$N(C_{1-3}烷基)-、-C(O)(C_{1-4}烷基)-、-(O)C(C_{1-4}烷基)N(C_{1-2}烷基)$_2$或-C(O)O(C_{1-4}烷基)。在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q独立地选自-C(O)-、C_{1-4}烷基、-(C_{0-4}烷基)NH_2、-(C_{0-4}烷基)NH(C_{1-4}烷基)、-(C_{0-4}烷基)N(C_{1-4}烷基)$_2$、-(C_{0-4}烷基)OH、-(C_{0-4}烷基)O(C_{1-4}烷基)、-C(O)OH、-C(O)O(C_{1-4}烷基)。在其它实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q是C_{1-4}烷基。在其它实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q是C_{1-4}烷基、-O-或-C(O)-。

[0173] 在一个或多个实例中，当R^4是环A时，J^Q是Q^2。

[0174] 在另一个实例中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2是3-7元杂环基或碳环基；该杂环基具有1-3个选自氧、氮或硫的杂原子。在其它实例中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2独立地选自氧杂环丁烷基、四氢吡喃基、四氢呋喃基、环丙基、氮杂环丁烷基、吡咯烷基、哌嗪基、环丁基、硫代吗啉基或吗啉基。在另一个实例中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2独立地选自氧杂环丁烷基、四氢吡喃基或四氢呋喃基。在一些实例中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2是氧杂环丁烷基。

[0175] 在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2是具有0-5个选自氧、氮或硫的杂原子的7-12元完全饱和、部分不饱和或芳族双环。在一些实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2是具有0-5个选自氧、氮或硫的杂原子的8-12元完全饱和、部分不饱和或芳族双环。在另一个实例中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，Q^2独立地选自5,6,7,8-四氢咪唑并[1,5-a]吡嗪基或5,6,7,8-四氢咪唑并[1,2-a]吡嗪基。

[0176] 在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中2次出现的J^Q与环A一起形成桥连环系。

[0177] 在其它实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^Q是=O。

[0178] 在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^R是具有1-3个选自氧、氮或硫的杂原子的3-6元杂环基。在其它实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^R独立地选自氧杂环丁烷基、哌啶基、氮杂环丁烷基、哌嗪基、吡咯烷基或吗啉基。在另一个实施方案中，本发明是由结构式I或I-A表示的化合物，其中当R^4是环A时，J^R是哌嗪基。

[0179] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 A 时，J^R 独立地选自卤素、= O、-OH、C_{1-4} 烷基、-(C_{0-4} 烷基)N(C_{1-4} 烷基)$_2$ 或 -(C_{0-4} 烷基)O(C_{1-4} 烷基)。

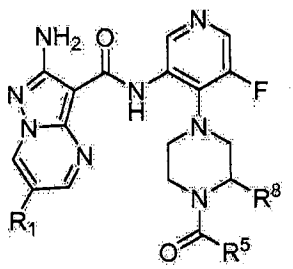
[0180] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 A 时，同一原子上的 2 次出现的 J^R 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元芳族或非芳族环。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 A 时，J^R 独立地选自氧杂环丁烷基或氮杂环丁烷基。

[0181] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 2 次出现的 J^R 与环 A 一起形成桥连环系。

[0182] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 J^T 是具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 J^T 是氧杂环丁烷基。在另一个实施方案中，J^T 是 C_{1-6} 脂族基团。在另一个实施方案中，J^T 是甲基。

[0183] 本发明的另一个方面提供式 I-A-1 的化合物：

[0184]



I-A-1 ；

[0185] 其中：

[0186] R^5 选自 C_{1-4} 脂族基团、3-6 元环烷基或具有 1-2 个选自氧或硫的杂原子的 3-6 元杂环基；

[0187] R^8 选自 H 或 C_{1-3} 烷基；或

[0188] R^5 和 R^8 与它们所连接的原子一起形成具有 1-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环。

[0189] 在另一个实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中式 I-A-1 中的 R^1 是氟。

[0190] 在另一个实例中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 是 C_{1-4} 脂族基团。在另一个实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 独立地选自甲基或乙基。

[0191] 在一些实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 是 3-6 元环烷基。在其它实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 是环丙基。

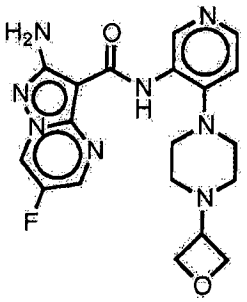
[0192] 在另一个实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 是具有 1-2 个选自氧或硫的杂原子的 3-6 元杂环基。在一些实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5 是四氢呋喃基或氧杂环丁烷基。

[0193] 在其它实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中 R^5和 R^8与它们所连接的原子一起形成具有 1-2 个选自氧、氮或硫的杂原子的 5-6 元非芳族环。在另一个实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中由 R^5和 R^8形成的环是 5 元环。在另一个实施方案中，本发明是由结构式 I-A-1 表示的化合物，其中由 R^5和 R^8形成的环是 6 元环。

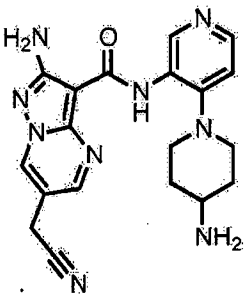
[0194] 在另一个实例中，本发明式 I、I-A 和 I-A-1 的化合物呈现在表 2 中。

[0195] 表 2

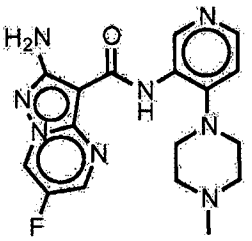
[0196]



I-N-1



I-N-2



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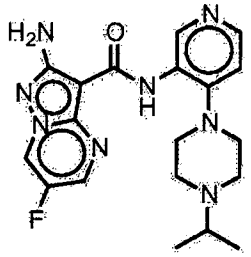

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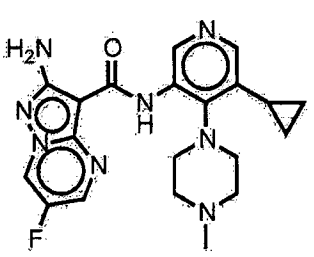

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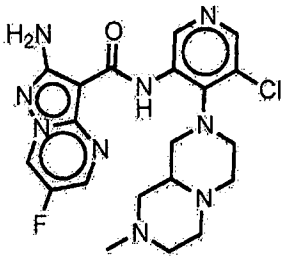

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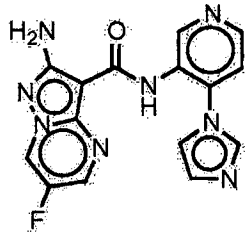

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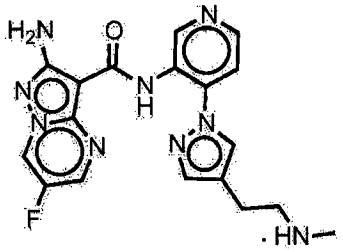

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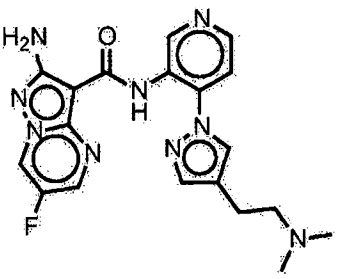

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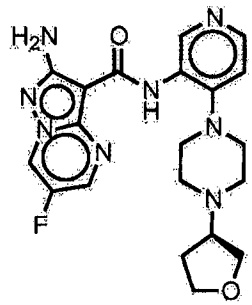

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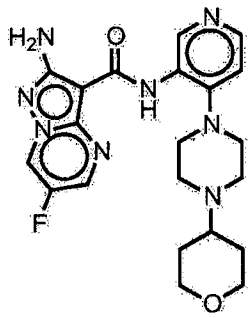

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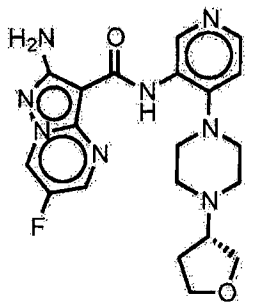

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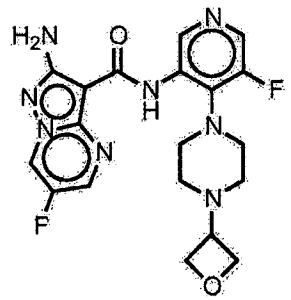

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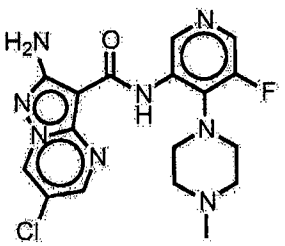

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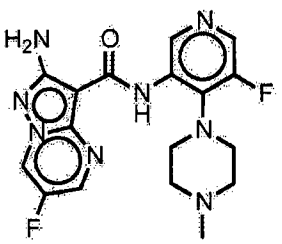

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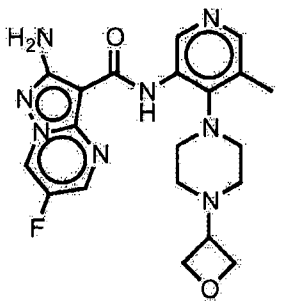

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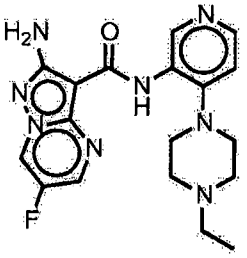

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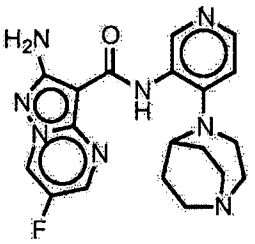

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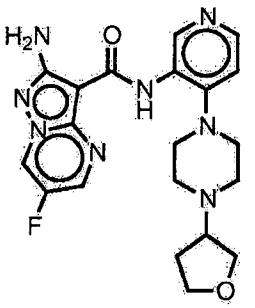

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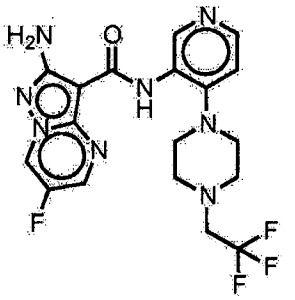

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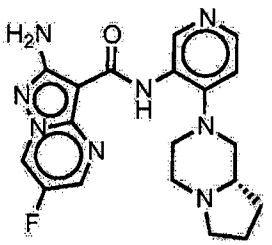

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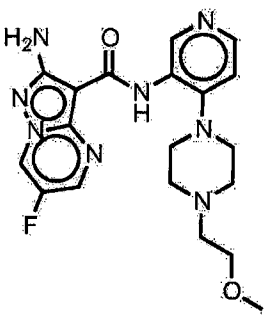

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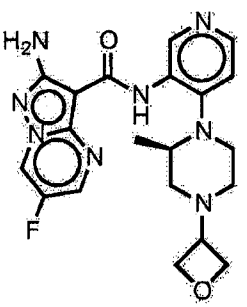

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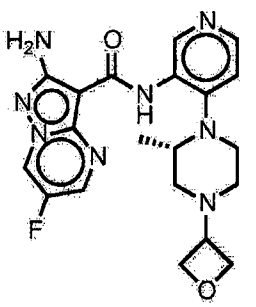

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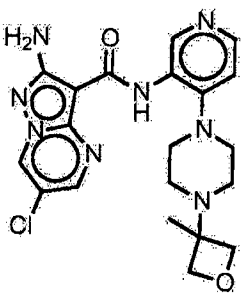

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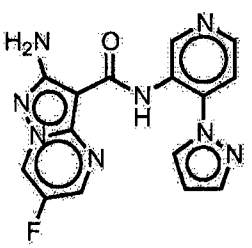

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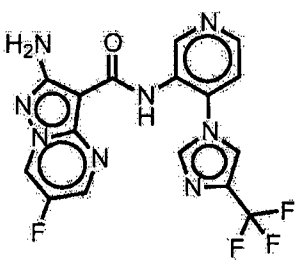

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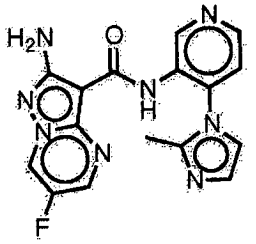

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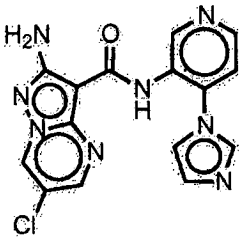

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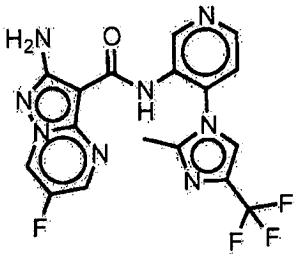

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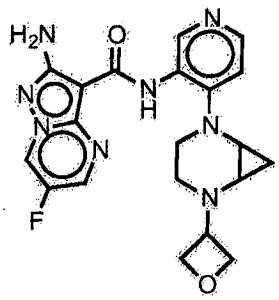

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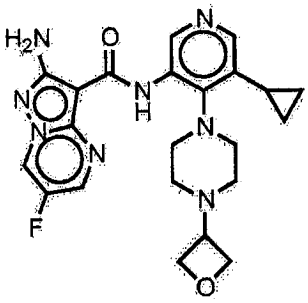

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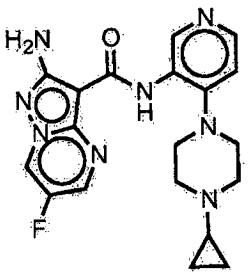

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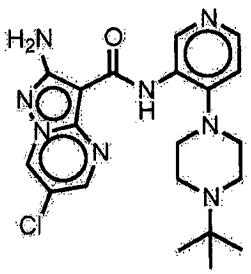

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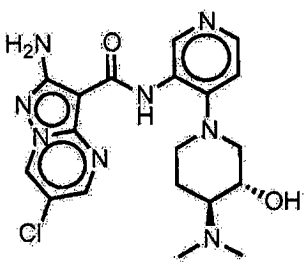

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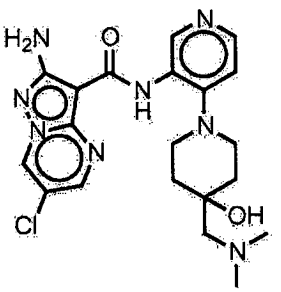
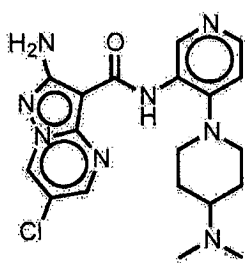


I-N-36



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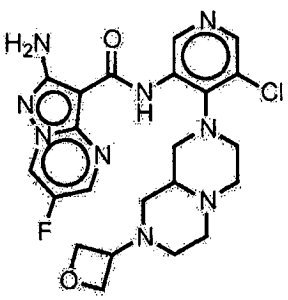

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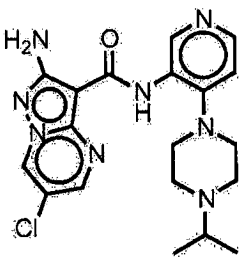

I-N-39

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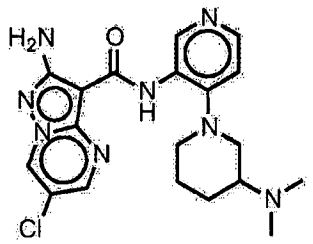
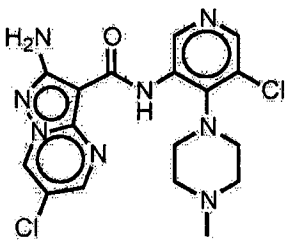


I-N-40



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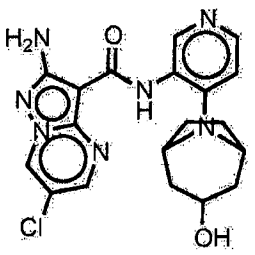
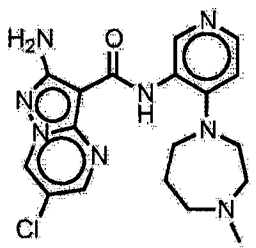


I-N-42



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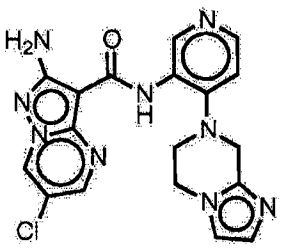

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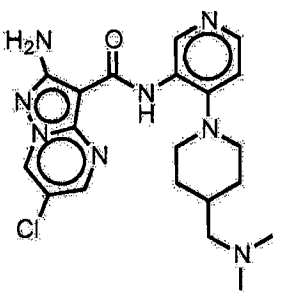

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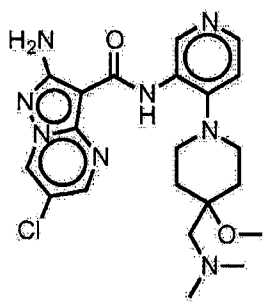

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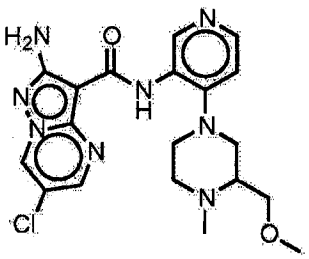

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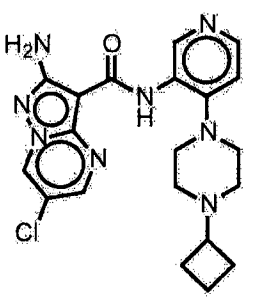

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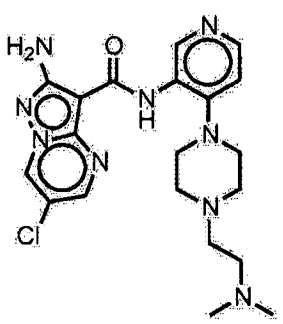
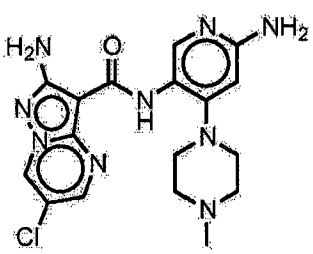
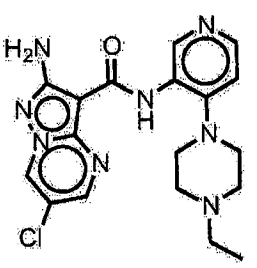


I-N-49



I-N-50



I-N-51

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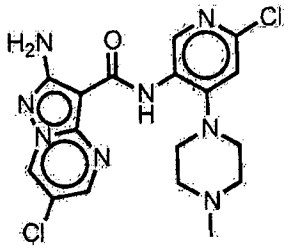
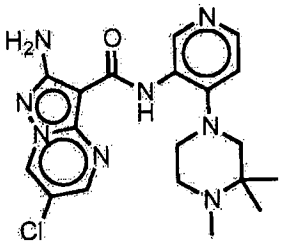


I-N-52



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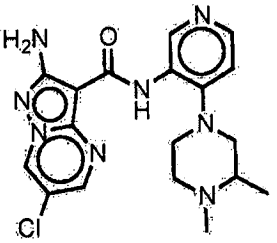

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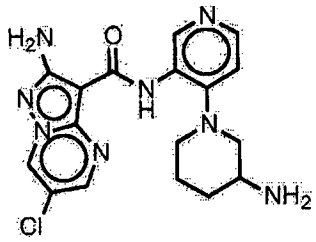

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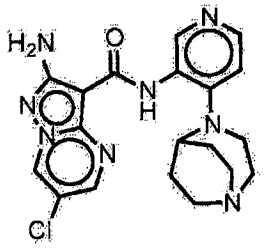
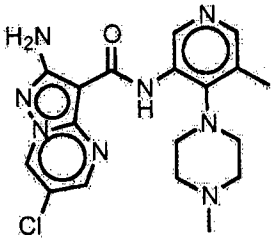
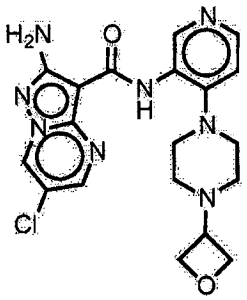


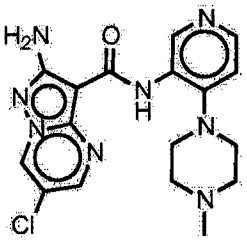
I-N-56



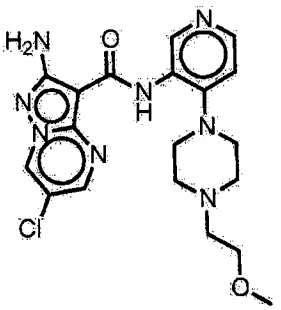
I-N-57



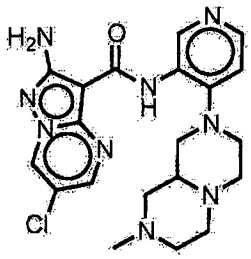
I-N-58



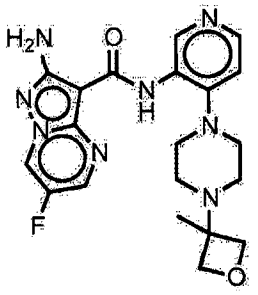
I-N-59



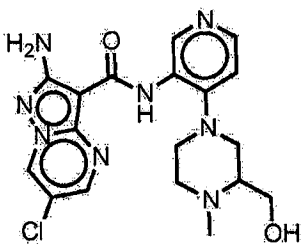
I-N-60



I-N-61

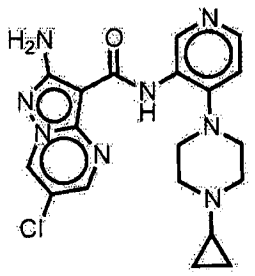


I-N-62

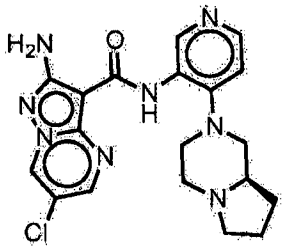


I-N-63

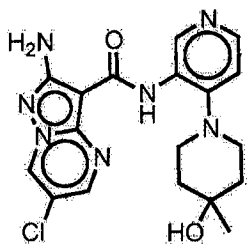
[0202]



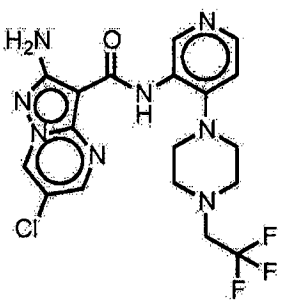
I-N-64



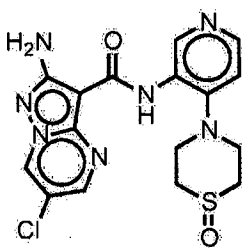
I-N-65



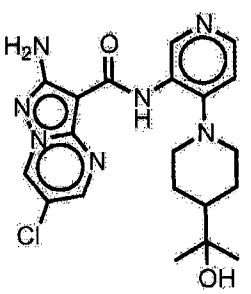
I-N-66



I-N-67



I-N-68



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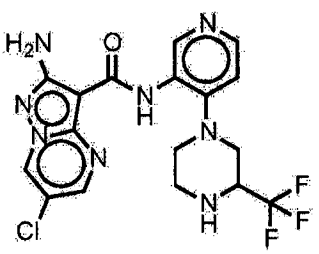
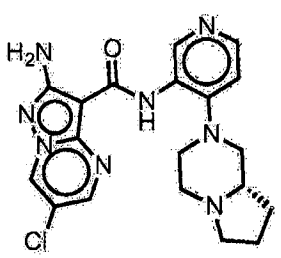
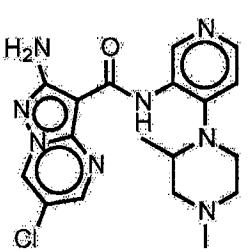


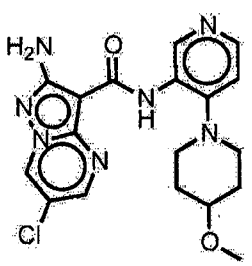
I-N-70



I-N-71

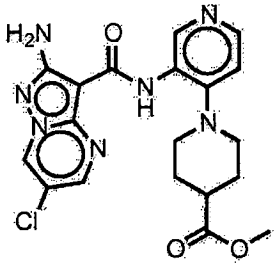


I-N-72

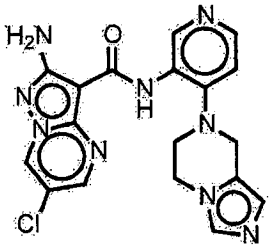


I-N-73

[0203]



I-N-74



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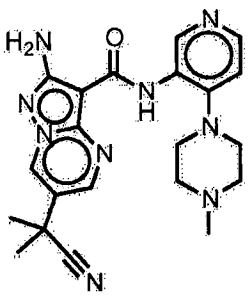

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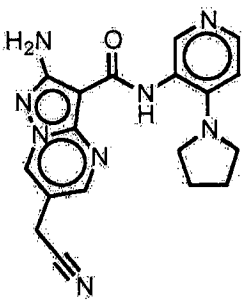
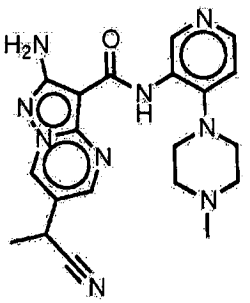
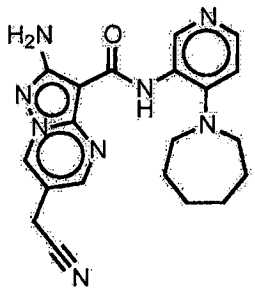


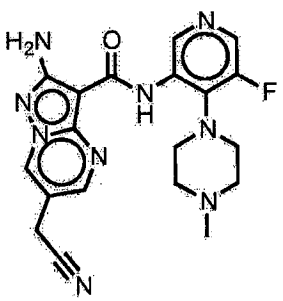
I-N-77



I-N-78



I-N-79



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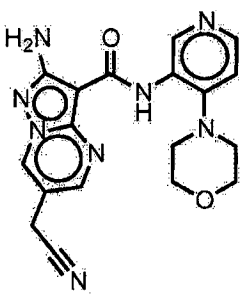
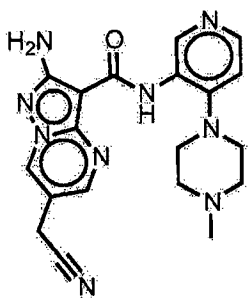
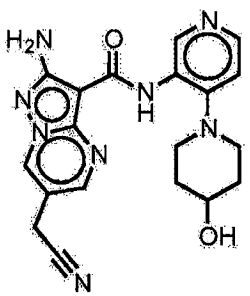


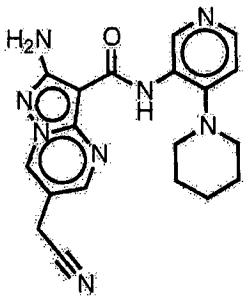
I-N-81



I-N-82



I-N-83



I-N-84

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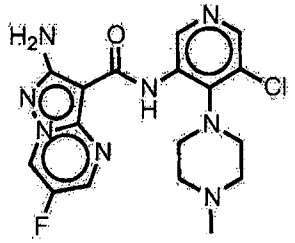
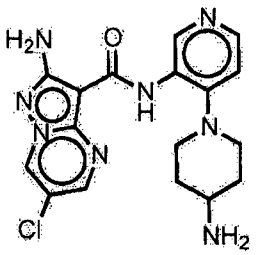
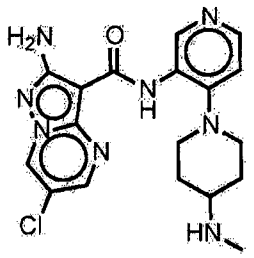


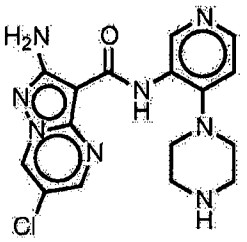
I-N-85



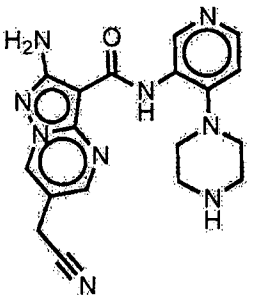
I-N-86



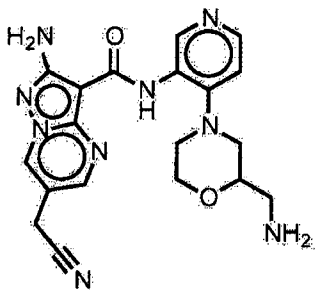
I-N-87



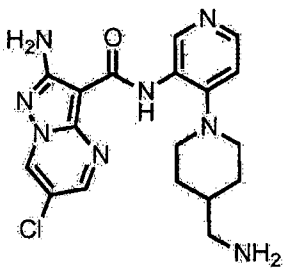
I-N-88



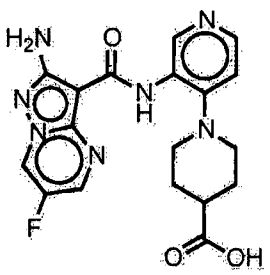
I-N-89



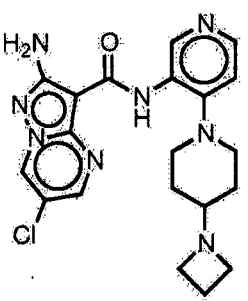
I-N-90



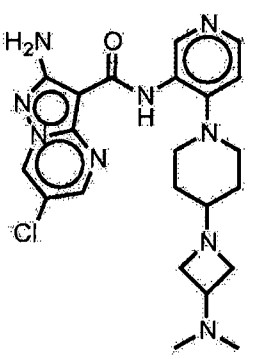
I-N-91



I-N-92

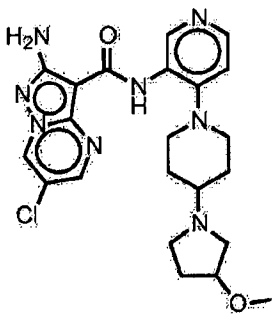


I-N-93

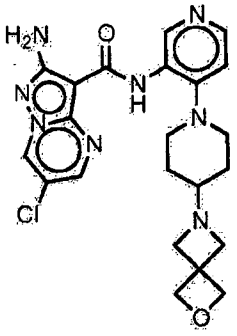


I-N-94

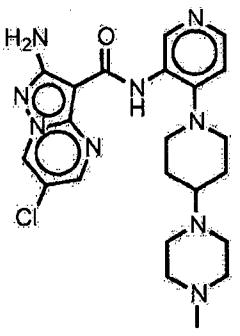
[0205]



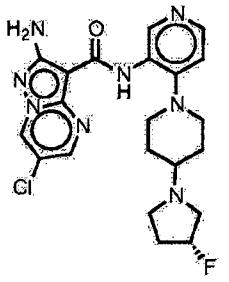
I-N-95



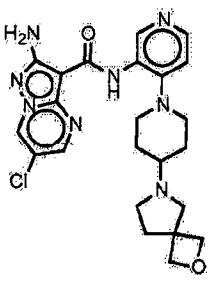
I-N-96



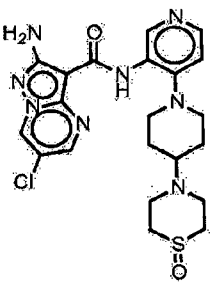
I-N-97



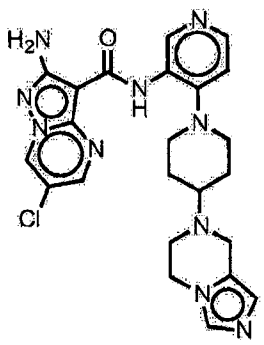
I-N-98



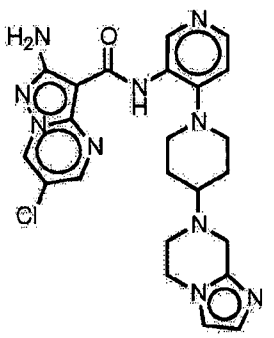
I-N-99



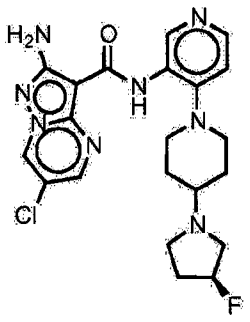
I-N-100



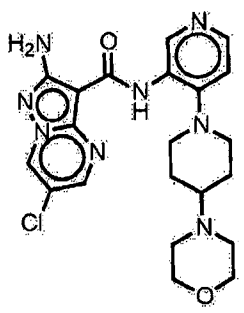
I-N-101

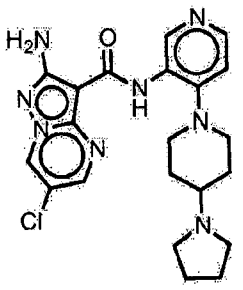


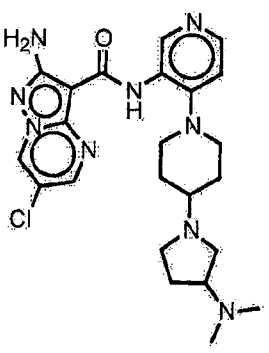
I-N-102



I-N-103







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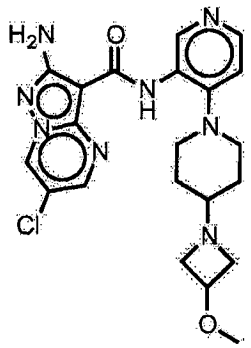
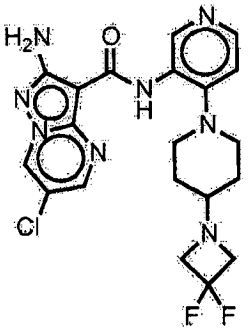
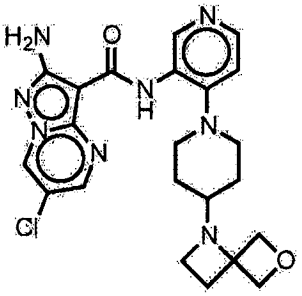
I-N-104



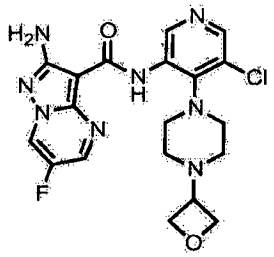
I-N-105



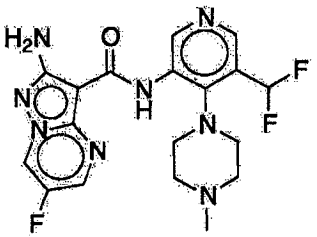
I-N-106



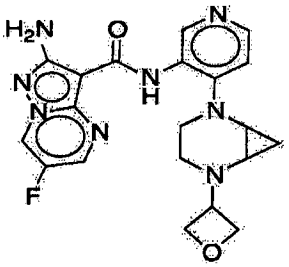
I-N-107



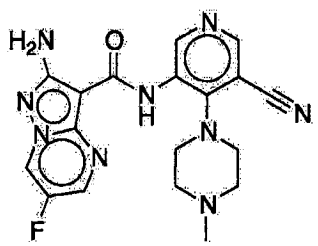
I-N-108



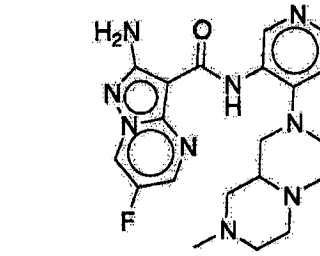
I-N-109



I-N-110



I-N-111

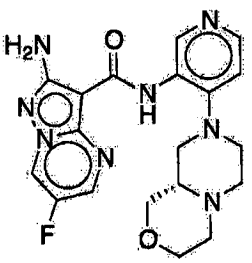


I-N-112

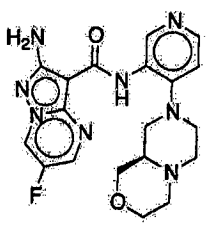
I-N-113

I-N-114

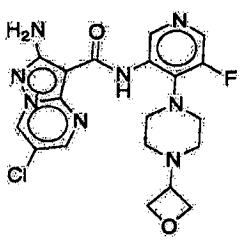
I-N-115



I-N-116



I-N-117



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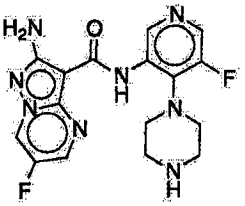

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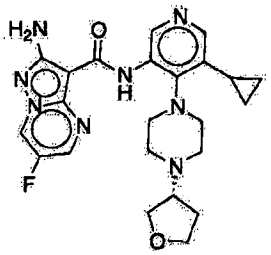

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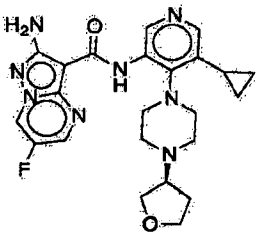

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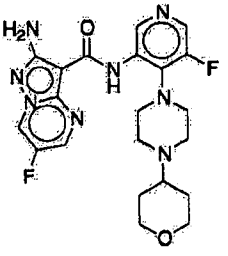

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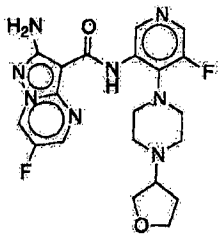

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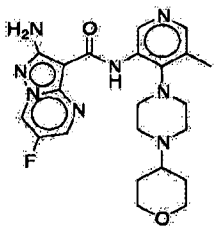

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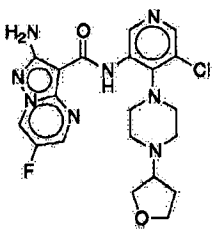

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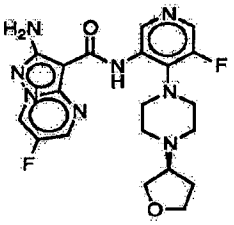
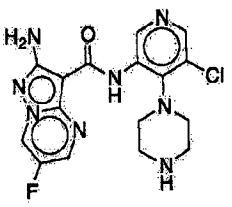


I-N-125



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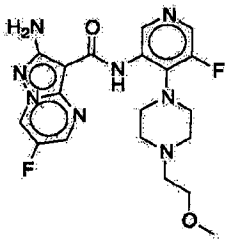

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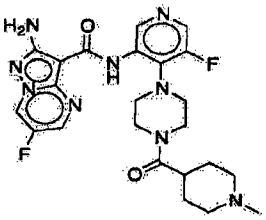

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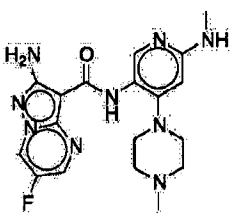

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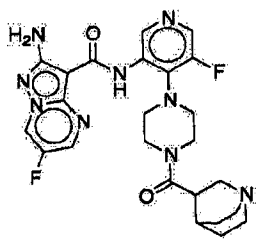

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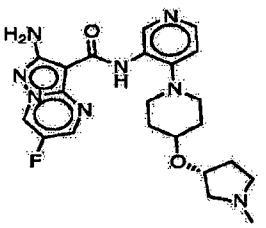

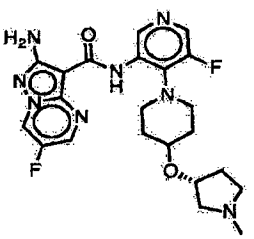

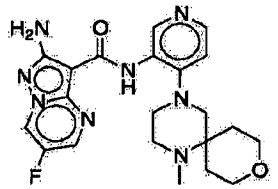

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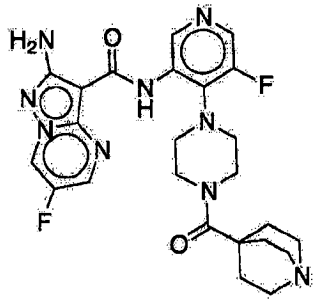
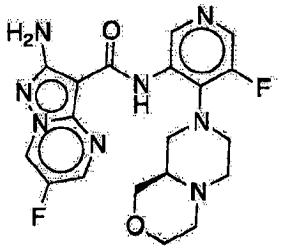
I-N-131



I-N-132



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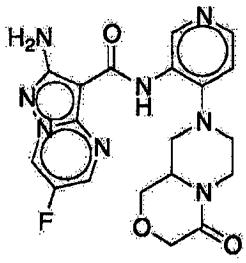

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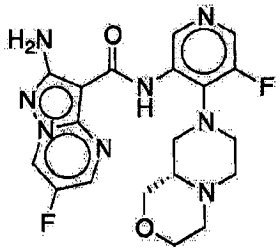

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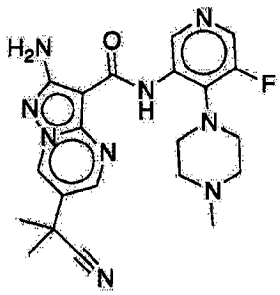

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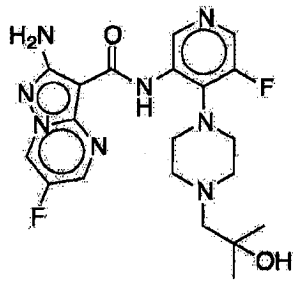

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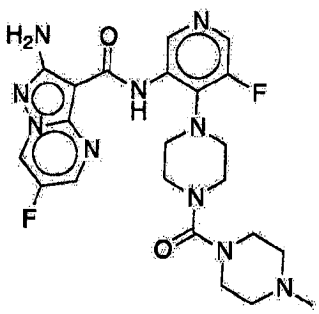

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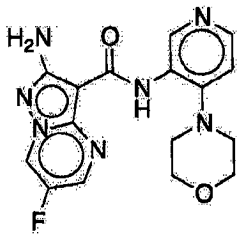

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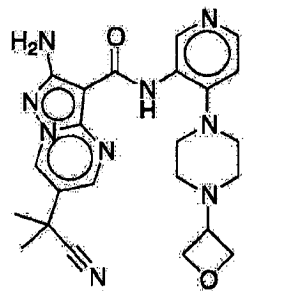

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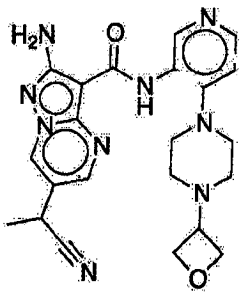
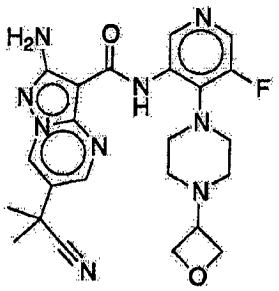
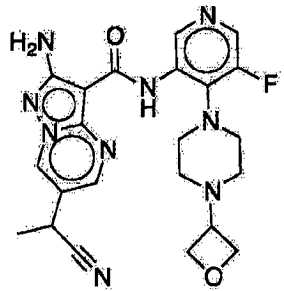


I-N-141



I-N-142



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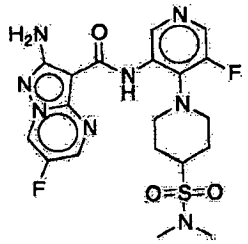
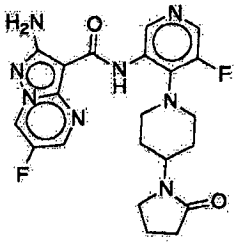
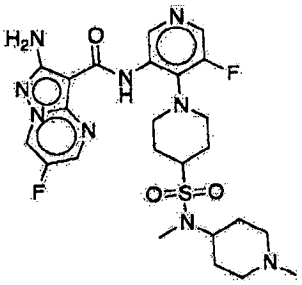
I-N-143



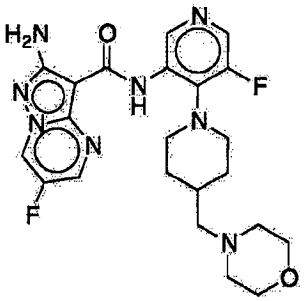
I-N-144



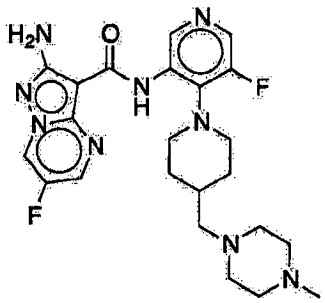
I-N-145



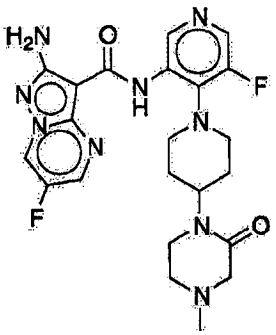
I-N-146



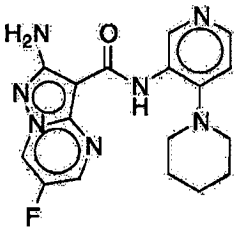
I-N-147



I-N-148



I-N-149



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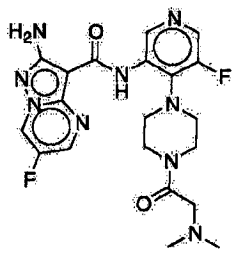
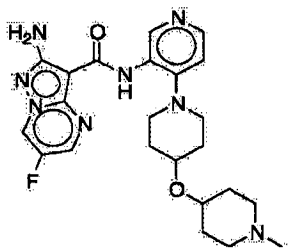
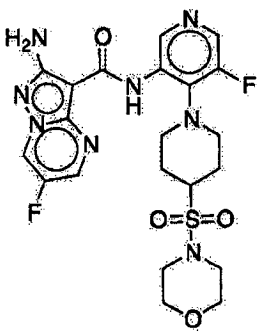


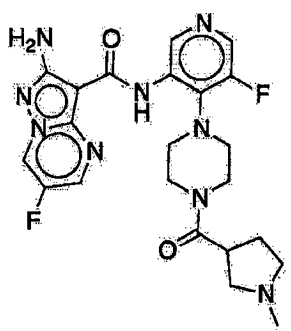
I-N-151



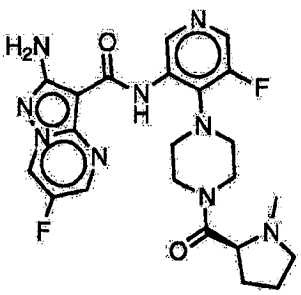
I-N-152



I-N-153



I-N-154



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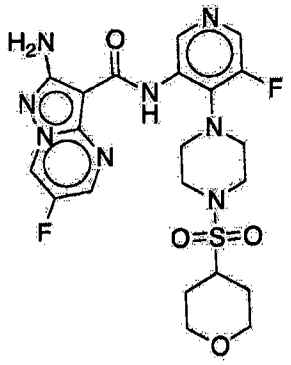
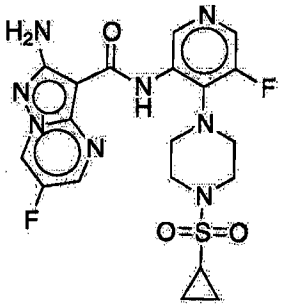
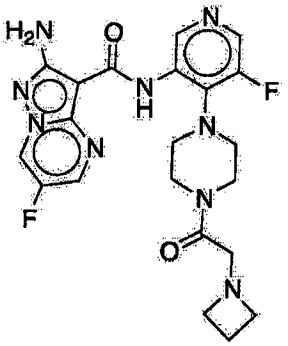
I-N-155



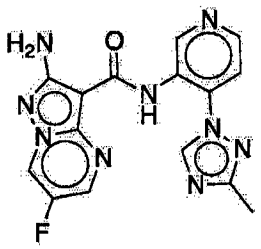
I-N-156



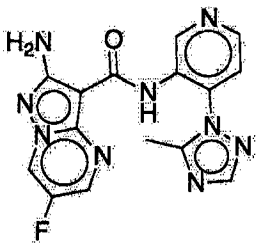
I-N-157



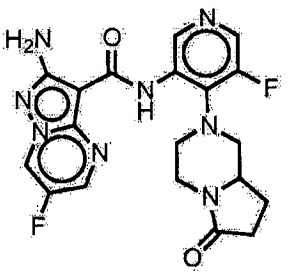
I-N-158



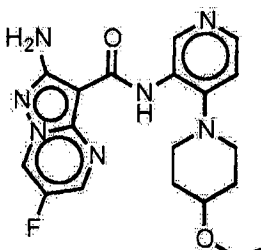
I-N-159



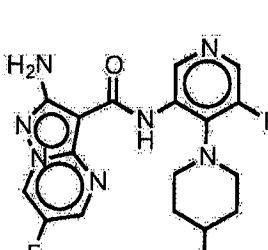
I-N-160



I-N-161



I-N-162

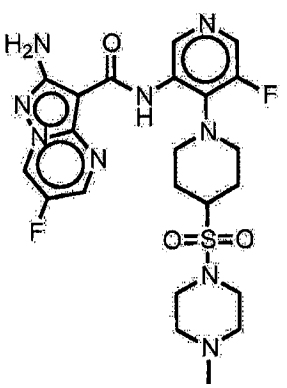


I-N-163

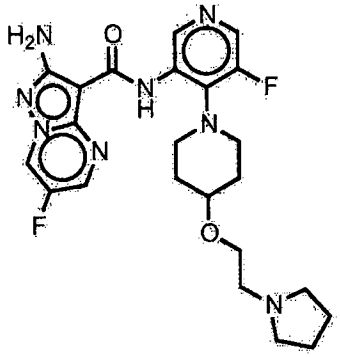
I-N-164

I-N-165

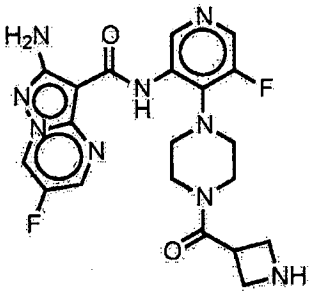
I-N-166



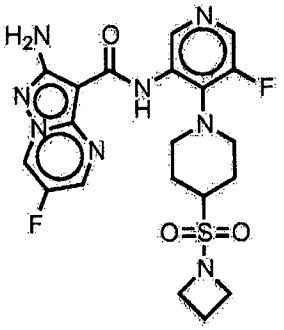
[0211]



I-N-167



I-N-168



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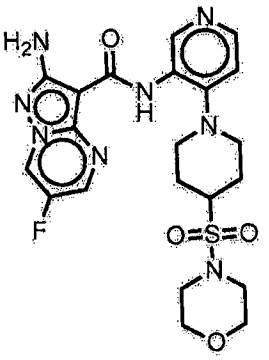

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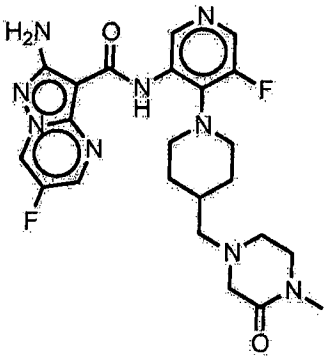

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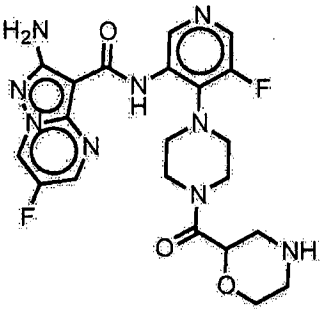

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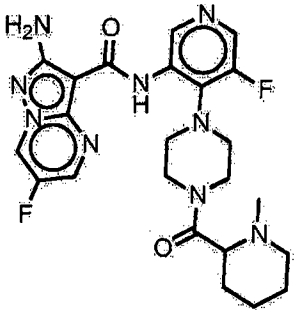

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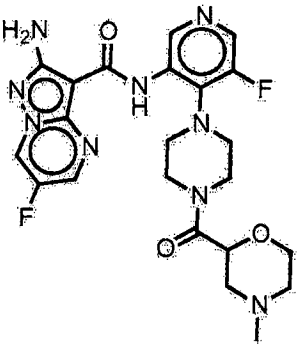

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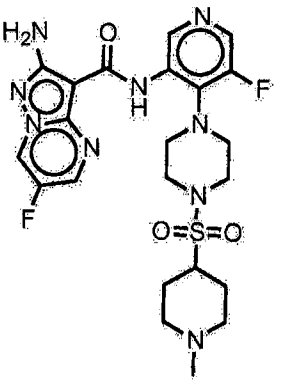

I-N-175

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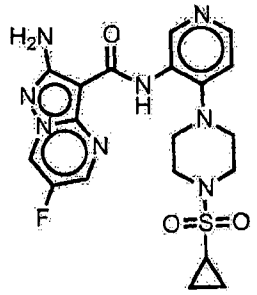

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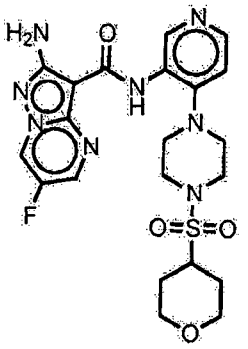

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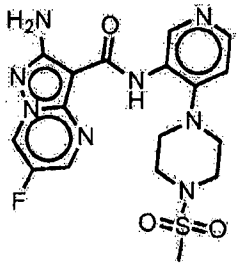

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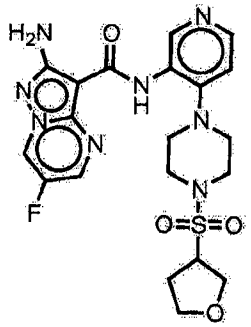

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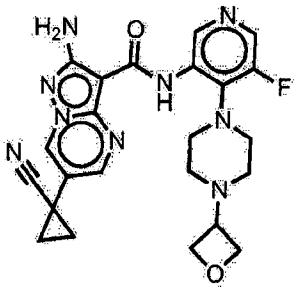

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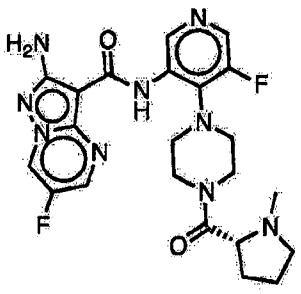

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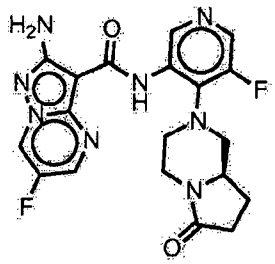

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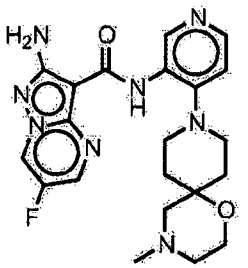

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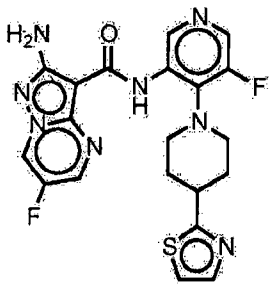

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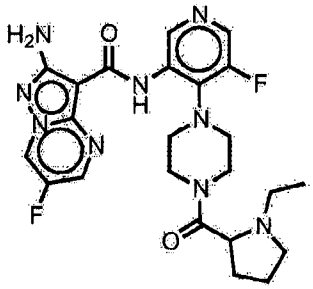

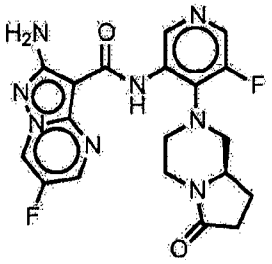

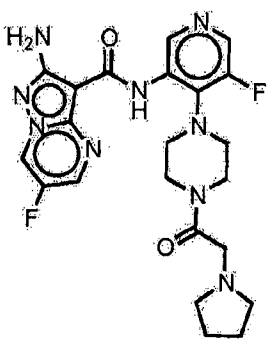

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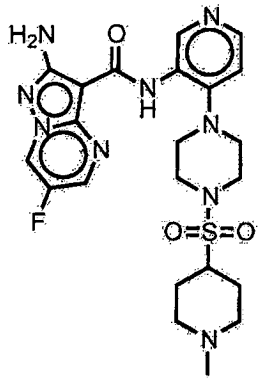

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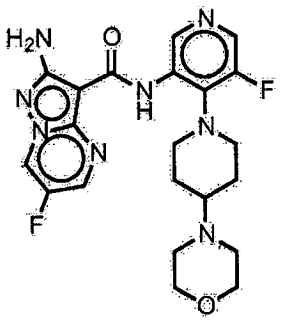

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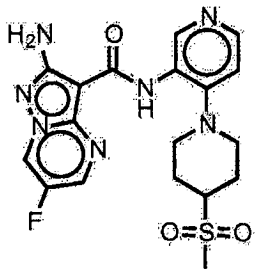

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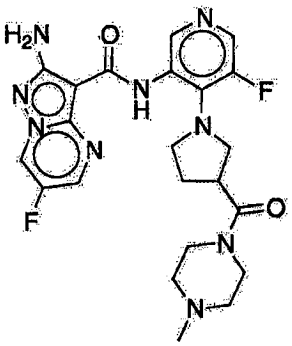

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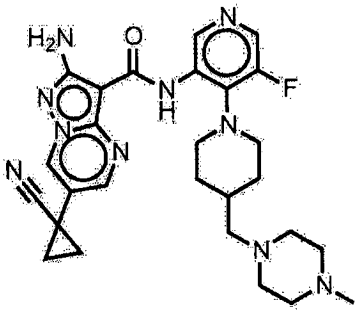

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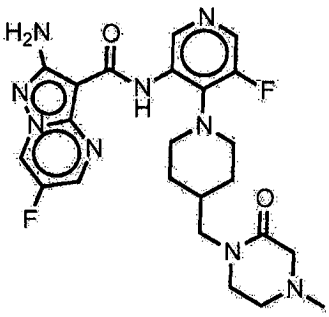

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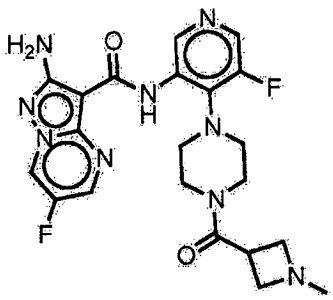

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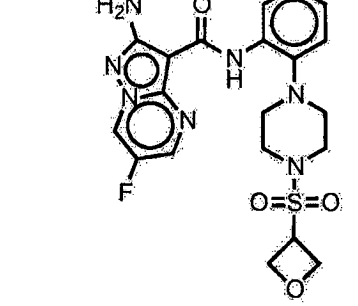
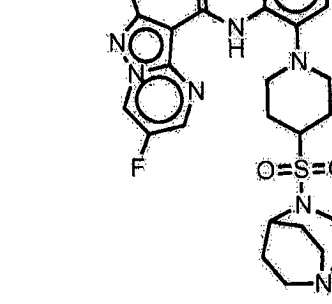


I-N-193

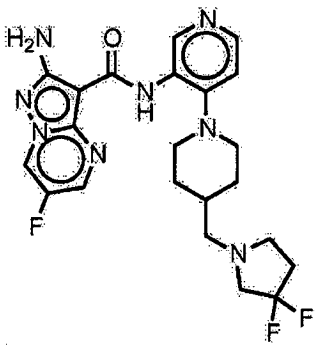


I-N-194

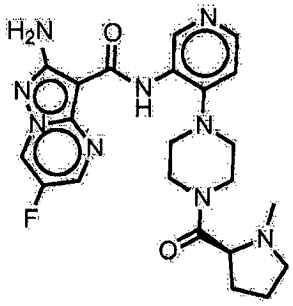
I-N-195

I-N-196

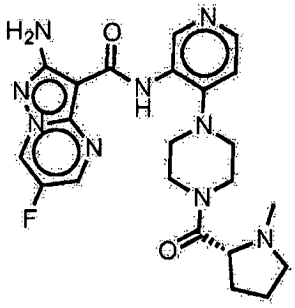
[0214]



I-N-197



I-N-198



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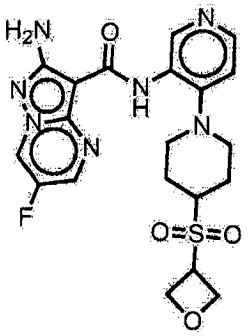
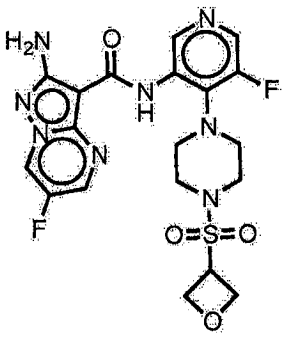


I-N-200



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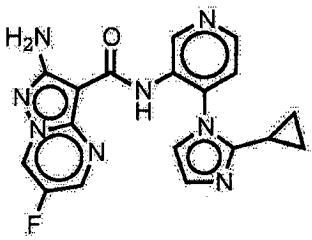

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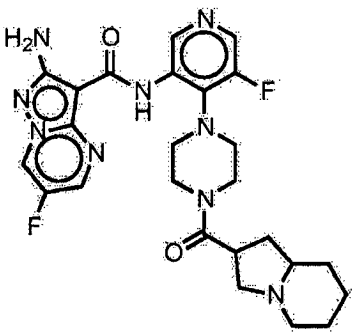

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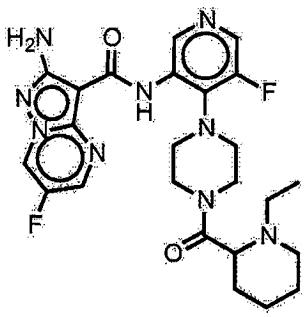

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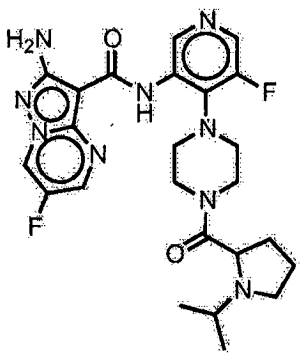
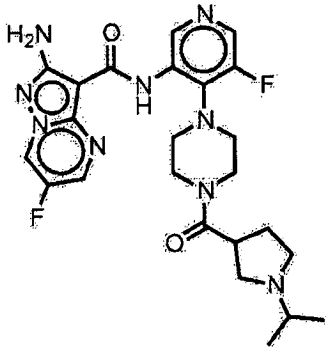


I-N-205

[0215]



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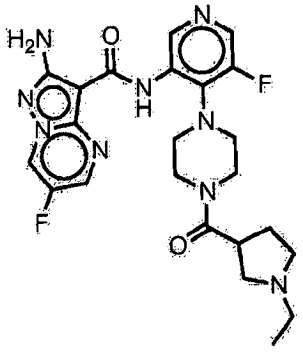

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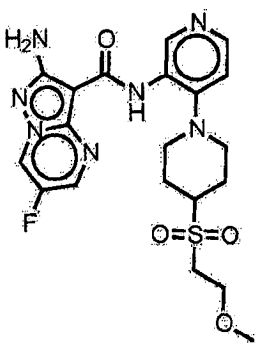

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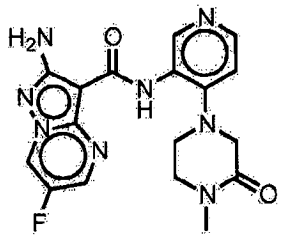
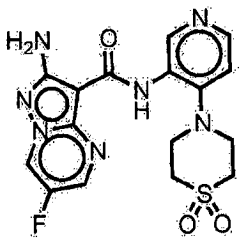


I-N-209



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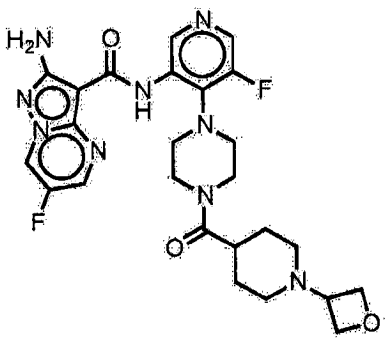
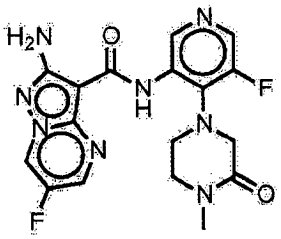
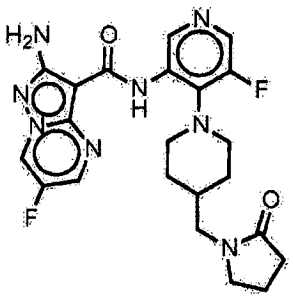


I-N-211



I-N-212



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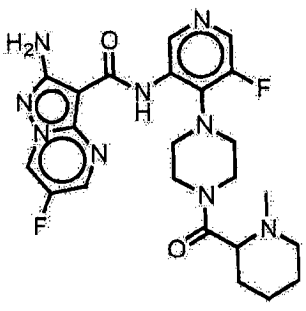
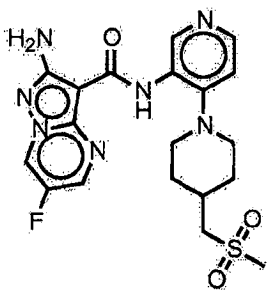
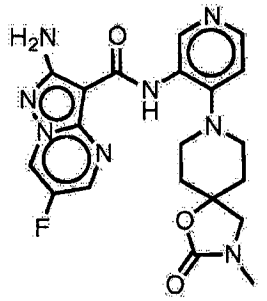


I-N-214

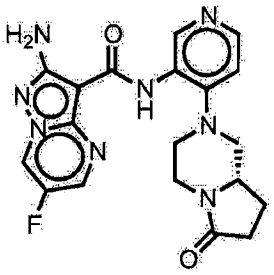


I-N-215

[0216]



I-N-216



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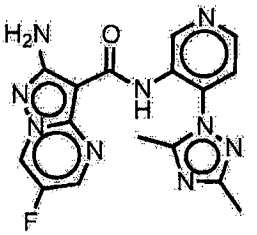
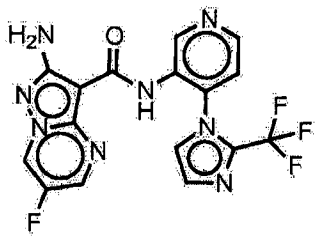
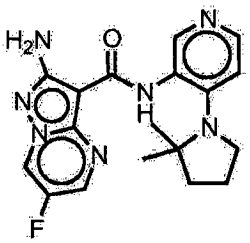


I-N-218



I-N-219



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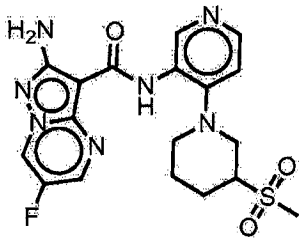

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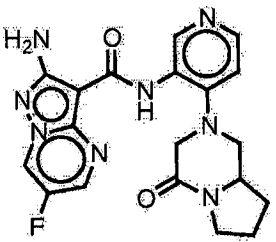

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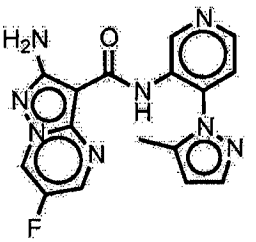

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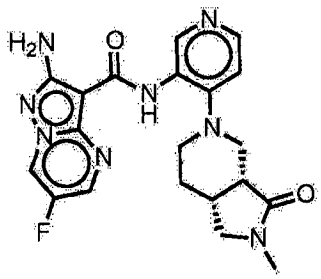

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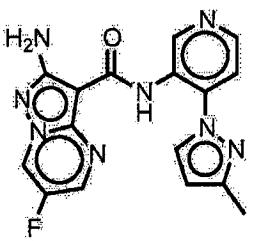

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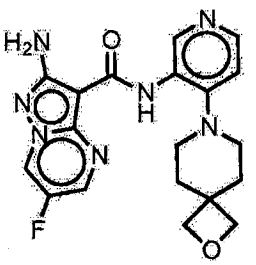
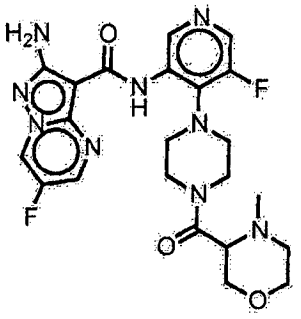


I-N-226

[0217]



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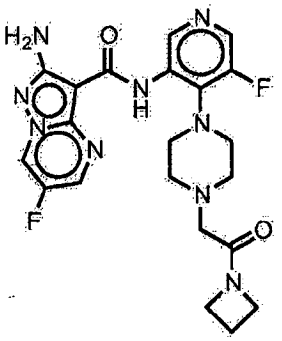

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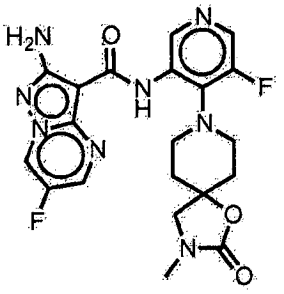

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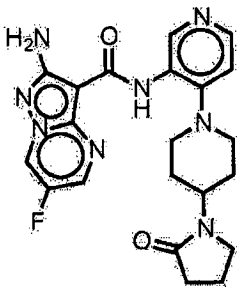

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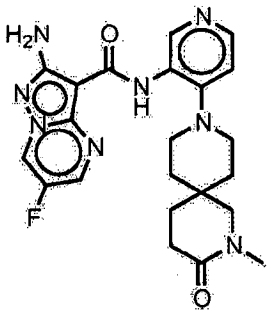

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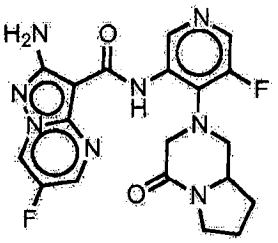

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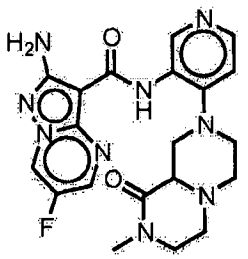

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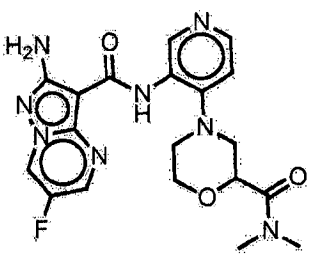

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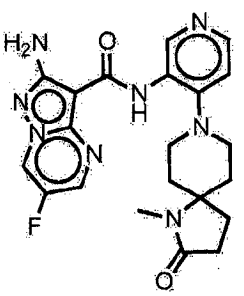

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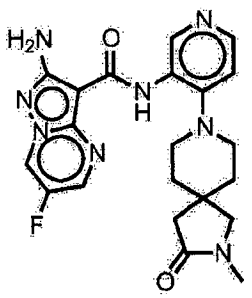

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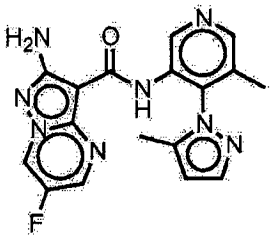

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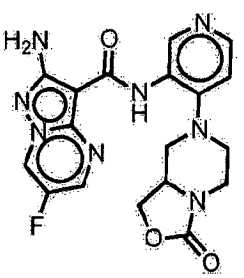

I-N-238

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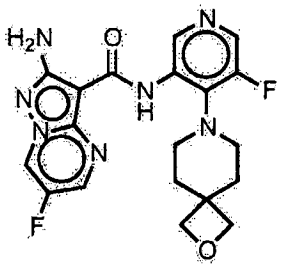

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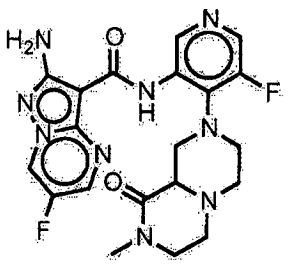

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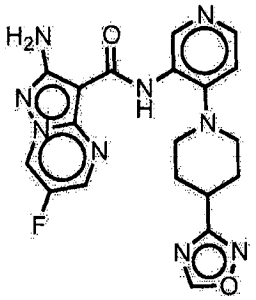

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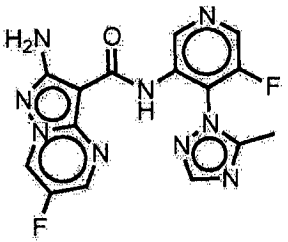

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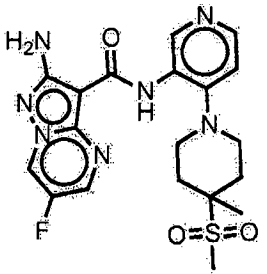

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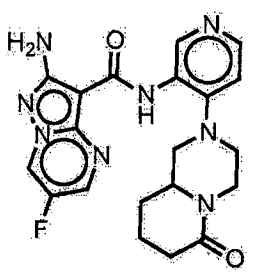

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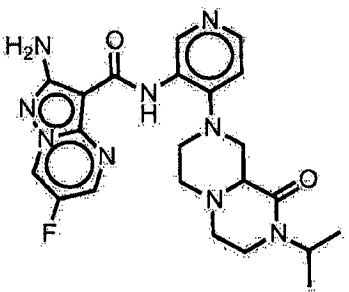

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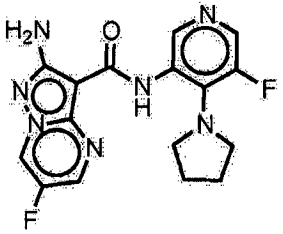

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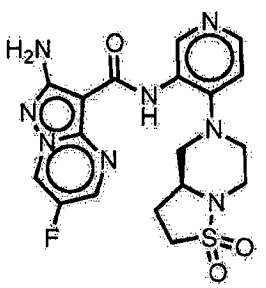

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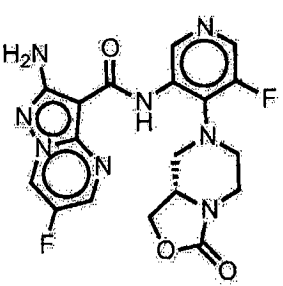
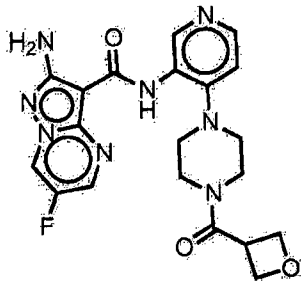


I-N-248

[0219]



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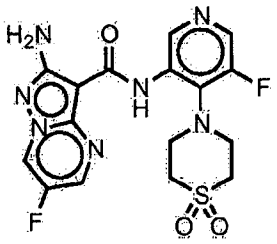

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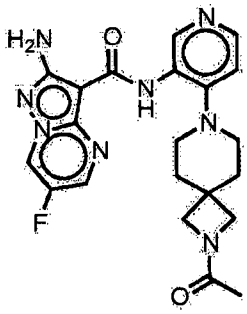

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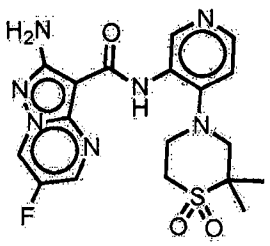

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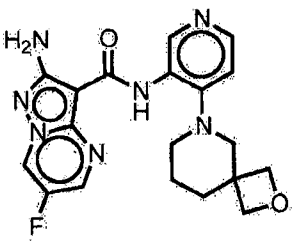

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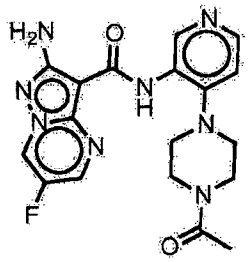

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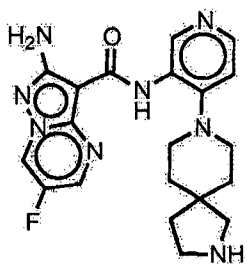

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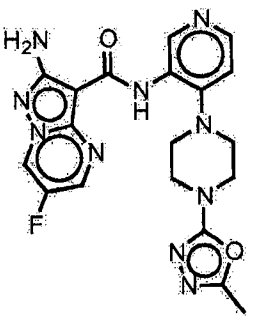

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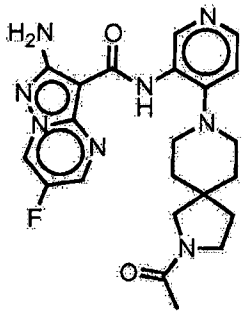

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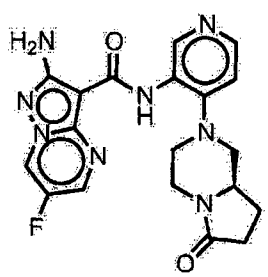

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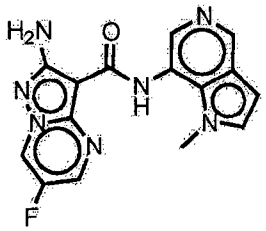
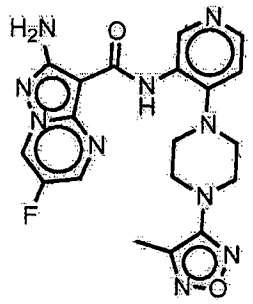


I-N-259

[0220]



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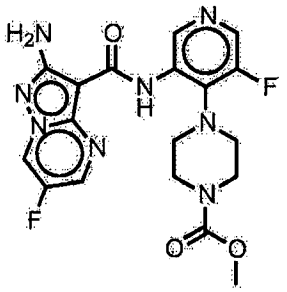

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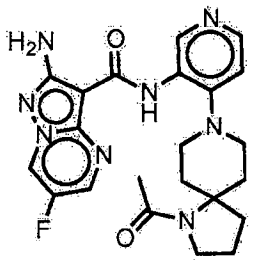

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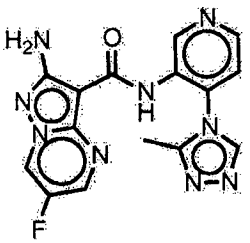

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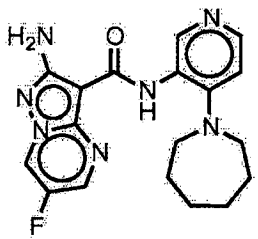

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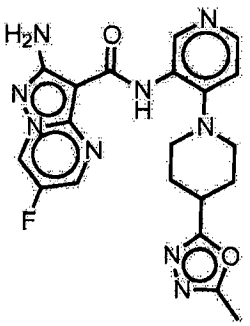

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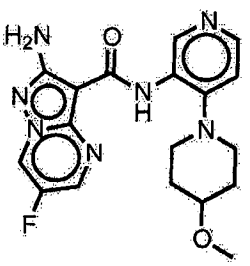

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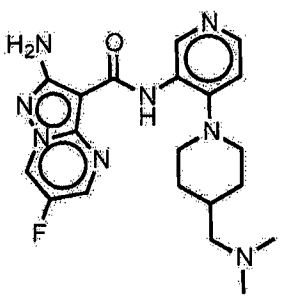

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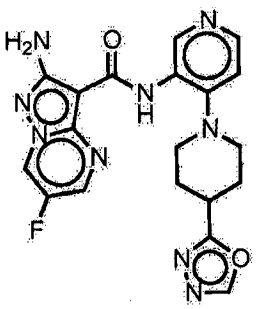

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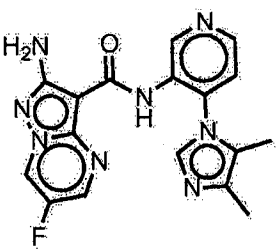
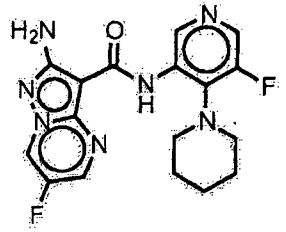


I-N-269

[0221]



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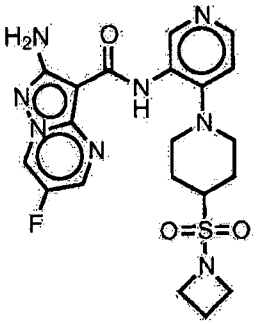
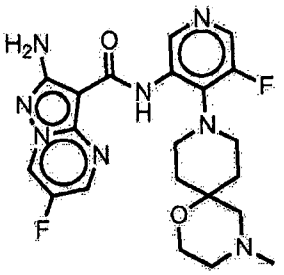
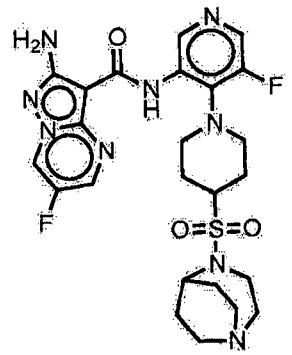


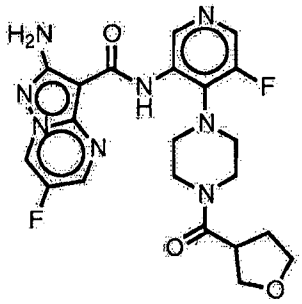
I-N-271



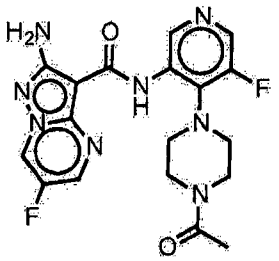
I-N-272



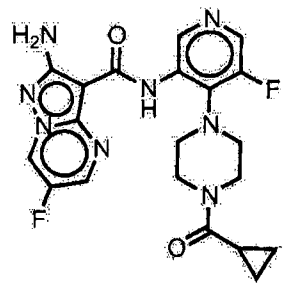
I-N-273



I-N-274



I-N-275



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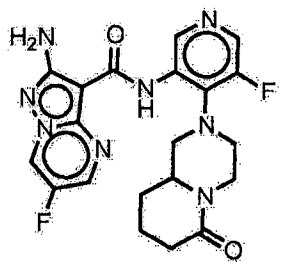

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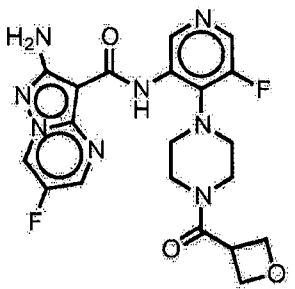

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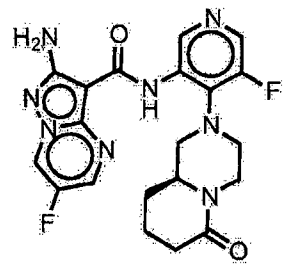

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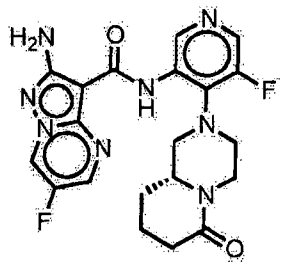

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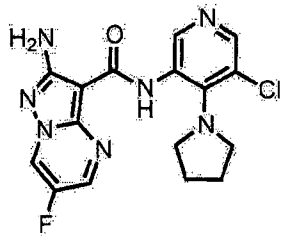
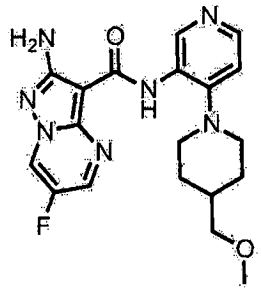
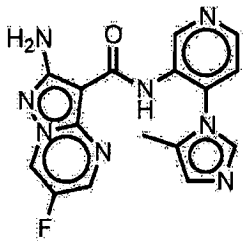


I-N-281

[0222]



I-N-282



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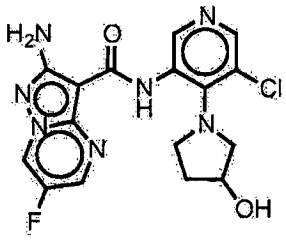
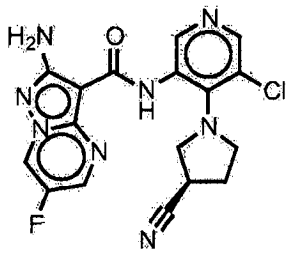
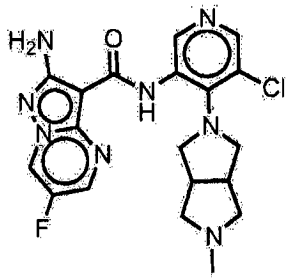


I-N-284



I-N-285



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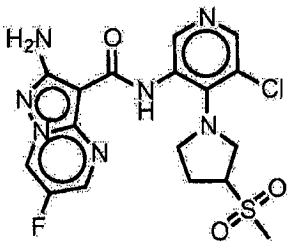
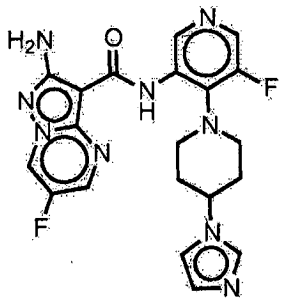
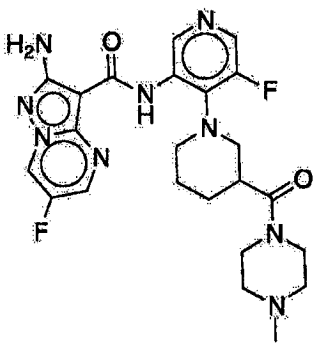


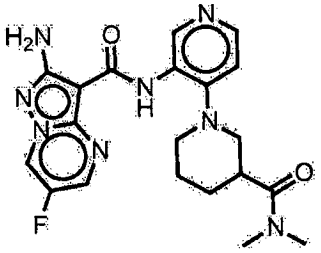
I-N-287



I-N-288



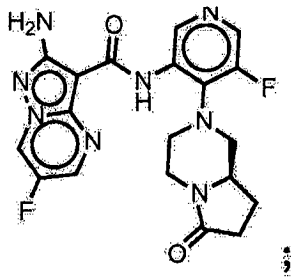
I-N-289



I-N-290。

[0223] 在其它实施方案中，本发明的化合物选自如下化合物之一：

[0224]



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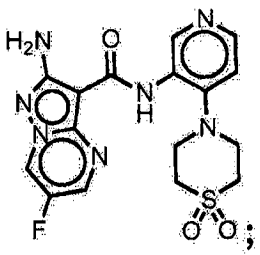
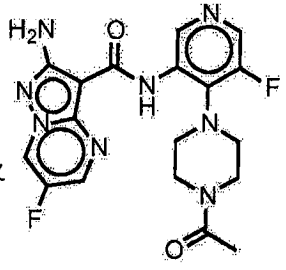


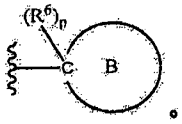
；以及



I-N-182 I-N-210 I-N-275。

[0225] 在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^4 是环 B，其表示为如下结构：

[0226]



[0227] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 p 是 1。

[0228] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 p 是 1 时，环 B 是具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元脂环族环或杂环。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 p 是 1 时，环 B 独立地选自环丙基、环丁基、环戊基、环己基、环庚基、吡咯烷基、哌啶基、氮杂庚环基、吡唑烷基、异噁唑烷基、噁唑烷基、噻唑烷基、咪唑烷基、哌嗪基、吗啉基、硫代吗啉基、1,3-噁嗪烷基、1,3-噻嗪烷基、二氢吡啶基、二氢咪唑基、1,3-四氢嘧啶基、二氢嘧啶基、1,4-二氮杂庚环基、1,4-氧杂氮杂庚环基、1,4-硫杂氮杂庚环基、1,2,3,6-四氢吡啶和氮杂环丁烷基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中环 B 是哌啶基。

[0229] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 B，J^Q 是 -C(O)- 或 C_{1-4} 烷基。在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 B 时，J^Q 是 C_{1-4} 烷基。

[0230] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 B 时，J^Q 是 Q^2。在一些实施方案中，当 R^4 是环 B 时，本发明是由结构式 I 或 I-A 表示的化合物，其中 Q^2 独立地选自氧杂环丁烷基、四氢吡喃基、四氢呋喃基、环丙基、氮杂环丁烷基、吡咯烷基、哌嗪基、哌啶基、环丁基、硫代吗啉基或吗啉基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 R^4 是环 B 时，Q^2 是氧杂环丁烷基。

[0231] 在一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 p 是 0。

[0232] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 p 是 0 时，环 B 独立地选自苯基、吡啶基、吡嗪基、嘧啶基、四氢吡啶基、哒嗪基 (pyridizinyl) 或吡唑基。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 p 是 0 时，环 B 是咪唑基。在其它实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中当 p 是 0 时，环 B 独立地选自苯基或吡啶基。

[0233] 在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^4 是 $-CH_2-(R^7)$。在另一个实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 R^7 是 H。

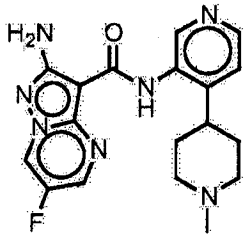
[0234] 在其它实施方案中，本发明是由结构式表 I 或 I-A 示的化合物，其中 R^3 和 R^4 与它们所连接的原子一起形成具有 0-2 个选自氧的杂原子的 5-6 元非芳族环。

[0235] 在一些实施方案中，本发明是由结构式 I 或 I-A 表示的化合物，其中 J^Z 独立地选自→ 0 或 C_{1-4} 烷基。

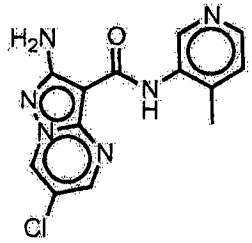
[0236] 在另一个实例中，本发明是由结构式 I 或 I-A 表示的化合物，其中本发明的化合物表示在表 3 中。

[0237] 表 3

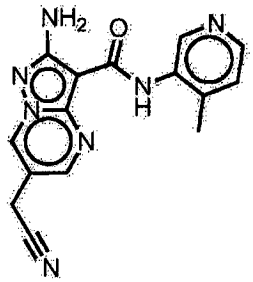
[0238]



I-C-1

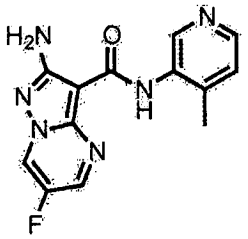


I-C-2

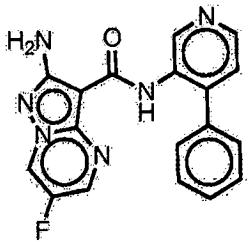


I-C-3

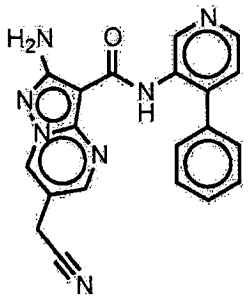
[0239]



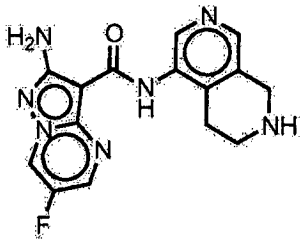
I-C-4



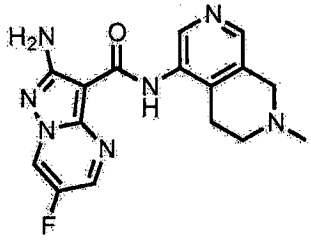
I-C-5



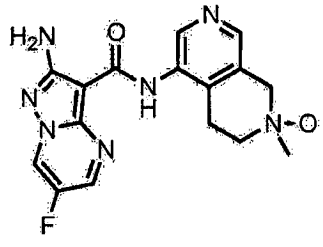
I-C-6



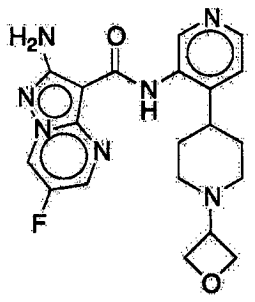
I-C-7



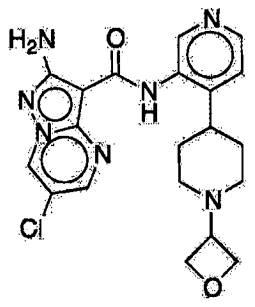
I-C-8



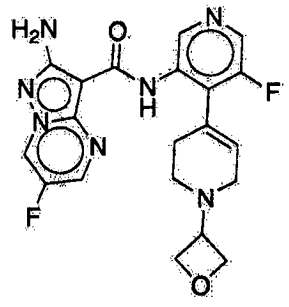
I-C-9



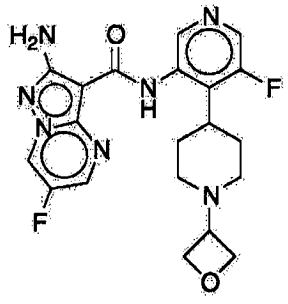
I-C-10



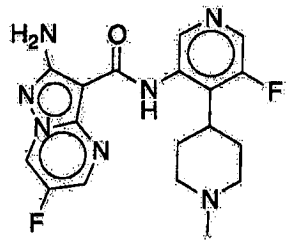
I-C-11



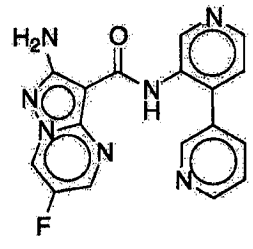
I-C-12



I-C-13

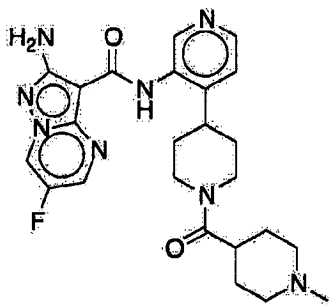


I-C-14

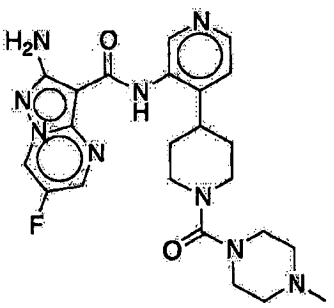


I-C-15

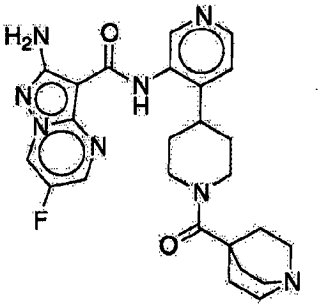
[0240]



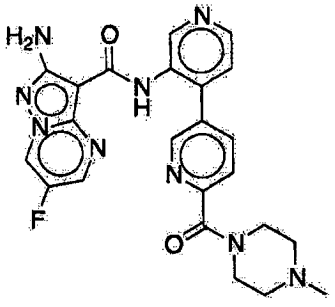
I-C-16



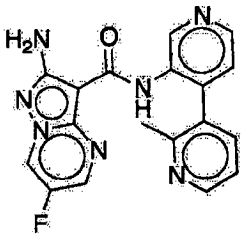
I-C-17



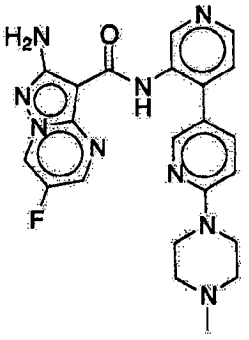
I-C-18



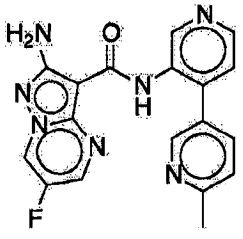
I-C-19



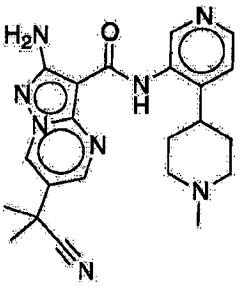
I-C-20



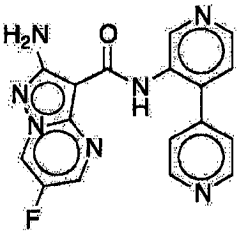
I-C-21



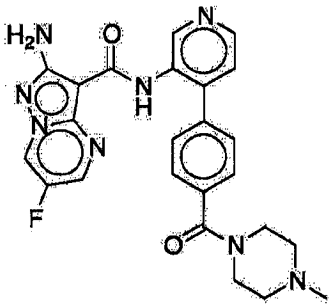
I-C-22



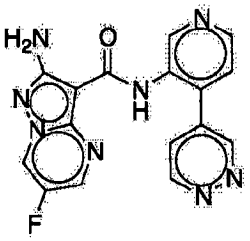
I-C-23



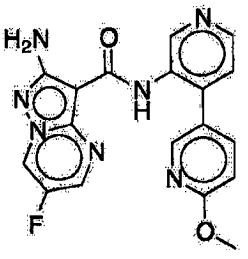
I-C-24



I-C-25

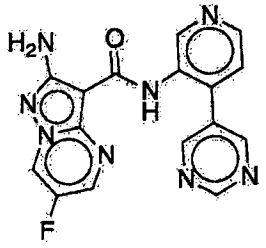


I-C-26

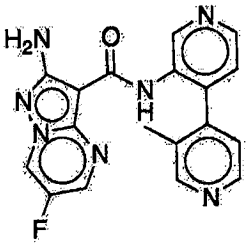


I-C-27

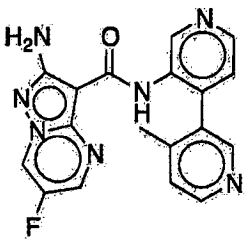
[0241]



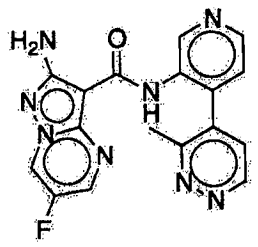
I-C-28



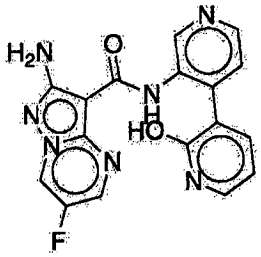
I-C-29



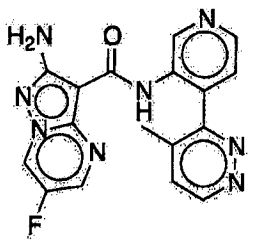
I-C-30



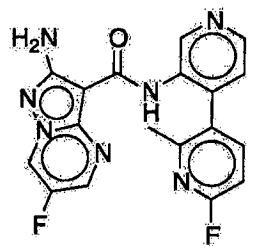
I-C-31



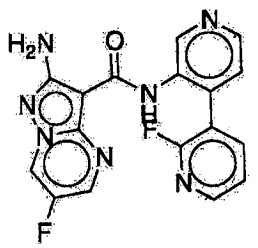
I-C-32



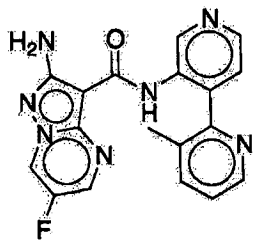
I-C-33



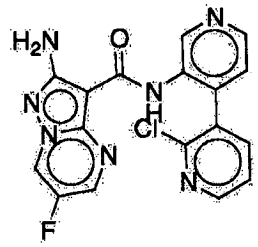
I-C-34



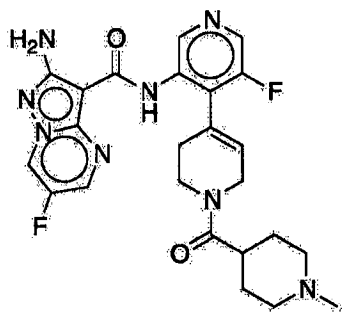
I-C-35



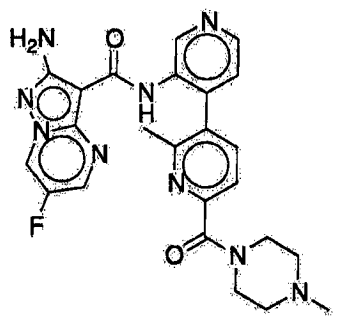
I-C-36



I-C-37

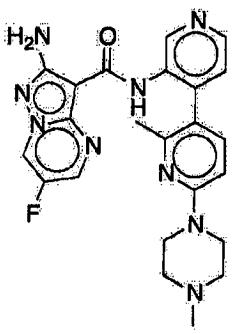


I-C-38

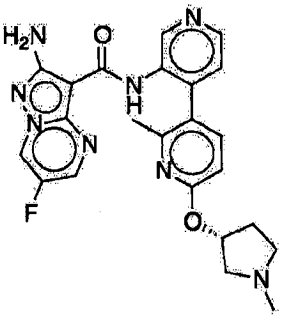


I-C-39

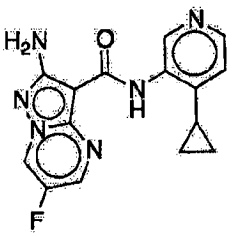
[0242]



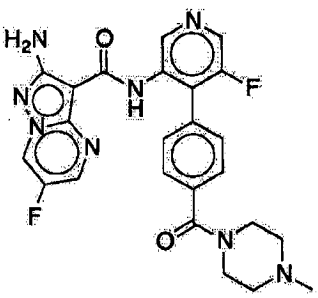
I-C-40



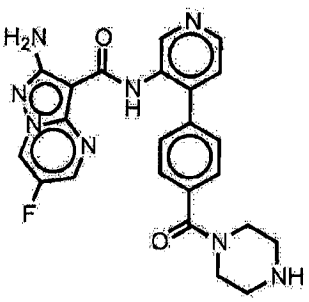
I-C-41



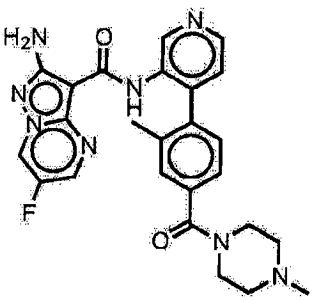
I-C-42



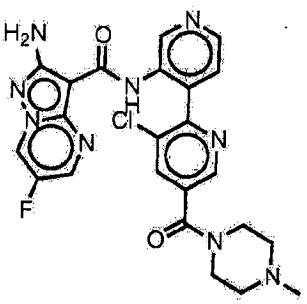
I-C-43



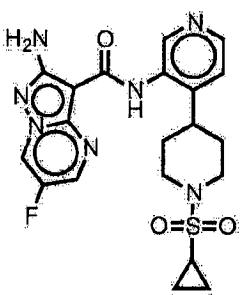
I-C-44



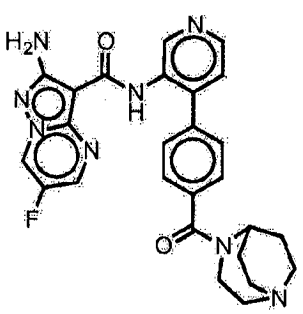
I-C-45



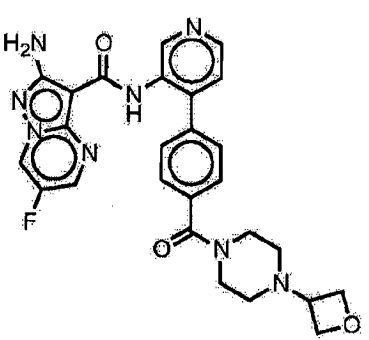
I-C-46



I-C-47

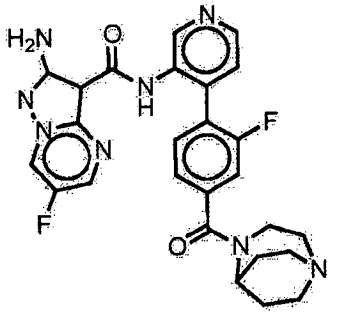


I-C-48

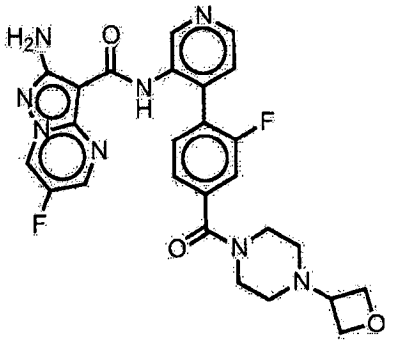


I-C-49

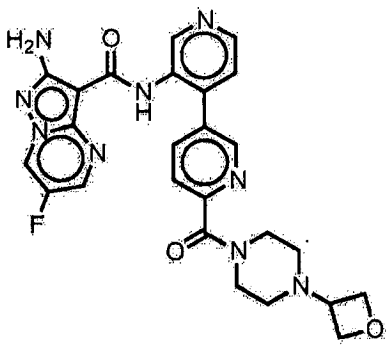
[0243]



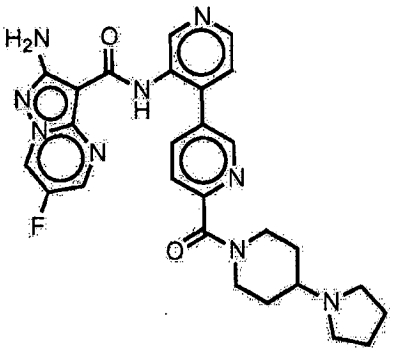
I-C-50



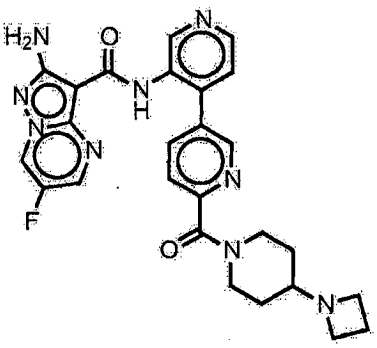
I-C-51



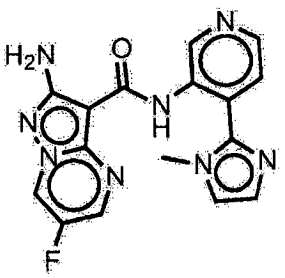
I-C-52



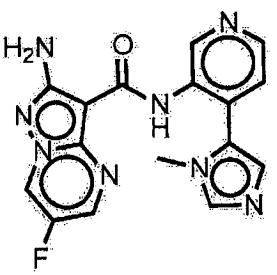
I-C-53



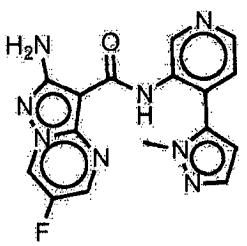
I-C-54

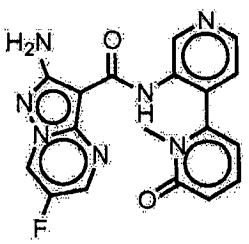


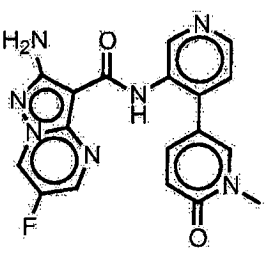
I-C-55



I-C-56

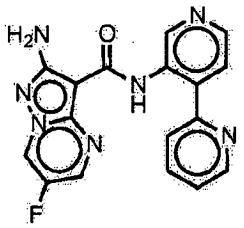




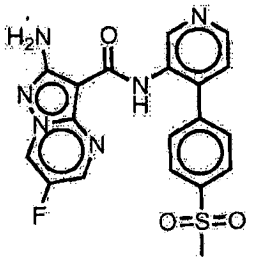


[0244]

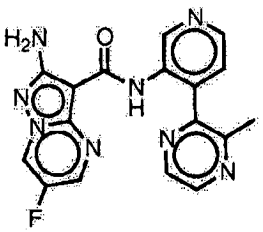
I-C-57 I-C-58 I-C-59



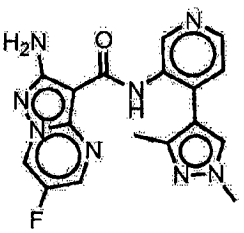
I-C-60



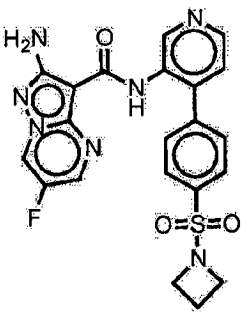
I-C-61



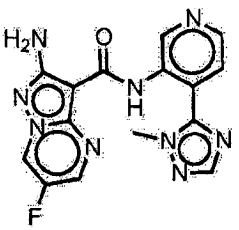
I-C-62



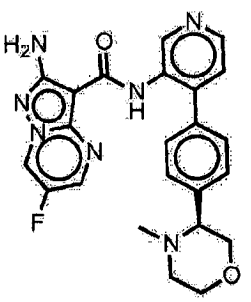
I-C-63



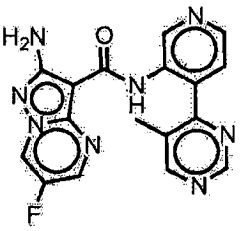
I-C-64



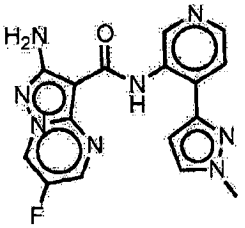
I-C-65



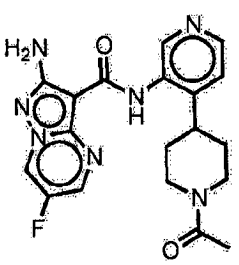
I-C-66



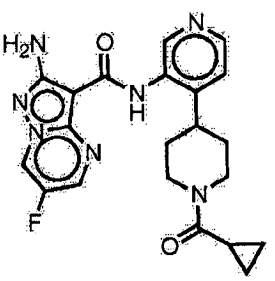
I-C-67



I-C-68

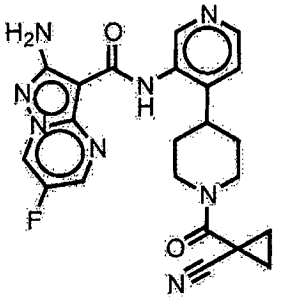


I-C-69

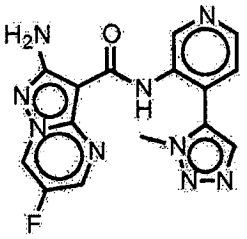


I-C-70

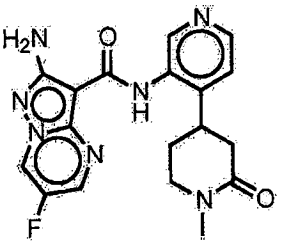
[0245]



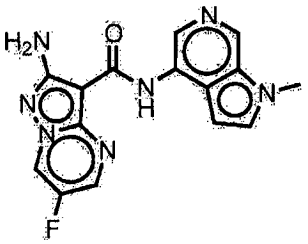
I-C-71



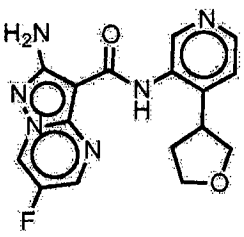
I-C-72



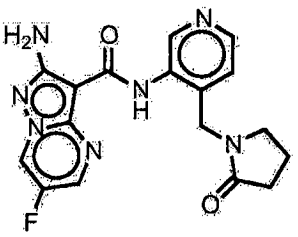
I-C-73



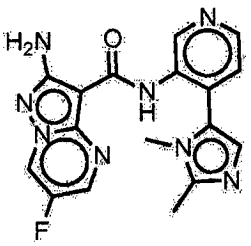
I-C-74



I-C-75



I-C-76



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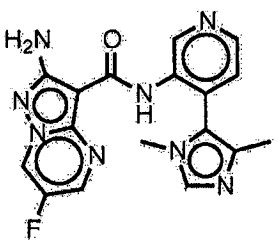

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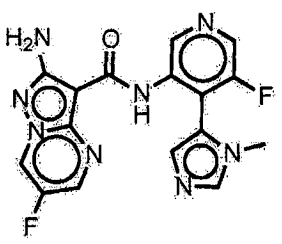
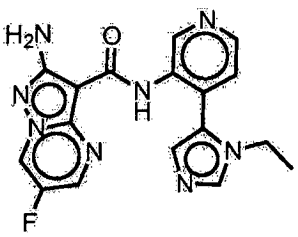
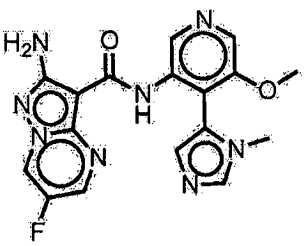


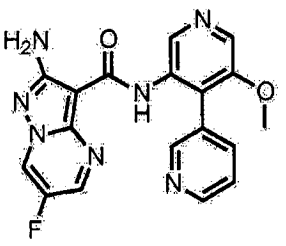
I-C-79



I-C-80

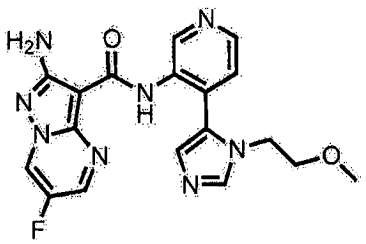


I-C-81

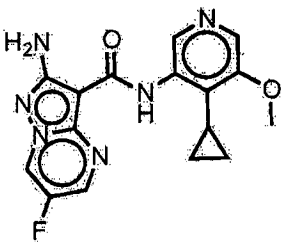


I-C-82

[0246]



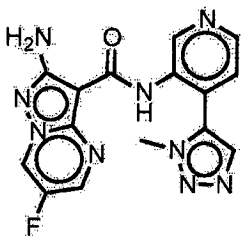
I-C-83



I-C-84。

[0247] 在另一个实施方案中，本发明的化合物选自如下化合物之一：

[0248]



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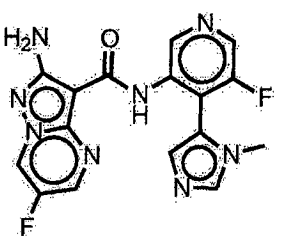
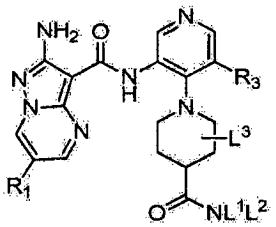


I-C-72 I-C-79。

[0249] 具有式 I-B 的化合物：

[0250]



I-B

[0251] 或其药学上可接受的盐或前药，其中：

[0252] R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

[0253] J^1独立地选自 H 或 C_{1-2}烷基；或

[0254] 2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0255] R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0256] L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

[0257] L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

[0258] L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

[0259] 环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

[0260] J^G独立地选自卤素；-N(R°)$_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$-替代；J^G各自任选地被 0-2 次出现的 J^K取代。

[0261] 同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

[0262] 2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

[0263] J^K是具有 0-2 个选自氧、氮或硫的杂原子到 3-7 元芳族或非芳族环；

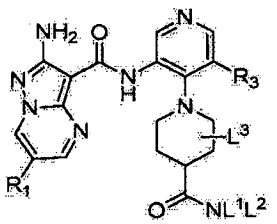
[0264] L^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$-替代；

[0265] n 是 0、1 或 2；且

[0266] R 和 R° 是 H 或 C_{1-4}烷基。

[0267] 本发明的另一个方面提供式 I-B 的化合物：

[0268]



I-B

[0269] 或其药学上可接受的盐或前药，其中：

[0270] R^1独立地选自氟、氯或 -C(J^1)$_2$CN；

[0271] J^1独立地选自 H 或 C_{1-2}烷基；或

[0272] 2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0273] R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$-替代；

[0274] L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$-替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

[0275] L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$-替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

[0276] L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

[0277] 环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

[0278] J^G独立地选自卤素；-CN；-N(R°)$_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$替代；J^G各自任选地被 0-2 次出现的 J^K取代。

[0279] 同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

[0280] 2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

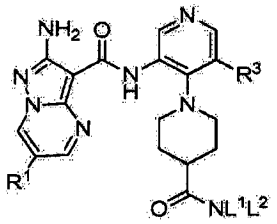
[0281] J^K是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

[0282] n 是 0、1 或 2；且

[0283] R 和 R° 是 H 或 C_{1-4}烷基。

[0284] 本发明的另一个方面提供式 I-B 的化合物：

[0285]



I-B

[0286] 或其药学上可接受的盐或前药，其中：

[0287] R^1独立地选自氟、氯或 -C(J^1)$_2$CN；

[0288] J^1独立地选自 H 或 C_{1-2}烷基；或

[0289] 2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0290] R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$替代；

[0291] L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

[0292] L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 -S(O)$_n$替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

[0293] L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

[0294] 环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

[0295] J^G独立地选自卤素；=O；-CN；-N(R°)$_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地

被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；J^G各自任选地被 0-2 次出现的 J^K取代。

[0296] 同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

[0297] 2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

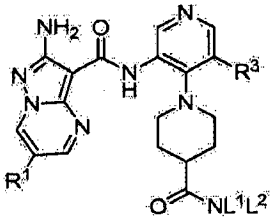
[0298] J^K是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

[0299] n 是 0、1 或 2；且

[0300] R 和 R° 是 H 或 C_{1-4}烷基。

[0301] 本发明的另一个方面提供式 I-B 的化合物：

[0302]



I-B

[0303] 或其药学上可接受的盐或前药，其中：

[0304] R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

[0305] J^1独立地选自 H 或 C_{1-2}烷基；或

[0306] 2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0307] R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；-CN；或 C_{1-3}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；

[0308] L^1是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^1各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；

[0309] L^2是 H；具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；或 C_{1-6}脂族链，其中所述脂族链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；L^2各自任选地被 C_{1-4}脂族基团；-CN；卤素；-OH；或具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元非芳族环取代；或

[0310] L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

[0311] 环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 1-5 个选自氧、氮或硫的杂原子的 7-12 元完全饱和或部分不饱和双环；

[0312] J^G独立地选自卤素；$-N(R°)_2$；3-6 元碳环基；具有 1-2 个选自氧、氮或硫的杂原子的 3-6 元杂环基；或 C_{1-4}烷基链，其中所述烷基链的至多 2 个亚甲基单元任选地被 -O-、-NR-、-C(O)- 或 $-S(O)_n$替代；J^G各自任选地被 0-2 次出现的 J^K取代。

[0313] 同一原子上的 2 次出现的 J^G与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环；

[0314] 2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；

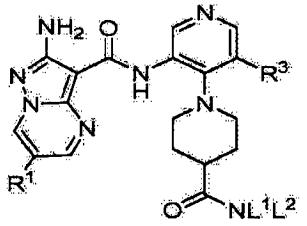
[0315] J^K是具有 0-2 个选自氧、氮或硫的杂原子的 3-7 元芳族或非芳族环；

[0316] n 是 0、1 或 2；且

[0317] R 和 R° 是 H 或 C_{1-4}烷基。

[0318] 本发明的另一个方面提供式 I-B 的化合物：

[0319]



I-B

[0320] 或其药学上可接受的盐或前药，其中：

[0321] R^1独立地选自氟、氯或 $-C(J^1)_2CN$；

[0322] J^1独立地选自 H 或 C_{1-2}烷基；或

[0323] 2 次出现的 J^1与它们所连接的碳原子一起形成任选取代的 3-4 元碳环；

[0324] R^3独立地选自 H；氯；氟；任选地被 1-3 次出现的卤素取代的 C_{1-4}烷基；C_{3-4}环烷基；或 -CN；

[0325] L^1是任选取代的 C_{1-6}脂族基团；

[0326] L^2是任选取代的 C_{1-6}脂族基团；或

[0327] L^1和 L^2与它们所连接的氮一起形成环 D；环 D 任选地被 0-5 次出现的 J^G取代；

[0328] 环 D 独立地选自具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环；或具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和或部分不饱和双环；

[0329] J^G独立地选自 C_{1-4}烷基、$-N(R°)_2$或 3-5 元碳环基；或

[0330] 2 次出现的 J^G与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系；且

[0331] R° 是 H 或 C_{1-4}烷基。

[0332] 在另一个实例中，式 I-B 的 R^1是氟。在另一个实例中，式 I-B 的 R^1是 $-CH_2CN$。在其它实例中，式 I-B 的 R^1是氯。

[0333] 在一些实施方案中，式 I-B 的 R^3独立地选自 H、氯、氟、环丙基或 C_{1-4}烷基。在一个或多个实施方案中，式 I-B 的 R^3独立地选自 H、氯或氟。在另一个实施方案中，式 I-B 的 R^3是 H。在其它实施方案中，式 I-B 的 R^3是氯。在其它实施方案中，式 I-B 的 R^3是氟。

[0334] 在另一个实施方案中，本发明是由结构式 I-B 表示的化合物，其中 L^1和 L^2独立地选自 H；$-(C_{1-3}$烷基$)O(C_{1-2}$烷基$)$；$-(C_{1-3}$烷基$)N(C_{1-2}$烷基$)_2$；C_{1-4}烷基；氮杂环丁烷基；哌啶基；氧杂环丁烷基；或吡咯烷基。在另一个实施方案中，本发明是由结构式 I-B 表示的化合物，其中 L^1和 L^2是 C_{1-3}烷基。

[0335] 在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中 L^1和 L^2与它们所连接的氮一起形成环 D。在另一个实施方案中，本发明是由结构式 I-B 表示的化合物，其中环 D 是具有 1-2 个选自氧、氮或硫的杂原子的 3-7 元杂环。在一些实施方案中，本发明是由结构式 I-B 表示的化合物，其中环 D 独立地选自哌嗪基、哌啶基、吗啉基、四氢吡喃基、氮杂环丁烷基、吡咯烷基或 1,4- 二氮杂庚环基。在另一个实施方案中，本发明是由结构式 I-B

表示的化合物，其中环 D 是哌嗪基、哌啶基、1,4- 二氮杂庚环基、吡咯烷基或氮杂环丁烷基。在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中环 D 是哌啶基或哌嗪基。在其它实施方案中，环 D 是哌嗪基。

[0336] 在一个或多个方面，本发明是由结构式 I-B 表示的化合物，其中环 D 是具有 0-5 个选自氧、氮或硫的杂原子的 8-12 元完全饱和或部分不饱和双环。在其它实例中，本发明是由结构式 I-B 表示的化合物，其中环 D 是八氢吡咯并 [1,2-a] 吡嗪或八氢吡咯并 [3,4-c] 吡咯。在另一个实例中，环 D 是八氢吡咯并 [1,2-a] 吡嗪。

[0337] 在另一个实例中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是卤素、C_{1-4} 烷基、-O(C_{1-3} 烷基）、C_{3-6} 环烷基、3-6 元杂环基、-NH(C_{1-3} 烷基）、-OH 或 -N(C_{1-4} 烷基）$_2$。在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是甲基、-N(C_{1-4} 烷基）$_2$、乙基、-O(C_{1-3} 烷基）、环丙基、氧杂环丁烷基、环丁基、吡咯烷基、哌啶基或氮杂环丁烷基。在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是甲基、-O(C_{1-3} 烷基）、氧杂环丁烷基、吡咯烷基、哌啶基或氮杂环丁烷基。在另一个实例中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是 C_{1-4} 烷基、C_{3-5} 环烷基或 -N(C_{1-4} 烷基）$_2$。在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是甲基、乙基或环丙基。在一些实施方案中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是甲基。在其它实施方案中，本发明是由结构式 I-B 表示的化合物，其中 J^G 是氧杂环丁烷基。

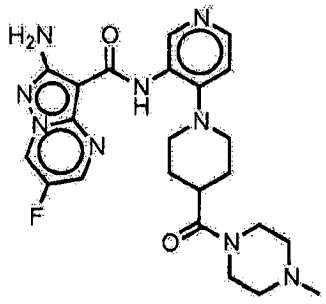
[0338] 在另一个实例中，本发明是由结构式 I-B 表示的化合物，其中 2 次出现的 J^G 与环 D 一起形成 6-10 元饱和或部分不饱和桥连环系。在一些实例中，本发明是由结构式 I-B 表示的化合物，其中所述桥连环系是 1,4- 二氮杂双环 [3.2.2] 壬烷、1,4- 二氮杂双环 [3.2.1] 辛烷或 2,5- 二氮杂双环 [2.2.1] 庚烷。在一些实例中，本发明是由结构式 I-B 表示的化合物，其中所述桥连环系是 1,4- 二氮杂双环 [3.2.2] 壬烷。

[0339] 在一些实施方案中，本发明是由结构式 I-B 表示的化合物，其中同一原子上的 2 次出现的 J^G 与它们所连接的原子一起形成具有 0-2 个选自氧、氮或硫的杂原子的 3-6 元环。本发明是由结构式 I-B 表示的化合物，其中在其它实施方案中，由同一原子上的 2 次出现的 J^G 形成的环选自氧杂环丁烷基或环丙基。

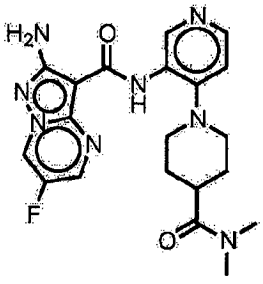
[0340] 在另一个实例中，本发明是由结构式 I、I-A 和 I-B 表示的化合物，其中本发明的化合物表示在表 4 中。

[0341] 表 4

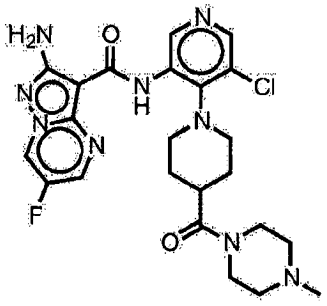
[0342]



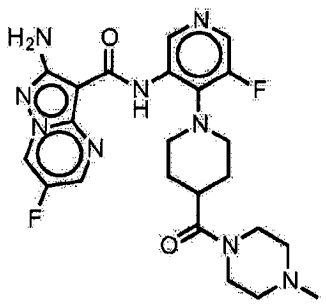
I-G-1



I-G-2



I-G-3



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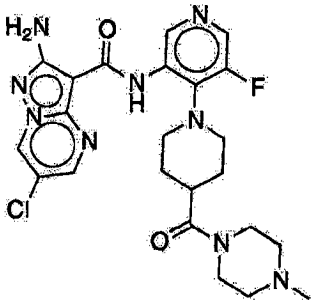

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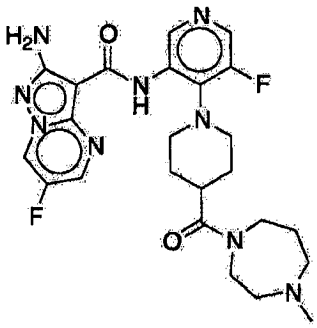
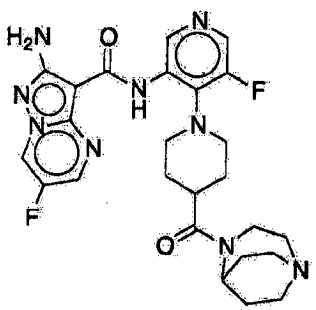


I-G-6



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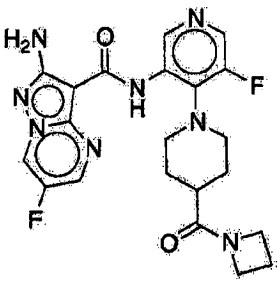
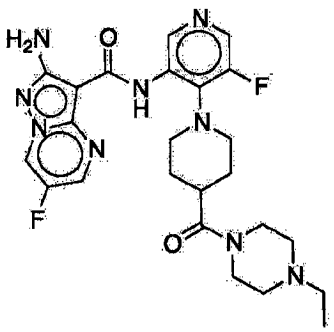
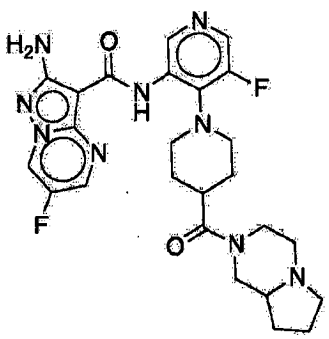
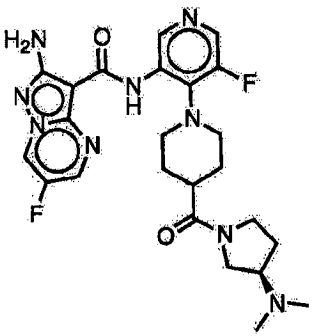


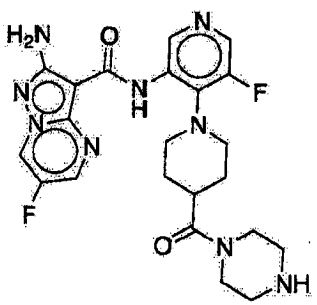
I-G-8



I-G-9

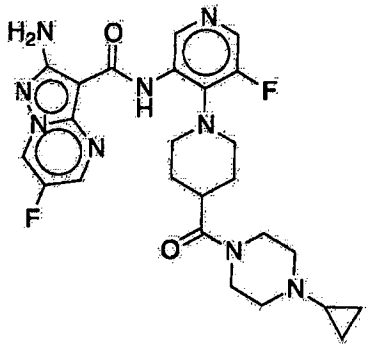






[0343]

I-G-10



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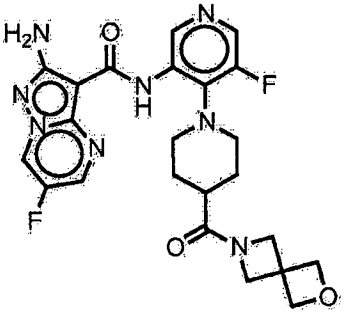
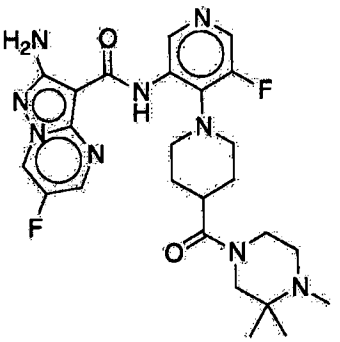
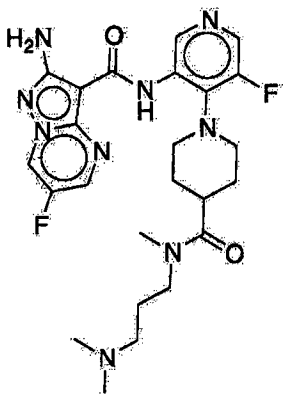


I-G-12



I-G-13



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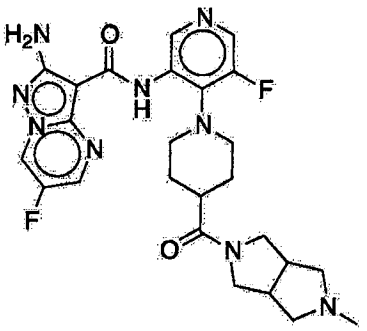
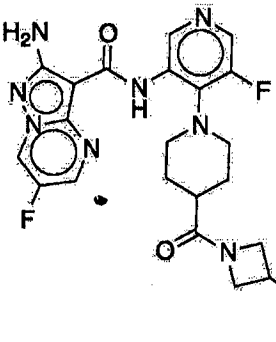
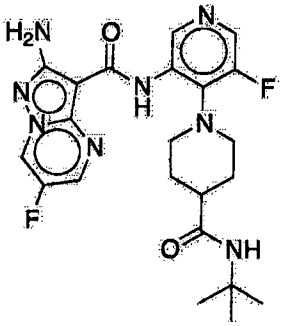


I-G-15



I-G-16



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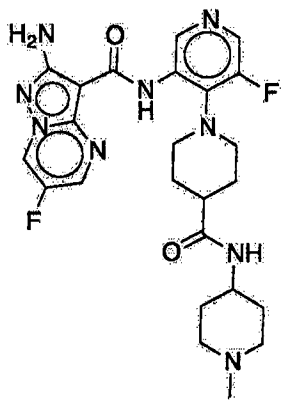
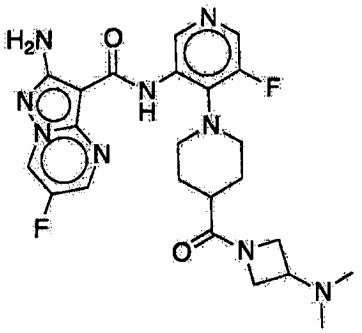


I-G-19

I-G-20

I-G-21

[0344]



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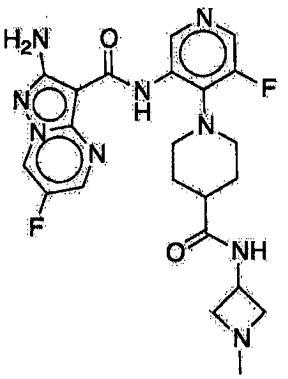

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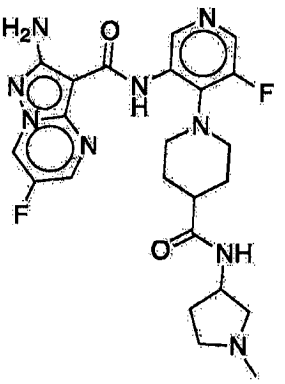

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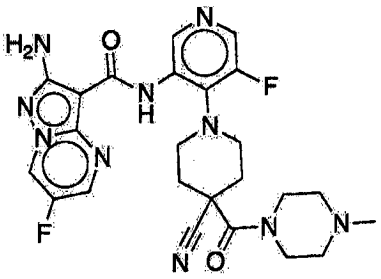

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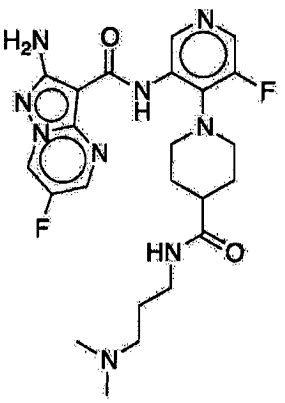

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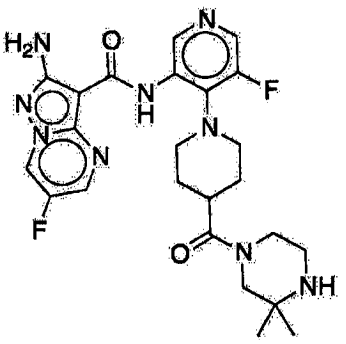

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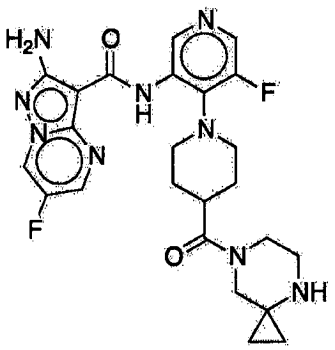

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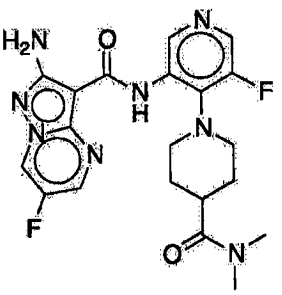

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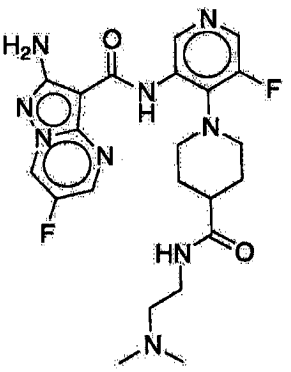
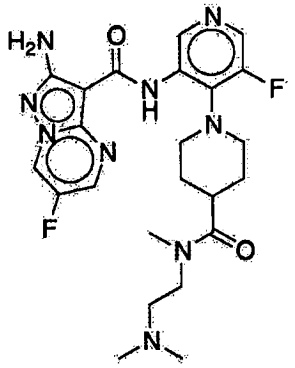


I-G-30

[0345]



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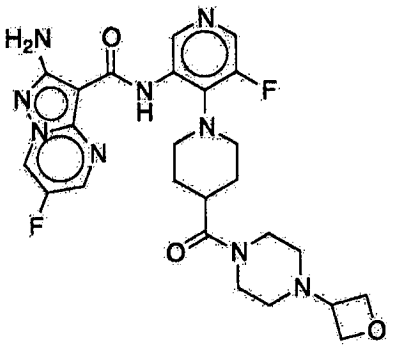

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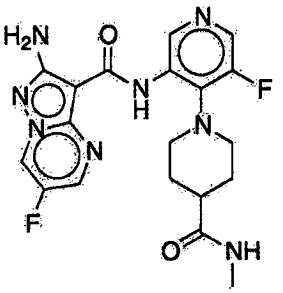

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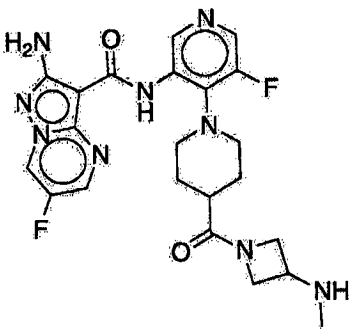

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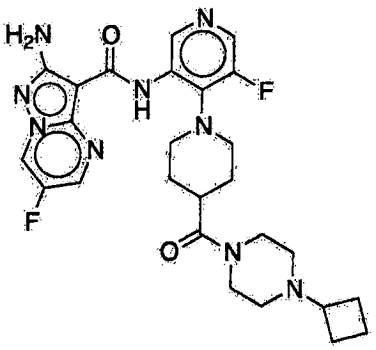

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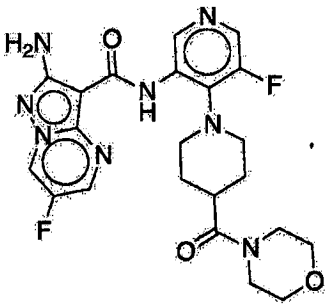

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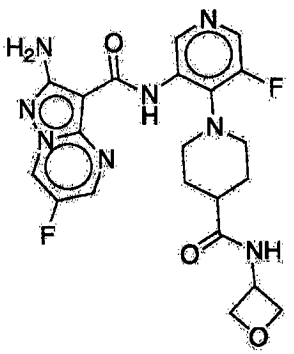

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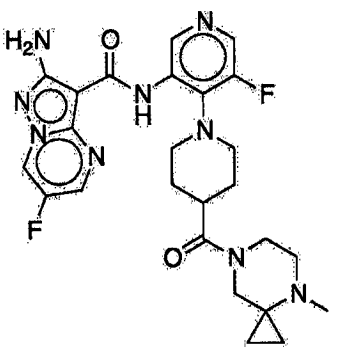
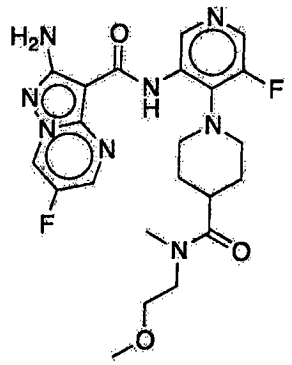
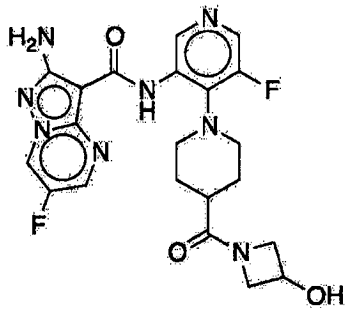


I-G-38

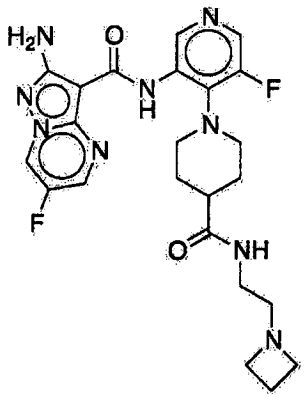
[0346]



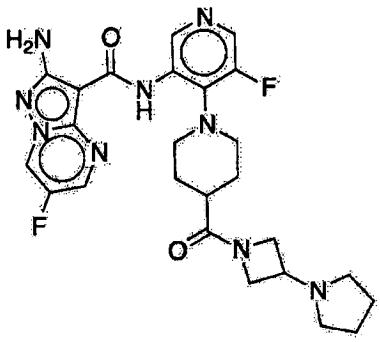
I-G-40



I-G-41



I-G-42



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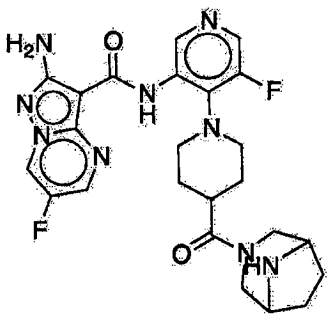
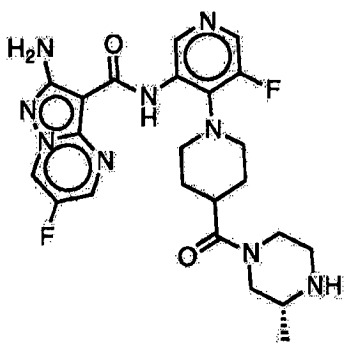


I-G-44



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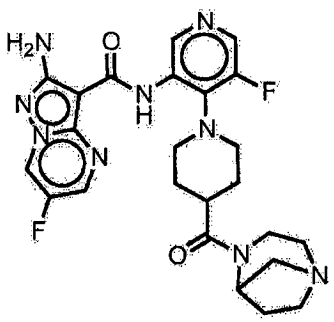

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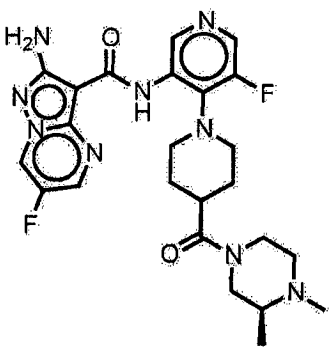

I-G-47

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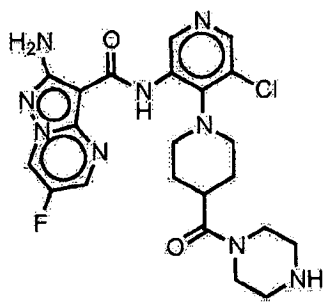
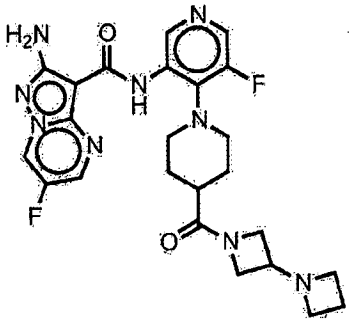


I-G-48



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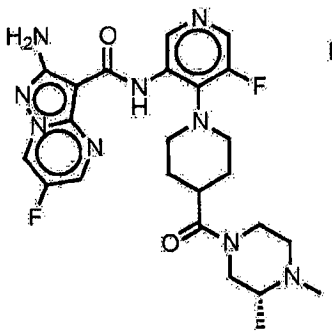

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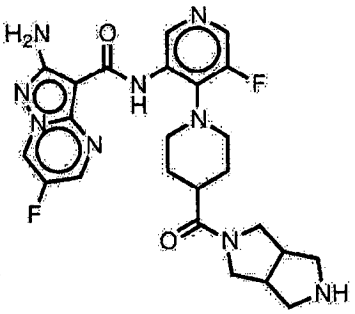

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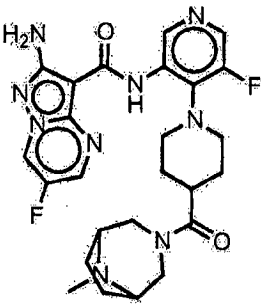

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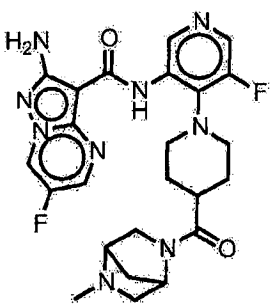

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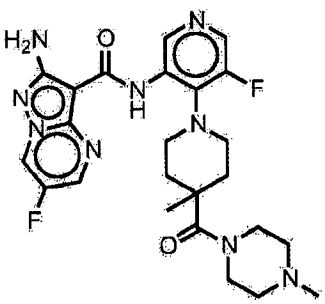

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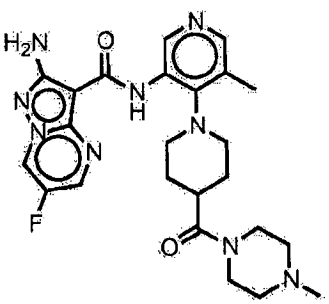

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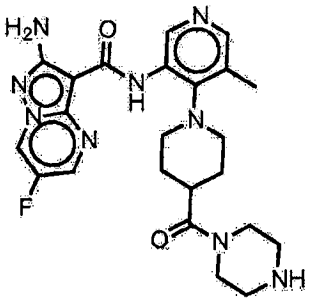

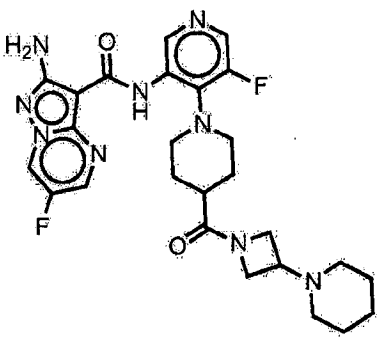

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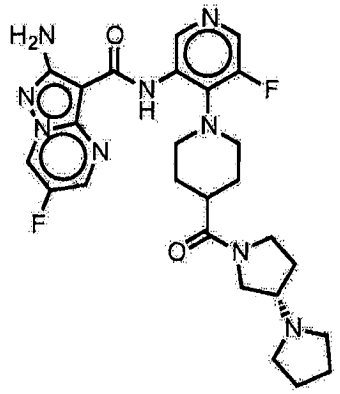
I-G-56



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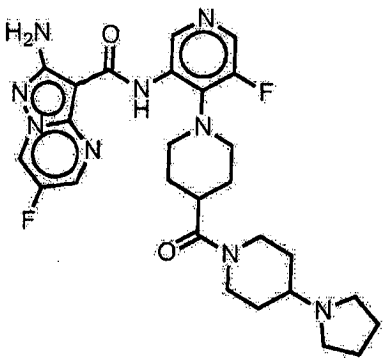

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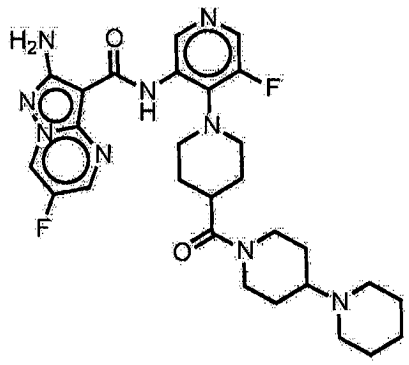

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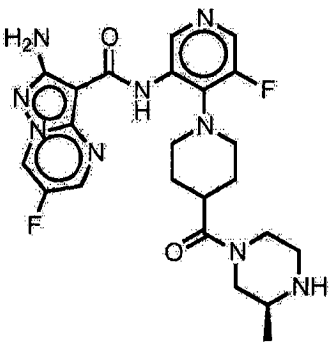
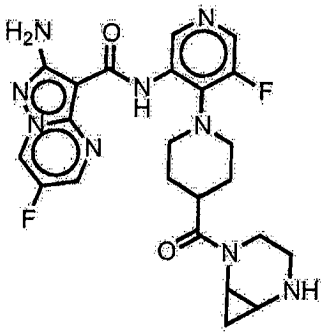


I-G-60

I-G-61

I-G-62



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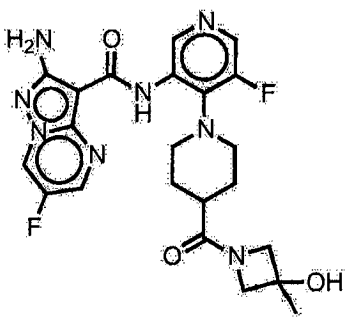

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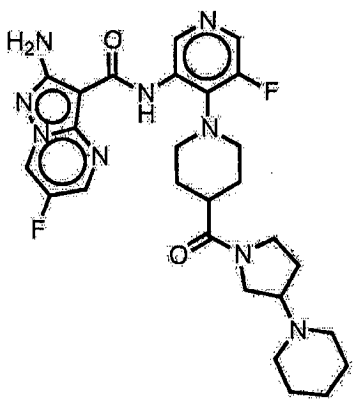

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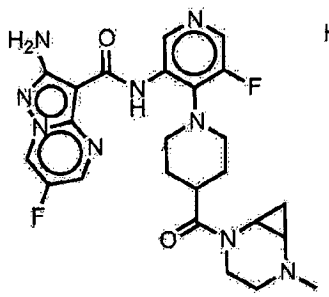

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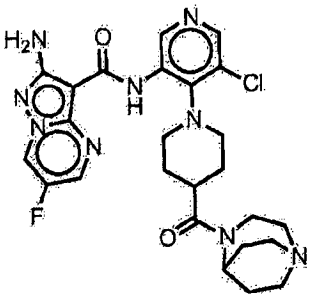

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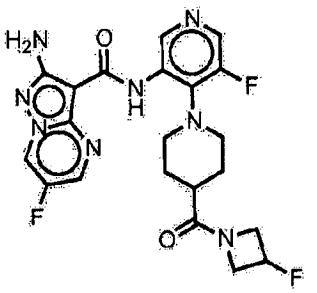
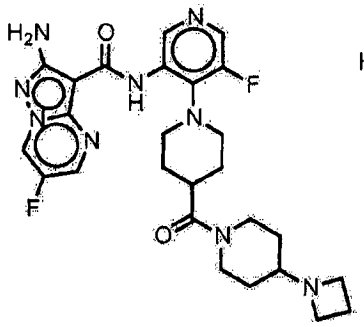
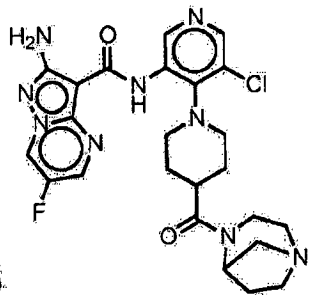


I-G-67



I-G-68



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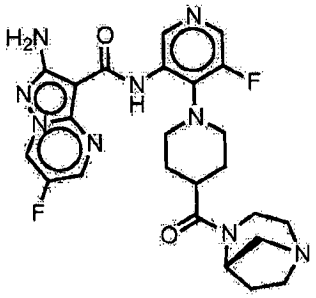

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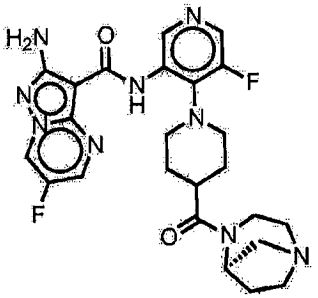

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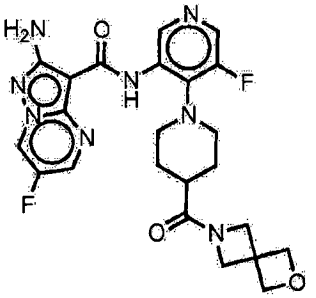
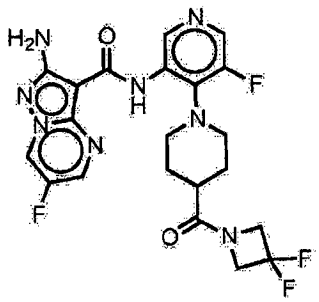


I-G-72



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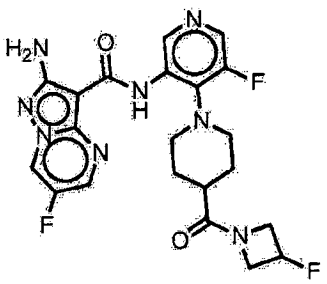
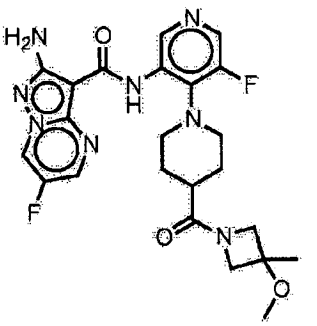


I-G-74



I-G-75

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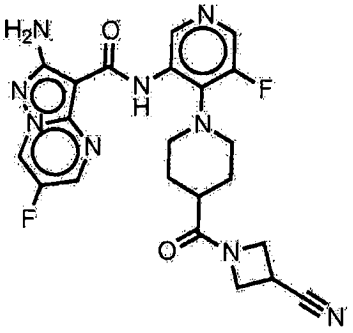
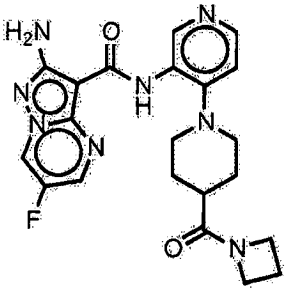
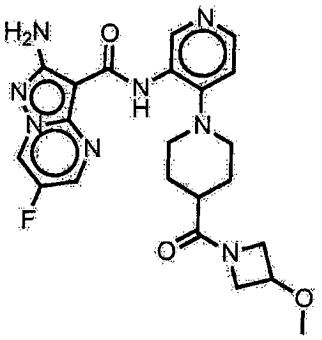


I-G-76



I-G-77



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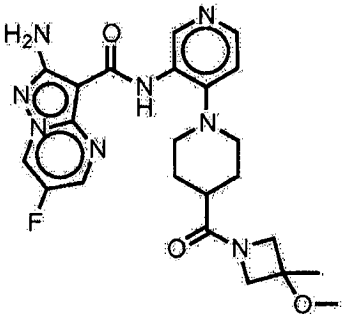

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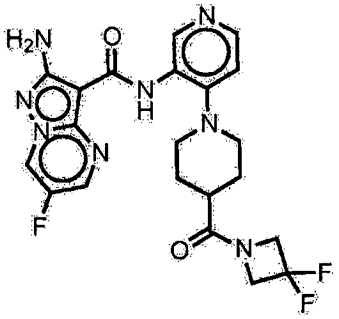
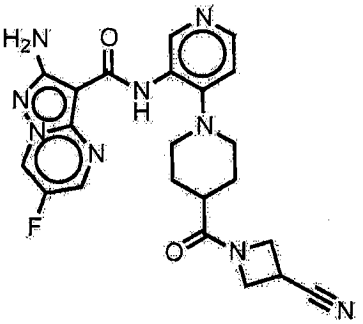


I-G-80



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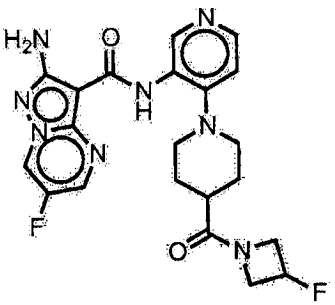
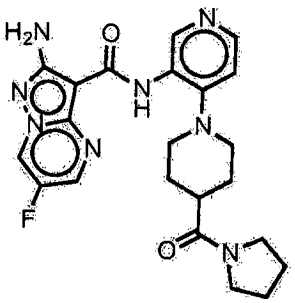


I-G-82



I-G-83

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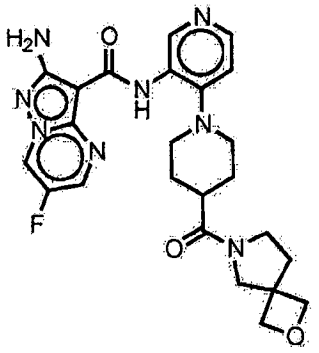
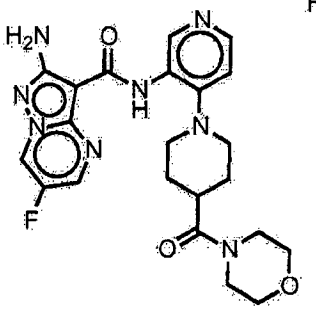
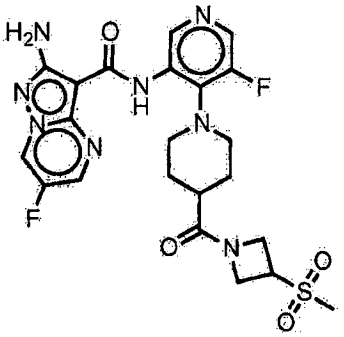


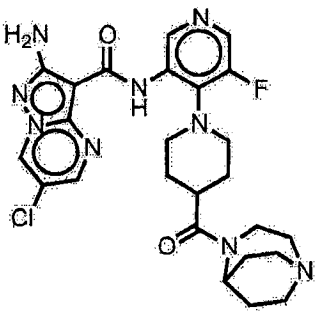
I-G-84



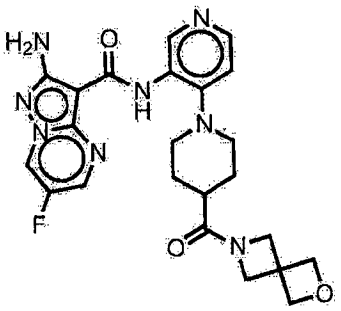
I-G-85



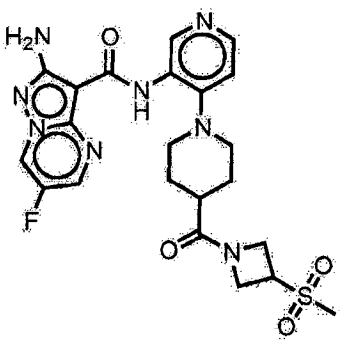
I-G-86



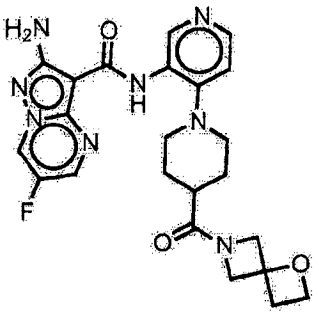
I-G-87



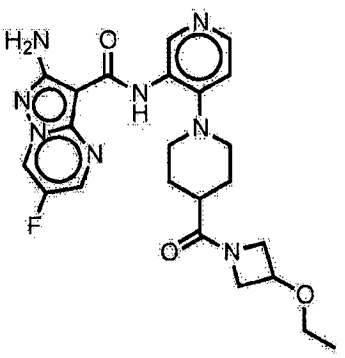
I-G-88



I-G-89



I-G-90



I-G-91

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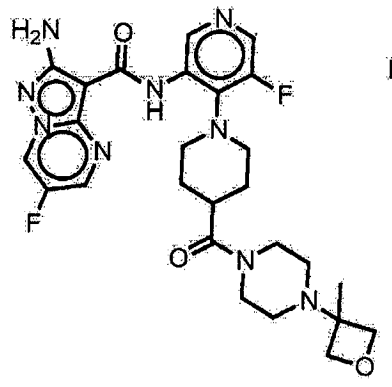
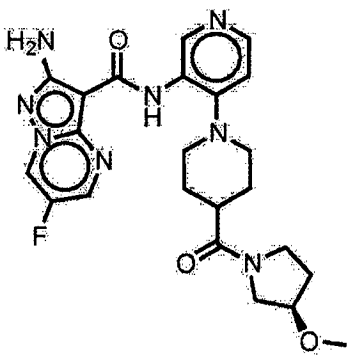
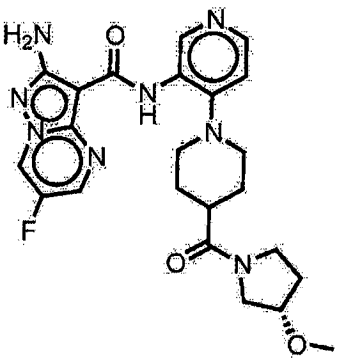


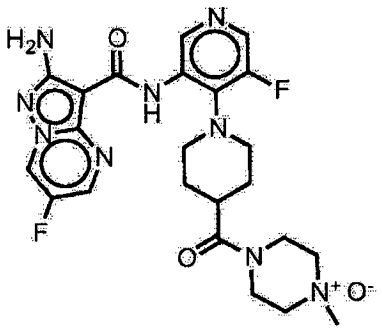
I-G-92



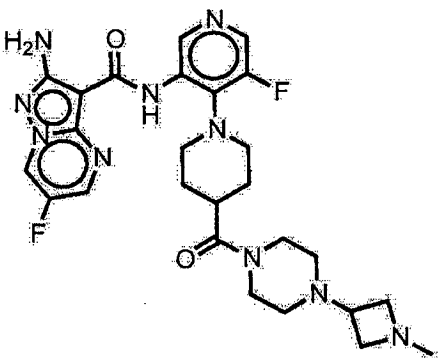
I-G-93



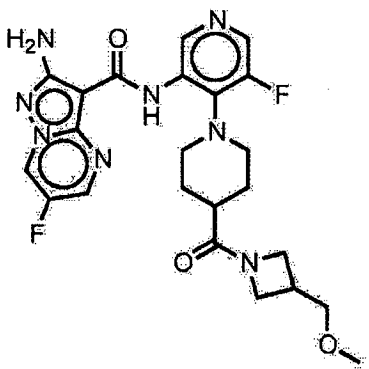
I-G-94



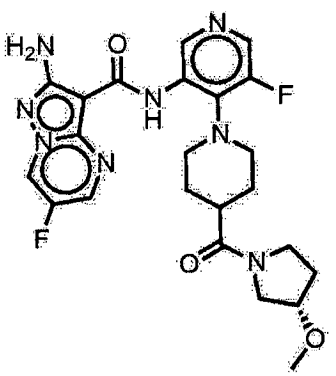
I-G-95



I-G-96



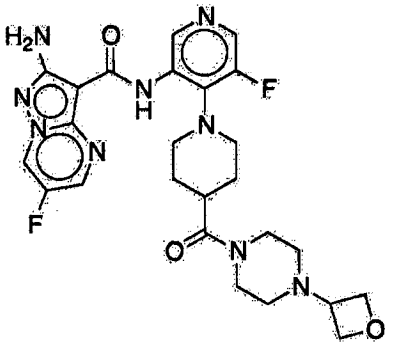
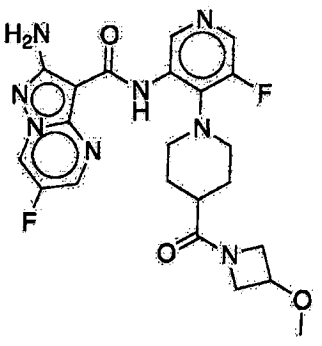
I-G-98



I-G-99。

[0353] 在另一个实施方案中，本发明的化合物选自如下化合物之一：

[0354]

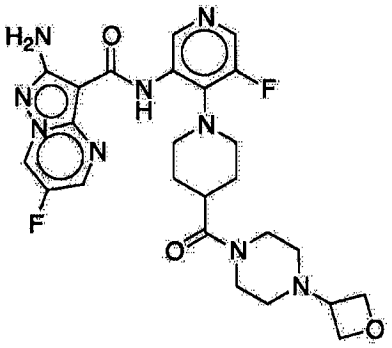



和

I-G-32 **I-G-21。**

[0355] 优选地，所述化合物具有结构 I-G-32：

[0356]

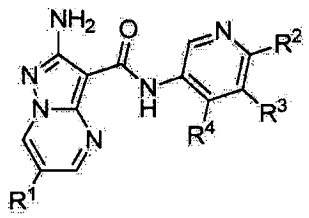


I-G-32

[0357] 或其药学上可接受的盐。

[0358] 本发明的另一个方面包含制备式 I-A 的化合物的方法：

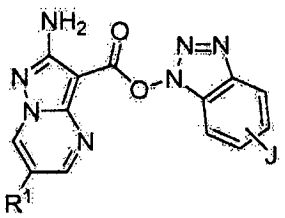
[0359]



I-A

[0360] 其包含使式 6 的化合物：

[0361]



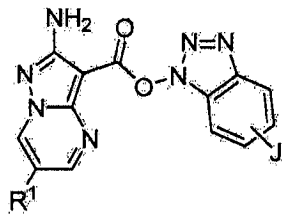
6

[0362] 在适合的条件下反应，形成酰胺键，其中 J、R^1、R^2、R^3和 R^4如本申请中所定义。

[0363] 在一些实例中，用于形成酰胺键的适合的条件包括使式 6 的化合物与取代的 3- 氨基吡啶在非质子溶剂中在加热下反应。在其它实例中，所述非质子溶剂选自 NMP、任选取代的吡啶或 DMF。在另一个实施方案中，所述非质子溶剂是任选取代的吡啶。在其它实施方案中，反应温度是至少 80℃。在另一个实施方案中，反应温度是至少 100℃。

[0364] 在另一个实施方案中，上述方法还包含制备式 6 的化合物：

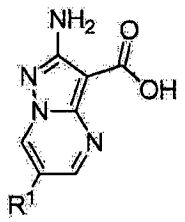
[0365]



6

[0366] 其通过使式 5 的化合物：

[0367]



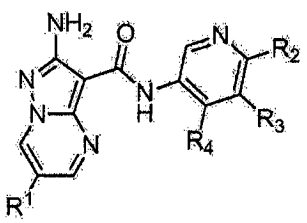
5

[0368] 在适合的条件下反应形成活化酯来进行，其中 J 和 R^1 如本申请中所定义。

[0369] 在一些实施方案中，用于形成活化酯的适合的条件包括使式 5 的化合物与酰胺偶合剂在有机碱的存在下反应。在其它实施方案中，所述有机碱是脂族胺。在其它实施方案中，所述有机碱独立地选自三乙胺或 DIPEA。在一个或多个实施方案中，所述酰胺偶合剂独立地选自 EDCI、TBTU、TCTU、HATU、T3P 或 COMU。在另一个实施方案中，所述酰胺偶合剂独立地选自 TBTU 或 TCTU。在另一个实施方案中，所述酰胺偶合剂是 TCTU。

[0370] 本发明的另一个方面包含用于制备式 I-A 的化合物的方法：

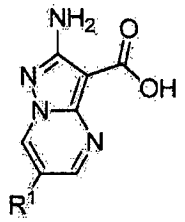
[0371]



I-A

[0372] 其包含使式 5 的化合物：

[0373]

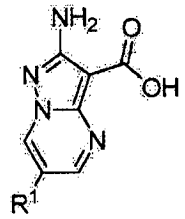


5

[0374] 在适合的条件下反应形成酰胺键，其中 R^1、R^2、R^3和 R^4如本申请中所定义。

[0375] 本发明的另一个方面包含用于制备式 5 的化合物的方法：

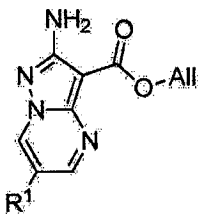
[0376]



5

[0377] 其通过使式 4 的化合物：

[0378]



4

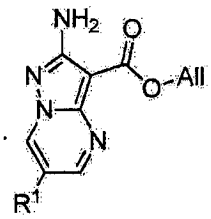
[0379] 在适合的水解条件下反应来进行，其中 R^1如本申请中所定义。

[0380] 在一些实施方案中，适合的水解条件包括使式 4 的化合物与硅烷在金属催化剂的存在下反应。在其它实施方案中，硅烷是苯基硅烷。在另一个实施方案中，金属催化剂是钯催化剂。在另一个实施方案中，钯催化剂是 $Pd(PPh_3)_4$。在另一个实施方案中，适合的水解条件包括使式 4 的化合物与 4- 甲基苯亚磺酸酯在金属催化剂的存在下反应。

[0381] 在其它实施方案中，适合的水解条件包括使式 4 的化合物与碱金属水溶液反应。在一些实施方案中，所述碱金属水溶液选自 LiOH、NaOH 或 KOH。

[0382] 本发明的另一个方面包含用于制备式 4 的化合物的方法：

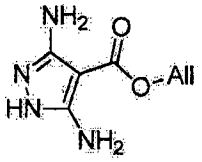
[0383]



4

[0384] 其通过使式 3 的化合物：

[0385]



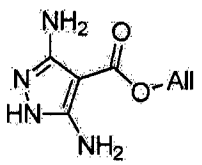
3

[0386] 在适合的缩合条件下反应形成嘧啶环来进行。

[0387] 在一些实施方案中，形成嘧啶环的适合的缩合条件包括使式 3 的化合物与 1,3- 二亲电类物质在溶剂的存在下反应。在另一个实施方案中，1,3- 二亲电类物质选自 1,3- 二醛或 3-(二烷基氨基)- 丙 -2- 烯醛。在其它实施方案中，所述溶剂选自 DMF 或 DMSO 的水溶液。在其它实施方案中，1,3- 二亲电类物质在原位由被保护的 1,3- 二亲电类物质生成。在另一个实施方案中，1,3- 二亲电类物质在磺酸的存在下由缩酮生成。在另一个实施方案中，磺酸是 PTSA。

[0388] 本发明的另一个方面包含用于制备式 3 的化合物的方法：

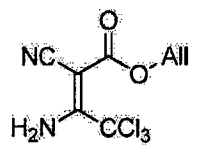
[0389]



3

[0390] 其通过使式 2 的化合物：

[0391]



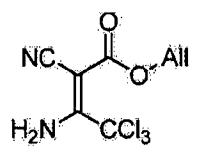
2

[0392] 在适合的缩合条件下反应形成吡唑环来进行。

[0393] 在一些实施方案中，形成吡唑环的适合的缩合条件包括使式 2 的化合物与肼或水合肼在非质子溶剂的存在下在碱性条件下反应。在另一个实施方案中，所述非质子溶剂是 DMF。在另一个实施方案中，所述碱性条件包括使式 2 的化合物在乙酸钾或乙酸钠的存在下反应。

[0394] 本发明的另一个方面包含用于制备式 2 的化合物的方法：

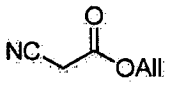
[0395]



2

[0396] 其通过使式 1 的化合物：

[0397]



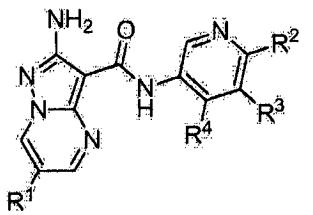
1

[0398] 在适合的阴离子缩合条件下反应来进行。

[0399] 在一些实施方案中，适合的阴离子缩合条件包含 1) 使式 1 的化合物与碱在溶剂的存在下反应，生成式 1 的化合物的阴离子；以及 2) 使式 1 的化合物的阴离子与三氯乙腈反应。在其它实施方案中，所述碱是乙酸钾。在另一个实施方案中，所述溶剂是醇。在其它实施方案中，所述溶剂是异丙醇。

[0400] 本发明的一个实施方案包含用于制备式 I-A 的化合物的方法：

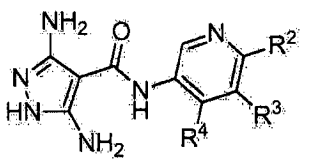
[0401]



I-A

[0402] 其包含使式 9 的化合物：

[0403]



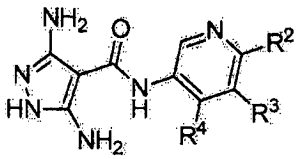
9

[0404] 在适合的缩合条件下反应，形成嘧啶环，其中 R^1、R^2、R^3和 R^4如本申请中所定义。

[0405] 在一些实施方案中，形成嘧啶环的适合的缩合条件包括使式 9 的化合物与 1,3- 二亲电类物质在溶剂的存在下反应。在另一个实施方案中，1,3- 二亲电类物质选自 1,3- 二醛或 3-(二烷基氨基)- 丙 -2- 烯醛。在其它实施方案中，所述溶剂选自 DMF 或 DMSO 的水溶液。在其它实施方案中，1,3- 二亲电类物质在原位由被保护的 1,3- 二亲电类物质生成。在另一个实施方案中，1,3- 二亲电类物质在磺酸的存在下由缩酮生成。在另一个实施方案中，磺酸是 PTSA。

[0406] 本发明的另一个实施方案包含用于制备式 9 的化合物的方法：

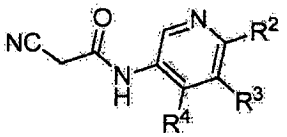
[0407]



9

[0408] 其通过使式 8 的化合物：

[0409]



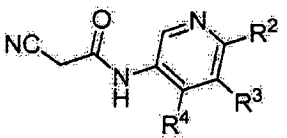
8

[0410] 在适合的缩合条件下反应形成吡唑环来进行。

[0411] 在一些实施方案中，形成吡唑环的适合的缩合条件包含 1) 使式 8 的化合物与碱在溶剂的存在下反应，生成式 1 的化合物的阴离子；2) 使所述阴离子与三氯乙腈反应；以及 3) 使来自 2) 的产物与肼或水合肼在非质子溶剂的存在下反应。在另一个实施方案中，所述非质子溶剂是 NMP 或 DMF。在一些实施方案中，所述碱选自乙酸钠或乙酸钾。

[0412] 本发明的另一个实施方案包含用于制备式 8 的化合物的方法：

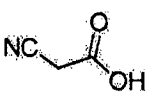
[0413]



8

[0414] 其通过使式 7 的化合物：

[0415]



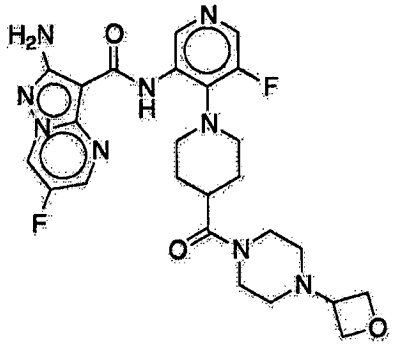
7

[0416] 在适合的条件下反应，形成酰胺键来进行。

[0417] 在一些实例中，用于形成酰胺键的适合的条件包括使式 7 的化合物与取代的 3- 氨基吡啶与酰胺偶合剂在非质子溶剂和有机碱的存在下反应。在其它实例中，所述非质子溶剂选自 NMP 或 DMF。在另一个实施方案中，所述有机碱是脂族胺。在其它实施方案中，所述有机碱独立地选自三乙胺或 DIPEA。在另一个实施方案中，所述酰胺偶合剂独立地选自 TBTU 或 TCTU。

[0418] 本发明的另一个方面提供制备式 I-G-32 的化合物的方法：

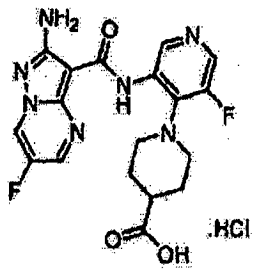
[0419]



I-G-32

[0420] 其包含使式 30 的化合物：

[0421]



30

[0422] 与式 25 的化合物：

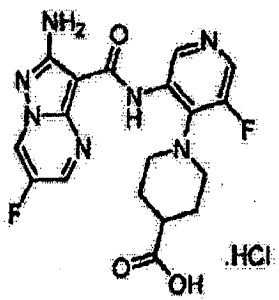
[0423]

25

[0424] 在适合的条件下反应形成酰胺键的步骤。

[0425] 本发明的其它实施方案包含提供用于制备式 30 的化合物的方法：

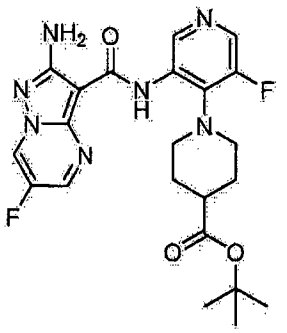
[0426]



30

[0427] 其通过使式 28 的化合物：

[0428]

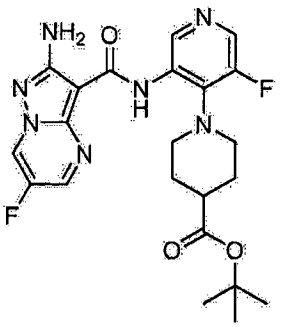


28

[0429] 在适合的脱保护条件下反应形成羧酸来进行。

[0430] 另一个实施方案提供用于制备式 28 的化合物的方法：

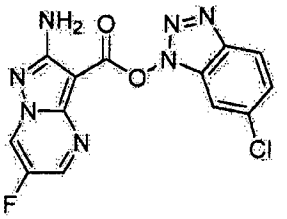
[0431]



28

[0432] 其通过使式 6a* 的化合物：

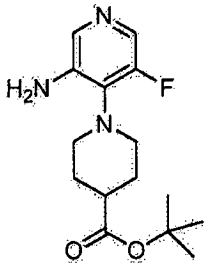
[0433]



6a*

[0434] 与式 27 的化合物：

[0435]



27

[0436] 在适合的条件下反应形成酰胺键来进行。

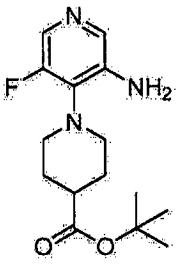
[0437] 在一些实施方案中，用于形成酰胺键的适合的条件包括使式 29 的化合物与式 25 的化合物在酰胺偶合配偶体、非质子溶剂和碱的存在下反应。在其它实施方案中，所述非质子溶剂独立地选自 NMP、DMF 或四氢呋喃。在其它实施方案中，所述非质子溶剂是四氢呋喃。在另一个实施方案中，所述碱是脂族胺。在另一个实施方案中，所述碱是 DIPEA。在一些实施方案中，所述酰胺偶合配偶体独立地选自 TBTU 或 TCTU。在一个或多个实施方案中，所述酰胺偶合配偶体是 TCTU。

[0438] 在其它实施方案中，适合的脱保护条件包括使式 28 的化合物与酸在溶剂的存在下反应。在一些实施方案中，所述酸是 HCl。在另一个实施方案中，所述溶剂是 1,4- 二噁烷。

[0439] 在另一个实施方案中，用于形成酰胺键的适合的条件包括使式 6a* 的化合物与式 27 的化合物在非质子溶剂的存在下在加热下反应。在其它实施方案中，所述非质子溶剂独立地选自 NMP、吡啶或 DMF。在另一个实施方案中，所述非质子溶剂是吡啶。在一些实施方案中，该反应在至少 80℃的温度下进行。

[0440] 本发明的另一个方面提供制备式 27 的化合物的方法：

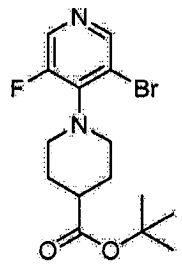
[0441]



27

[0442] 其包含使式 26 的化合物：

[0443]



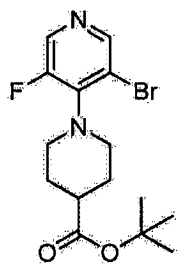
26

[0444] 在适合的条件下反应形成胺的步骤。

[0445] 在一些实施方案中，形成胺的适合的条件包括使式 27 的化合物在本领域技术人员已知的 Buchwald-Hartwig 氨基化条件下反应。

[0446] 另一个实施方案提供用于制备式 26 的化合物的方法：

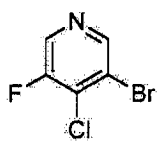
[0447]



26

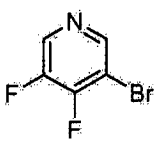
[0448] 其通过如下步骤进行：1) 使式 18 的化合物：

[0449]



18

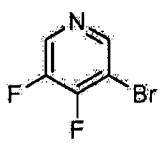
[0450] 在适合的卤素交换条件下反应生成式 32 的化合物，

[0451]  以及

32;

[0452] 2) 使式 32 的化合物：

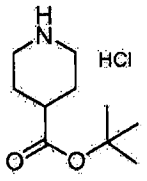
[0453]



32

[0454] 与式 22 的化合物：

[0455]



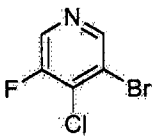
22

[0456] 在适合的置换条件下反应。

[0457] 在一些实施方案中，适合的卤素交换条件包括使式 18 的化合物与氟化钾在非质子溶剂和相转移催化剂的存在下反应。在其它实施方案中，所述非质子溶剂独立地选自 DMSO、DMF 或环丁砜。在其它实施方案中，所述相转移催化剂是 Me_4NCl。在其它实施方案中，适合的置换条件包括使式 32 的化合物与式 22 的化合物在碱的存在下反应。在另一个实施方案中，所述碱是脂族胺。在一些实施方案中，所述脂族胺是 DIPEA。

[0458] 本发明的其它实施方案提供用于制备式 18 的化合物的方法：

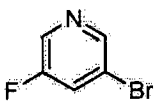
[0459]



18

[0460] 其通过使式 31 的化合物：

[0461]



31

[0462] 在适合卤化条件下反应来进行。

[0463] 在一些实施方案中，适合的卤化条件包含 1) 使式 31 的化合物与碱反应，生成阴离子；以及 2) 使所述阴离子与氯化剂反应。在另一个实施方案中，所述碱是 LDA。在另一个实施方案中，所述氯化剂是 1,1,1,2,2,2- 六氯乙烷。

[0464] 对于本申请的目的，将被理解的是，实施方案、实施例和方面这几个术语可以互换使用。

[0465] 对于本申请的目的，将被理解的是，当 2 次出现的 J^Q 与 Q^1 一起形成桥连环系时，2 次出现的 J^Q 连接至 Q^1 的单独的原子。另外，当 2 次出现的 J^R 与 Q^2 一起形成桥连环系时，2 次出现的 J^R 连接至 Q^2 的单独的原子。此外，当 2 次出现的 J^T 与 Q^3 一起形成桥连环系时，2 次出现的 J^T 连接至 Q^3 的单独的原子。此外，当 2 次出现的 J^W 与 W 一起形成桥连环系时，2 次出现的 J^W 连接至 W 的单独的原子。最后，当 2 次出现的 J^G 与环 D 一起形成桥连环系时，2 次出现的 J^G 连接至环 D 的单独的原子。

[0466] 本领域技术人员将会理解，→ O 中的箭头表示配价键。

[0467] 本发明的化合物包括本申请中一般性描述的化合物，且它们由本申请中公开的

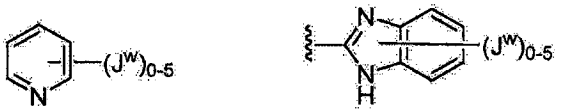
类、亚类和具体化合物进一步举例说明。如本文所述，除非另有说明，否则应当适用如下定义。对于本发明目的而言，化学元素根据Periodic Table of the Elements，CAS version，Handbook of Chemistry and Physics，75th Ed.（元素周期表，CAS 版，《化学与物理手册》，第 75 版）标识。另外，有机化学的一般原理在“Organic Chemistry”，Thomas Sorrell，University Science Books，Sausalito:1999（《有机化学》，Thomas Sorrell，大学科学书籍出版社，索萨利托，1999 年）和“March’s Advanced Organic Chemistry”，5th Ed.，Ed.:Smith，M.B.and March，J.，John Wiley&Sons，New York:2001（《马奇高等有机化学》，第 5 版，Smith，M.B. 和 March，J. 编辑，约翰·威利父子出版公司，纽约，2001 年）中有所描述，在此以引用方式将其全部内容并入本申请。

[0468] 如本文所述，原子的指定数量范围包括其中的任何整数。例如，具有 1-4 个原子的基团可具有 1、2、3 或 4 个原子。

[0469] 如本文所述，本发明化合物可任选被一个或多个取代基取代，所述取代基为例如本申请中一般性说明的取代基或以本发明的特别类、亚类和具体取代基所举例说明的取代基。应当理解，短语“任选取代的”与短语“取代的或未取代的”互换使用。一般来讲，术语“取代的”无论前面是否有术语“任选”均表示用特定取代基基团替代给定结构中的氢基团。除非另外指明，否则任选取代的基团可在该基团的每一个可取代的位置上具有取代基，并且当任何给定的结构中不止一个位置可以被不止一个选自指定群组的取代基所取代时，在每个位置上的取代基可能相同或者不同。本发明所预想的取代基组合优选是能够形成稳定的或化学上可行的化合物的取代基组合。

[0470] 除非另外指明，否则从环中心画出的键所连接的取代基意指该取代基可键合至该环中的任何位置上。在如下实例 i 中，例如，J^W可键合至吡啶基环上的任何位置。对于双环而言，贯穿两个环画出的键表示该取代基可从该双环的任何位置上键合。在如下实例 ii 中，例如，J^W可键合至 5 元环（例如键合于氮原子上）和键合至 6 元环。

[0471]



i ii

[0472] 本申请中所用的术语“稳定的”是指这样的化合物，在经受一些使得能够对它们进行制备、检测、回收、纯化以及用于本申请中所公开的一个或多个目的的条件时，该化合物实质上不会发生改变。在一些实施方案中，稳定的化合物或化学上可行的化合物是在没有水分或其它化学反应性条件存在的情况下在 40℃或更低的温度下保持至少一周时实质上不会发生改变的化合物。

[0473] 本申请中所用的术语“配价键”定义为在分子种类之间发生相互作用时形成的配位键，所述分子种类之一用作形成的配合物中共有的电子对的供体，而另一个用作其受体。

[0474] 本申请中所用的术语“脂族”或“脂族基团”意指直链（即无支链）、支链或环状的取代或未取代的烃链，该烃链是完全饱和的或含有一个或多个不饱和单元，其与分子其余部分具有单个连接点。

[0475] 除非另外指明，否则脂族基团含有 1-20 个脂族碳原子。在一些实施方案中，脂族

基团含有 1-10 个脂族碳原子。在其它实施方案中，脂族基团含有 1-8 个脂族碳原子。在其它实施方案中，脂族基团含有 1-6 个脂族碳原子，并且在其它实施方案中，脂族基团含有 1-4 个脂族碳原子。脂族基团可为直链或支链的、取代或未取代的烷基、烯基或炔基。具体实例包括但不限于甲基、乙基、异丙基、正丙基、仲丁基、乙烯基、正丁烯基、乙炔基和叔丁基。脂族基团也可以是环状的，或者具有直链或支链基团与环状基团的组合。这些类型的脂族基团的实例包括但不限于环丙基、环丁基、环戊基、环己基、环己烯基、$-CH_2-$ 环丙基、$CH_2CH_2CH(CH_3)-$ 环己基。

[0476] 术语“脂环族的”（或者“碳环”或“碳环基”）是指单环 C_3-C_8 烃或双环 C_8-C_{12} 烃，该烃是完全饱和的或者含有一个或多个不饱和单元，但其不是芳族的，其与分子的其余部分具有单个连接点，其中所述双环环系中的任何单独的环具有 3-7 个成员。脂环族基团的实例包括但不限于环烷基和环烯基。具体实例包括但不限于环己基、环丙基和环丁基。

[0477] 本申请中所用的术语“杂环”、“杂环基”或“杂环的”意指非芳族单环、双环或三环环系，其中一个或多个环成员是独立选择的杂原子。在一些实施方案中，“杂环”、“杂环基”或“杂环”基团具有三至十四个环成员，其中一个或多个环成员是独立选自氧、硫、氮或磷的杂原子，并且系统中的每个环含有 3 至 7 个环成员。

[0478] 杂环的实例包括但不限于 3-1H- 苯并咪唑 -2- 酮、3-(1- 烷基）- 苯并咪唑 -2- 酮、2- 四氢呋喃基、3- 四氢呋喃基、2- 四氢噻吩基、3- 四氢噻吩基、2- 吗啉代、3- 吗啉代、4- 吗啉代、2- 硫代吗啉代、3- 硫代吗啉代、4- 硫代吗啉代、1- 吡咯烷基、2- 吡咯烷基、3- 吡咯烷基、1- 四氢哌嗪基、2- 四氢哌嗪基、3- 四氢哌嗪基、1- 哌啶基、2- 哌啶基、3- 哌啶基、1- 吡唑啉基、3- 吡唑啉基、4- 吡唑啉基、5- 吡唑啉基、1- 哌啶基、2- 哌啶基、3- 哌啶基、4- 哌啶基、2- 噻唑烷基、3- 噻唑烷基、4- 噻唑烷基、1- 咪唑烷基、2- 咪唑烷基、4- 咪唑烷基、5- 咪唑烷基、二氢吲哚基、四氢喹啉基、四氢异喹啉基、苯并硫杂环戊烷、苯并二噻烷和 1,3- 二氢 - 咪唑 -2- 酮。

[0479] 环状基团（例如脂环族和杂环）可以是线性稠合、桥连或螺环的。

[0480] 术语“杂原子”意指氧、硫、氮、磷或硅中的一者或多者（包括氮、硫、磷或硅的任何氧化形式；任何碱性氮的季铵化形式；或杂环的可取代氮，例如 N（如在 3,4- 二氢 -2H- 吡咯基中）、NH（如在吡咯烷基中）或 NR^+（如在 N- 取代的吡咯烷基中））。

[0481] 本申请中所用的术语“不饱和的”意指部分具有一个或多个不饱和单元。正如本领域技术人员所知的，不饱和基团可以是部分不饱和的或完全不饱和的。部分不饱和基团的实例包括但不限于丁烯、环己烯和四氢吡啶。完全不饱和基团可以是芳族、反芳族或非芳族的。完全不饱和基团的实例包括但不限于苯基、环辛四烯、吡啶基、噻吩基和 1- 甲基吡啶 -2(1H)- 酮。

[0482] 本申请中所用的术语“烷氧基”或“硫代烷基”是指经由氧（“烷氧基”）或硫（“硫烷基”）原子连接的如先前所定义的烷基。

[0483] 术语“卤代烷基”、“卤代烯基”、“卤代脂族基”和“卤代烷氧基”意指视情况而被一个或多个卤素原子取代的烷基、烯基或烷氧基。该术语包括全氟化烷基，例如 $-CF_3$ 和 $-CF_2CF_3$。

[0484] 术语“卤素”、“卤代基”和“卤”意指 F、Cl、Br 或 I。

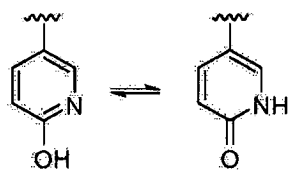
[0485] 单独使用或作为如“芳烷基”、“芳烷氧基”或“芳氧基烷基”等较大部分中一部分

的术语“芳基”是指具有总共五至十四个环成员的单环、双环和三环环系，其中该系统中的至少一个环是芳族的并且其中该系统中的每个环均含有 3 至 7 个环成员。术语“芳基”可以与术语“芳环”互换使用。

[0486] 单独使用或作为如“杂芳烷基”或“杂芳基烷氧基”等较大部分中的一部分的术语“杂芳基”是指具有总共五至十四个环成员的单环、双环和三环环系，其中该系统中的至少一个环是芳族的，该系统中的至少一个环含有一个或多个杂原子，并且其中该系统中的每个环均含有 3 至 7 个环成员。术语“杂芳基”可与术语“杂芳基环”或术语“杂芳族的”互换使用。杂芳基环的实例包括但不限于 2- 呋喃基、3- 呋喃基、N- 咪唑基、2- 咪唑基、4- 咪唑基、5- 咪唑基、苯并咪唑基、3- 异噁唑基、4- 异噁唑基、5- 异噁唑基、2- 噁唑基、4- 噁唑基、5- 噁唑基、N- 吡咯基、2- 吡咯基、3- 吡咯基、2- 吡啶基、3- 吡啶基、4- 吡啶基、2- 嘧啶基、4- 嘧啶基、5- 嘧啶基、哒嗪基（例如 3- 哒嗪基）、2- 噻唑基、4- 噻唑基、5- 噻唑基、四唑基（例如 5- 四唑基）、三唑基（例如 2- 三唑基和 5- 三唑基）、2- 噻吩基、3- 噻吩基、苯并呋喃基、苯并噻吩基、吲哚基（例如 2- 吲哚基）、吡唑基（例如 2- 吡唑基）、异噻唑基、1,2,3- 噁二唑基、1,2,5- 噁二唑基、1,2,4- 噁二唑基、1,2,3- 三唑基、1,2,3- 噻二唑基、1,3,4- 噻二唑基、1,2,5- 噻二唑基、嘌呤基、吡嗪基、1,3,5- 三嗪基、喹啉基（例如 2- 喹啉基、3- 喹啉基、4- 喹啉基）和异喹啉基（例如 1- 异喹啉基、3- 异喹啉基或 4- 异喹啉基）。

[0487] 应当理解，术语“杂芳基”包括某些类型的杂芳基环，这些杂芳基环以在两种不同形式之间的平衡形式存在。更具体地说，例如，例如氢化吡啶和吡啶酮（以及同样的，羟基嘧啶和嘧啶酮）等物质意在涵盖于“杂芳基”的定义内。

[0488]



[0489] 本申请中所用的术语“保护基”和“保护性基团”可互换使用，并且是指用于暂时封闭具有多个反应位点的化合物中的一个或多个所需官能团的试剂。在某些实施方案中，保护基具有如下特征中的一者或多者或优选为全部 :a) 以良好收率选择性地加至官能团而产生受保护的底物 ;b) 对于在一个或多个其它反应性位点发生的反应稳定 ;以及 c) 可用不会攻击该再生的、去保护的官能团的试剂以良好的收率选择性地移除。本领域的技术人员会理解，在一些情形中，所述试剂不攻击化合物中的其它反应性基团。在其它情况下，所述试剂也可与化合物中的其它反应性基团反应。保护基的实例在 Greene, T.W., Wuts, P.G in “Protective Groups in Organic Synthesis”, Third Edition, John Wiley&Sons, New York:1999(Greene, T.W., Wuts, P.G,《有机合成中的保护基》，第三版，约翰·威利父子出版公司，纽约，1999 年）（以及该书的其它版本）中有详细描述，该文献的全部内容据此以引用方式并入。本申请中所用的术语“氮保护基”是指用于暂时封闭多官能化合物中一个或多个所需氮反应性位点的试剂。优选的氮保护基还具有以上对保护基所示例的特征，并且某些示例性氮保护基也在 Chapter 7in Greene, T.W., Wuts, P.G in “Protective Groups in Organic Synthesis”, Third Edition, John Wiley&Sons, New York:1999(Greene, T.W.,

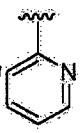
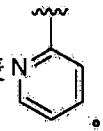
Wuts, P. G,《有机合成中的保护基》,第三版,约翰·威利父子出版公司,纽约,1999 年)的第 7 章中进行了详细描述,该文献的全部内容据此以引用方式并入。

[0490] 在一些实施方案中,烷基或脂族链的亚甲基单元任选被另一原子或基团替代。此类原子或基团的实例包括(但不限于)氮、氧、硫、-C(O)-、-C(=N-CN)-、-C(=NR)-、-C(=NOR)-、-SO- 和 $-SO_2-$。这些原子或基团可结合以形成更大的基团。这些更大的基团的实例包括但不限于 -OC(O)-、-C(O)CO-、$-CO_2-$、-C(O)NR-、-C(=N-CN)、-NRCO-、-NRC(O)O-、$-SO_2NR-$、$-NRSO_2-$、-NRC(O)NR-、-OC(O)NR- 和 $-NRSO_2NR-$,其中 R 是例如 H 或 C_{1-6}脂族基团。应当理解,这些基团可以经由单键、双键或三键与脂族链的亚甲基单元键合。经由双键与脂族链键合的任选替代基团(在这种情况下,是氮原子)的实例是 $-CH_2CH=N-CH_3$。在一些情况下,尤其是在末端上,任选的替代基团可以经由三键与脂族基团键合。这种情况的一个实例可以是 $CH_2CH_2CH_2C\equiv N$。应当理解,在这种情况下,末端氮未与另一个原子键合。

[0491] 还应当理解,术语"亚甲基单元"还可以指支链或取代的亚甲基单元。例如,在异丙基部分 $[-CH(CH_3)_2]$ 中,替换第一个所述"亚甲基单元"的氮原子(例如 NR)可以产生二甲胺 $[-N(CH_3)_2]$。在例如这些的情况下,本领域技术人员应当理解,氮原子将不具有任何另外的与其键合的原子,并且在这种情况下来自"NR"的"R"是不存在的。

[0492] 除非另外指明,否则任选的替代形成化学上稳定的化合物。任选的替代可在链内和/或在链的任一端处发生;即,在连接点处和/或也在末端。两个任选的替代也可以在链内彼此相邻,只要其产生化学上稳定的化合物即可。例如,C_3脂族基团可任选地被 2 个氮原子替代以形成 -C-N≡N。任选的替代还可完全替代链中的所有碳原子。例如,C_3脂族基团可任选被 -NR-、-C(O)- 和 -NR- 替代而形成 -NRC(O)NR-(脲)。

[0493] 除非另外指明,否则如果替代发生于末端上,那么替代原子与末端上的氢原子键合。例如,如果 $-CH_2CH_2CH_3$ 的亚甲基单元任选被 -O- 替代,那么所得的化合物可以是 $-OCH_2CH_3$、$-CH_2OCH_3$ 或 $-CH_2CH_2OH$。在另一个实例中,如果 $-CH_2CH_2CH_3$ 的亚甲基单元任选地被 -NH- 替代,则得到的化合物可以是 $-NHCH_2CH_3$、$-CH_2NHCH_3$ 或 $-CH_2CH_2NH_2$。应当理解,如果末端原子不含任何自由价电子,则在末端上不需要氢原子(例如 $-CH_2CH_2CH=O$ 或 $-CH_2CH_2C\equiv N$)。

[0494] 除非另外指明,否则本申请中描绘的结构也旨在包括该结构的所有同分异构(例如,对映异构、非对映异构、几何异构、构象异构和旋转异构)形式。例如,每个非对称中心的 R 和 S 构型、(Z) 和 (E) 双键异构体和 (Z) 和 (E) 构象异构体包括在本发明内。本领域的技术人员会理解,取代基可围绕任何可旋转键自由地旋转。例如,画为  的取代基也代表 

[0495] 因此,本发明化合物的单一立体化学异构体以及对映体、非对映体、几何、构象和旋转混合物均在本发明范围之内。

[0496] 除非另外指明,否则本发明化合物的所有互变异构形式均在本发明范围之内。

[0497] 另外,除非另外指明,否则本申请中描绘的结构也意在包括仅在一个或多个同位

素富集原子的存在方面不同的化合物。例如，具有本发明结构，不同的是用氘或氚替换氢或用富含 ^{13}C- 或 ^{14}C 的碳替换碳的化合物在本发明范围之内。这种化合物可用作（例如）生物测定法中的分析工具或探针。

[0498] 药学上可接受的盐、溶剂合物、笼形包合物、前药和其它衍生物

[0499] 本申请中所述的化合物可以以游离形式或如果适合作为盐的形式存在。属于药学上可接受的那些盐具有特别意义，因为它们可用于为医疗目的施用下述化合物。非药学上可接受的盐用于制备方法、用于分离和纯化目的，且在一些情况中，用于分离本发明化合物的立体异构体形式或其中间体。

[0500] 本申请中所用的术语“药学上可接受的盐”是指化合物的盐，在合理的医学判断范围内该盐适用于接触人体和低级动物的组织，而没有副作用，例如毒性、刺激性、过敏反应等，且与合理的有益 / 风险比相称。

[0501] 药学上可接受的盐是本领域众所周知的。例如，S. M. Berge 等在 J. Pharmaceutical Sciences，1977，66，1-19（《药物科学杂志》，1977 年，第 66 卷，第 1-19 页）中详细描述了药学上可接受盐，该文献以引用方式并入本文。本申请中所述的化合物的药学上可接受的盐包括那些衍生自适合的无机酸和碱以及有机酸和碱的盐。可在化合物的最终分离和纯化过程中原位制备这些盐。

[0502] 如果本申请中所述的化合物包含碱性基团或足够碱性的生物电子等排体，则可以通过下列方法制备酸加成盐：1）使纯化的化合物以其游离碱形式与适合的有机酸或无机酸反应；以及 2）分离由此形成的盐。实际上，酸加成的盐可能是应用的更便利形式，且应用盐相当于应用游离碱形式。

[0503] 药学上可接受的无毒性酸加成盐的实例是与无机酸或与有机酸形成的氨基的盐，所述无机酸例如盐酸、氢溴酸、磷酸、硫酸和高氯酸，所述有机酸例如乙酸、草酸、马来酸、酒石酸、柠檬酸、琥珀酸或丙二酸，或通过使用本领域中使用的其它方法例如离子交换形成的盐。其它药学上可接受的盐包括己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡糖酸盐 (digluconate)、十二烷基硫酸盐、乙磺酸盐、甲酸盐、富马酸盐、葡庚糖酸盐、甘油磷酸盐、羟乙酸盐、葡糖酸盐、羟乙酸盐、半硫酸盐、庚酸盐、己酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2- 羟基 - 乙磺酸盐、乳糖酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、甲磺酸盐、2- 萘磺酸盐、烟酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、扑酸盐 (palmoate)、果胶酸盐、过硫酸盐、3- 苯基丙酸盐、磷酸盐、苦味酸盐、新戊酸盐、丙酸盐、水杨酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一酸盐、戊酸盐等。

[0504] 如果本申请中所述的化合物包含羧基或足够酸性的生物电子等排体，则可以通过下列方法制备碱加成盐：1）使酸形式的纯化化合物与适合的有机碱或无机碱反应；以及 2）分离由此形成的盐。实际上，使用碱酸加成盐可能更便利，且应用盐形式内在地相当于应用游离酸形式。衍生自适合碱的盐包括碱金属（例如钠、锂和钾）、碱土金属（例如镁和钙）、铵和 $N^+(C_{1-4}$烷基$)_4$盐。本发明还关注本文公开的化合物的含任意碱性氮的基团的季铵化。可以通过这种季铵化得到水或油溶性或可分散产物。

[0505] 碱加成盐包括药学上可接受的金属盐和胺盐。适合的金属盐包括钠、钾、钙、钡、

锌、镁和铝盐。通常优选钠盐和钾盐。如果适合，另外药学上可接受的盐包括无毒性的铵、季铵和胺阳离子，其与例如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、低级烷基磺酸根和芳基磺酸根这样的抗衡离子形成。适合的无机碱加成盐由金属碱制备，包括氢化钠、氢氧化钠、氢氧化钾、氢氧化钙、氢氧化铝、氢氧化锂、氢氧化镁、氢氧化锌等。适合的胺碱加成盐由通常用于医学化学的胺类制备，因为它们的毒性低且对于医学应用而言具有可接受性。氨、乙二胺、N- 甲基 - 葡糖胺、赖氨酸、精氨酸、鸟氨酸、胆碱、N,N' - 二苄基乙二胺、氯普鲁卡因、二乙醇胺、普鲁卡因、N- 苄基苯乙胺、二乙胺、哌嗪、三（羟甲基）- 氨基甲烷、氢氧化四甲基铵、三乙胺、二苄基胺、二苯羟甲胺、去氢枞胺、N- 乙基哌啶、苄胺、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、乙胺、碱性氨基酸、二环己胺等是适合的碱加成盐的实例。

[0506] 其它自身并非药学上可接受的酸和碱可以用于制备盐，这些盐可用作得到本申请中所述的化合物及其药学上可接受的酸加成的盐或碱加成的盐的中间体。

[0507] 应理解本发明包括不同药学上可接受的盐的混合物 / 组合，并且还包括游离形式和药学上可接受的盐形式的化合物的混合物 / 组合。

[0508] 本申请中所述的化合物还可以作为药学上可接受的溶剂合物（例如水合物）和笼形包合物存在。本申请中所用的术语“药学上可接受的溶剂合物”是由一种或多种药学上可接受的溶剂分子与本申请中所述的化合物之一结合形成的溶剂合物。术语溶剂合物包括水合物（例如半水合物、一水合物、二水合物、三水合物、四水合物等）。

[0509] 本申请中所用的术语“水合物”是指还包括化学计算量或非化学计算量的通过非共价分子间作用力结合的水的本申请中所述的化合物或其盐。

[0510] 本申请中所用的术语“笼形包合物”是指晶格形式的本申请中所述的化合物或其盐，所述晶格包含具有其中俘获的包嵌分子（例如溶剂或水）的空间（例如通道）。

[0511] 除本申请中所述的化合物外，这些化合物的药学上可接受的衍生物或前药也可以用于治疗或预防本申请中所鉴定的病症的组合物中。

[0512] “药学上可接受的衍生物或前药”包括本申请中所述的化合物的任何药学上可接受的酯、酯的盐或其它衍生物或其盐，在施用于接受者时，它们能够直接或间接提供本申请中所述的化合物或抑制性的活性代谢物或其残留物。特别有利的衍生物或前药是这样的衍生物或前药：当该化合物被施用于患者（例如通过允许口服施用化合物以易于吸收入血液）时，它们增加该化合物的生物利用度，或相对于母体化合物它们增强母体化合物递送至生物隔室（例如脑或淋巴系统）。

[0513] 本申请中所用的且除非另有指定，否则术语“前药”是指可以在生物学条件下（体外或体内）水解、氧化或以其它方式反应以提供本申请中所述的化合物的化合物的衍生物。前药可以在生物学条件下经所述反应变成具有活性，或它们可以以其未反应形式具有活性。本发明关注的前药的实例包括，但不限于本发明化合物的类似物或衍生物，其包含可生物水解的部分，例如生物可水解的酰胺类、生物可水解的酯类、生物可水解的氨基甲酸酯类、生物可水解的碳酸酯类、生物可水解的酰脲类和生物可水解的磷酸酯类似物。其它前药的实例包括本申请中所述的化合物的衍生物，其包含 -NO、$-NO_2$、-ONO 或 $-ONO_2$ 部分。典型地，可以使用众所周知的方法制备前药，例如由 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY(1995)172-178,949-982(Manfred E。Wolff ed.，第 5 版）所述的那些方法。

[0514] 缩写

[0515] 使用如下缩写：

[0516] DMSO 二甲亚砜

[0517] DCM 二氯甲烷

[0518] ATP 腺苷三磷酸

[0519] ^{1}HNMR 质子核磁共振

[0520] HPLC 高效液相色谱法

[0521] LCMS 液相色谱法－质谱测定法

[0522] Rt 保留时间

[0523] RT 室温

[0524] TEA 三乙胺

[0525] NMP N-甲基-2-吡咯烷酮

[0526] TFA 三氟乙酸

[0527] Bp 沸点

[0528] DMF 二甲基甲酰胺

[0529] PTSA 对甲苯磺酸

[0530] DIPEA N,N-二异丙基乙胺

[0531] mCPBA 间氯过氧苯甲酸

[0532] HOBt 羟基苯并三唑

[0533] HATU 1-[双（二甲基氨基）亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化六氟磷酸盐

[0534] TBTU 2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基脲鎓四氟硼酸盐

[0535] T3P 丙基亚膦酸酐

[0536] COMU 1-[(1-(氰基-2-乙氧基-2-氧代亚乙基氨基氧基)-二甲基氨基-吗啉代)]脲鎓六氟磷酸盐

[0537] TCTU [(6-氯苯并三唑-1-基)氧基-(二甲基氨基)亚甲基]-二甲基-铵四氟硼酸盐

[0538] HBTU O-苯并三唑-N,N,N',N'-四甲基-脲鎓-六氟-磷酸盐

[0539] LDA 二异丙基氨基锂

[0540] EDCI 1-乙基-3-(3-二甲基氨基丙基）碳二亚胺

[0541] 化合物用途

[0542] 本发明的一个方面提供化合物，这些化合物是ATR激酶的抑制剂，并因此可用于治疗受试者或患者的疾病、病症或障碍或减轻其严重性，所述受试者或患者中所述疾病、病症或障碍牵涉ATR。

[0543] 本申请中所用的术语“受试者”和“患者”可以互换使用。术语“受试者”和“患者”是指动物，且更具体地是人。在一个实施方案中，所述受试者是非人的动物，例如家兔或狗。在一个优选的实施方案中，所述受试者是人。

[0544] 本发明的另一个方面提供可用于治疗特征在于过度或异常的细胞增殖的疾病、障

碍和病症的化合物。这类疾病包括增殖性或过度增殖性疾病。增殖性和过度增殖性疾病的实例包括而不限于癌和骨髓增殖性病症。

[0545] 在一些实施方案中，所述化合物选自由式 I-A 的化合物组成的组。在另一个方面，所述化合物由式 I-B 组成的组。在另一个方面，所述化合物选自由式 I 或 I-A-1 组成的组。术语“癌症”包括但不限于如下癌症。口部癌症：口腔癌、唇癌、舌癌、嘴癌、咽癌；心脏癌症：肉瘤（血管肉瘤、纤维肉瘤、横纹肌肉瘤、脂肪肉瘤）、粘液瘤、横纹肌瘤、纤维瘤、脂肪瘤和畸胎瘤；肺部癌症：支气管癌症（鳞状细胞癌或表皮样癌、未分化小细胞癌、未分化大细胞癌、腺癌）、肺泡（细支气管）癌、支气管腺瘤、肉瘤、淋巴瘤、软骨瘤性错构瘤、间皮瘤；胃肠癌症：食道癌症（鳞状细胞癌、喉癌、腺癌、平滑肌肉瘤、淋巴瘤）、胃癌（上皮细胞癌、淋巴瘤、平滑肌肉瘤）、胰腺癌症（导管腺癌、胰岛素瘤、胰高血糖素瘤、胃泌素瘤、类癌瘤、血管活性肠肽瘤 (vipoma)）、小肠癌症（腺癌、淋巴瘤、类癌瘤、卡波西氏 (Karposi’s) 肉瘤、平滑肌瘤、血管瘤、脂肪瘤、纤维神经瘤、纤维瘤）、大肠癌症（腺癌、管状腺瘤、绒毛状腺瘤、错构瘤、平滑肌瘤）、结肠癌、结肠 - 直肠癌、结肠直肠癌；直肠癌；泌尿生殖道癌症：肾癌症（腺癌、维耳姆斯 (Wilm’s) 瘤 [肾胚细胞瘤]、淋巴瘤、白血病）、膀胱和尿道癌症（鳞状细胞癌、移行细胞癌、腺癌）、前列腺癌症（腺癌、肉瘤）、睾丸癌症（精原细胞瘤、畸胎瘤、胚胎性癌、畸胎上皮细胞癌、绒毛膜癌、肉瘤、间质细胞癌、纤维瘤、纤维腺瘤、腺瘤样瘤、脂肪瘤）；肝脏癌症：肝细胞瘤（肝细胞癌）、胆管癌、肝胚细胞瘤、血管肉瘤、肝细胞性腺瘤、血管瘤、胆道癌；骨癌症：成骨肉瘤（骨肉瘤）、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤文氏 (Ewing’s) 肉瘤、恶性淋巴瘤（网状细胞肉瘤）、多发性骨髓瘤、恶性巨细胞瘤、脊索瘤、骨软骨纤维瘤 (osteochronfroma)（骨软骨性外生骨疣）、良性软骨瘤、成软骨细胞瘤、软骨粘液纤维瘤、骨样骨瘤和巨细胞瘤；神经系统癌症：颅骨癌症（骨瘤、血管瘤、肉芽肿、黄瘤、畸形性骨炎）、脑膜癌（脑膜瘤、脑膜肉瘤、神经胶质瘤病）、脑癌（星形细胞瘤、成神经管细胞瘤、神经胶质瘤、室管膜瘤、生殖细胞瘤 [松果体瘤]、多形性成胶质细胞瘤、少突神经胶质瘤、神经鞘瘤、成视网膜细胞瘤、先天性肿瘤）、脊髓神经纤维瘤、脑膜瘤、神经胶质瘤、肉瘤）；妇科癌症：子宫癌症（子宫内膜癌）、宫颈癌症（宫颈癌、肿瘤前宫颈非典型增生）、卵巢癌症（卵巢癌 [浆液性囊腺癌、粘液性囊腺癌、未分类癌瘤]、粒层 - 卵泡膜细胞瘤、塞 - 莱二氏 (Sertoli-Leydig) 细胞瘤、无性细胞瘤、恶性畸胎瘤）、外阴癌症（鳞状细胞癌、上皮内癌、腺癌、纤维肉瘤、黑素瘤）、阴道癌症（透明细胞癌、鳞状细胞癌、葡萄样肉瘤（胚胎性横纹肌肉瘤）、输卵管癌症（癌瘤）、乳腺癌；血液学癌症：血液癌症（骨髓性白血病 [急性和慢性]、急性成淋巴细胞性白血病、慢性淋巴细胞性白血病、骨髓增殖性疾病、多发性骨髓瘤、骨髓发育异常综合征）、霍奇金氏 (Hodgkin’s) 病、非霍奇金氏淋巴瘤 [恶性淋巴瘤]、毛细胞癌症；淋巴障碍；皮肤癌症：恶性黑素瘤、基底细胞癌、鳞状细胞癌、卡波西氏肉瘤、角化棘皮瘤、发育不良痣、脂肪瘤、血管瘤、皮肤纤维瘤、瘢痕瘤、牛皮癣；甲状腺癌症：乳头状甲状腺癌、滤泡性甲状腺癌、未分化甲状腺癌、髓样甲状腺癌、2A 型多发性内分泌腺瘤、2B 型多发性内分泌腺瘤、家族性髓样甲状腺癌、嗜铬细胞瘤、副神经节瘤；以及肾上腺癌症：成神经细胞瘤。

[0546] 在一些实施方案中，癌症选自肺癌或胰腺癌。在其它实施方案中，癌症选自肺癌、头颈部癌、胰腺癌、胃癌或脑癌。在其它实施方案中，癌症选自非小细胞肺癌、小细胞肺癌、胰腺癌、胆道癌、头颈部癌、膀胱癌、结肠直肠癌、成胶质细胞瘤、食道癌、乳腺癌、肝细胞癌

或卵巢癌。

[0547] 在一些实施方案中，所述癌症是肺癌。在其它实施方案中，所述癌症是非小细胞肺癌或小细胞肺癌。在另一个实施方案中，所述癌症是非小细胞肺癌。在另一个实施方案中，所述非小细胞肺癌是鳞状非小细胞肺癌。

[0548] 因此，如本文所提供的术语“癌细胞”包括受上文所鉴定的病症中的任一种侵害的细胞。在一些实施方案中，所述癌症选自结肠直肠癌、甲状腺癌或乳腺癌。在其它实施方案中，所述癌症是三阴性乳腺癌。

[0549] 术语“骨髓增殖性病症”包括例如以下的障碍：真性红细胞增多症、血小板增多症、伴有骨髓纤维变性的骨髓组织化生、高嗜酸性粒细胞综合征、青少年粒单核细胞白血病、全身性肥大细胞病和造血功能障碍，特别是急性骨髓性白血病（AML）、慢性骨髓性白血病（CML）、急性早幼粒细胞性白血病（APL）和急性淋巴细胞性白血病（ALL）。

[0550] 药物组合物

[0551] 本发明还提供可用作 ATR 激酶抑制剂的化合物和组合物。

[0552] 本发明的一个方面提供了药学上可接受的组合物，所述组合物包含本申请中所述的任何化合物并且任选包含药学上可接受的载体、辅剂或介质。

[0553] 本申请中所用的药学上可接受的载体、辅剂或介质包括任何及所有的适于所需特定剂型的溶剂、稀释剂或其它液体介质、分散或悬浮辅助剂、表面活性剂、等渗剂、增稠剂或乳化剂、防腐剂、固体粘合剂、润滑剂等。Remington's Pharmaceutical Sciences, Sixteenth Edition, E.W. Martin (Mack Publishing Co., Easton, Pa., 1980)（《雷氏药学大全》，第十六版，E.W. Martin，宾夕法尼亚州伊斯顿麦克出版有限公司，1980 年）公开了在配制药学上可接受的组合物中使用的各种载体及其已知的制备技术。除非任何常规的载体介质例如由于会产生任何不合乎需要的生物学效应或以别的方式与药学上可接受的组合物的一种或多种任何其它组分以有害的方式相互作用而与本发明化合物不相容，否则任何常规载体介质的使用也被认为处于本发明的范围内。

[0554] 可以充当药学上可接受的载体的物质的一些实例包括但不限于离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白如人血清白蛋白、缓冲物质如磷酸盐、甘氨酸、山梨酸或山梨酸钾、饱和植物脂肪酸的偏甘油酯混合物、水、盐或电解质，例如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐、胶态二氧化硅、三硅酸镁、聚乙烯吡咯烷酮、聚丙烯酸酯、蜡、聚乙烯 - 聚氧化丙烯 - 嵌段聚合物、羊毛脂；糖，例如乳糖、葡萄糖和蔗糖；淀粉，例如玉米淀粉和马铃薯淀粉；纤维素及其衍生物，例如羧甲基纤维素钠、乙基纤维素和醋酸纤维素；粉末状黄蓍胶；麦芽；明胶；滑石；赋形剂，例如可可脂和栓剂用蜡；油，例如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；二醇类，例如丙二醇或聚乙二醇；酯类，例如油酸乙酯和月桂酸乙酯；琼脂；缓冲剂，例如氢氧化镁和氢氧化铝；藻酸；无热原的水；等渗盐水；林格氏溶液；乙醇，和磷酸盐缓冲溶液，以及其它无毒的相容性润滑剂，例如月桂基硫酸钠和硬脂酸镁，以及着色剂、释放剂、包衣剂、甜味剂、调味剂和芳香剂，而且根据配制人员的判断，防腐剂和抗氧化剂也可以存在于组合物中。

[0555] 联合疗法

[0556] 本发明的另一个方面涉及治疗有需要的受试者的癌症的方法，该方法包括施用本发明化合物或其药学上可接受的盐以及另外的治疗剂。在一些实施例中，所述方法包括依

次或共同施用所述化合物或其药学上可接受的盐和另外的治疗剂。

[0557] 本申请中所用的术语“以组合方式”或“共同施用”可以互换使用，用以指一种以上疗法的应用（例如一种或多种治疗剂）。该术语的应用不限制其中施用于受试者的疗法（例如治疗剂）的次序。

[0558] 在一些实施方案中，所述另外的治疗剂是抗癌剂。在其它实施方案中，所述另外的治疗剂是DNA损伤剂。在其它实施方案中，所述另外的治疗剂选自放射疗法、化学疗法或典型地与放射疗法或化学疗法联合使用的其它药剂（例如放射增敏剂和化学增敏剂）。在其它实施方案中，所述另外的治疗剂是电离辐射。

[0559] 正如本领域技术人员所知，放射增敏剂是可以与放射疗法联合使用的药剂。放射增敏剂以多种不同的方式起作用，包括但不限于使癌细胞对放射疗法更敏感、与放射疗法起协同作用以提供改善的协同效应、与放射疗法起累加作用或防止周围的健康细胞受到放射疗法所引起的损伤。同样，化学增敏剂是可以与化学疗法联合使用的药剂。类似地，化学增敏剂以多种不同的方式起作用，包括但不限于使癌细胞对化学疗法更敏感、与化学疗法起协同作用以提供改善的协同效应、与化学疗法起累加作用或防止周围的健康细胞受到化学疗法所引起的损伤。

[0560] 可以与本发明化合物联合使用的DNA损伤剂的实例包括但不限于铂化(Platinating)剂，例如卡铂(Carboplatin)、奈达铂(Nedaplatin)、沙铂(Satraplatin)以及其它衍生物；Topo I抑制剂，例如托泊替康(Topotecan)、伊立替康(irinotecan)/SN38、鲁比替康(rubitecan)以及其它衍生物；抗代谢物，例如叶酸家族（甲氨蝶呤(Methotrexate)、培美曲塞(Pemetrexed)及相关物）；嘌呤拮抗剂和嘧啶拮抗剂（硫鸟嘌呤、氟达拉滨(Fludarabine)、克拉屈滨(Cladribine)、阿糖胞苷(Cytarabine)、吉西他滨(Gemcitabine)、6-巯嘌呤、5-氟尿嘧啶(5FU)及相关物）；烷化剂，例如氮芥类（环磷酰胺(Cyclophosphamide)、美法仑(Melphalan)、苯丁酸氮芥(Chlorambucil)、双氯乙基甲胺(mechlorethamine)、异环磷酰胺(Ifosfamide)及相关物）；亚硝基脲类（例如卡莫司汀(Carmustine)）；三氮烯类（达卡巴嗪(Dacarbazine)、替莫唑胺(temozolomide)）；烷基磺酸酯类（例如白消安(Busulfan)）；丙卡巴肼(Procarbazine)和氮丙啶类(Aziridine)；抗生素，例如羟基脲、蒽环类（亚多柔比星(doxorubicin)、柔红霉素(daunorubicin)、表柔比星(epirubicin)以及其它衍生物）；蒽二酮类（米托蒽醌(Mitoxantrone)及相关物）；链霉菌科（博来霉素(Bleomycin)、丝裂霉素C(Mitomycin C)、放线菌素(actinomycin)）；以及紫外光。

[0561] 可以与本发明的创造性药剂联合使用的其它疗法或抗癌剂包括外科手术、放射疗法（仅举几例，有γ-放射疗法、中子束放射疗法、电子束放射疗法、质子疗法、近距离放射疗法以及全身性放射性同位素等）、内分泌疗法、生物反应调节剂（干扰素、白细胞介素以及肿瘤坏死因子(TNF)等）、高温和冷冻疗法、减弱任何不良影响的药剂（例如止吐剂），以及其它经过批准的化学治疗药物，包括但不限于本文所列的DNA损伤剂、纺锤体毒素（长春碱(Vinblastine)、长春新碱(Vincristine)、长春瑞滨(Vinorelbine)、紫杉醇(Paclitaxel)）、鬼臼毒素（依托泊苷(Etoposide)、伊立替康、托泊替康）、亚硝基脲（卡莫司汀、洛莫司汀(Lomustine)）、无机离子（顺铂(Cisplatin)、卡铂）、酶类（天冬酰胺酶），以及激素类（他莫昔芬(Tamoxifen)、亮丙瑞林(Leuprolide)、氟他米特(Flutamide)以及

甲地孕酮(Megestrol))、Gleevec™、阿霉素(adriamycin)、地塞米松(dexamethasone)以及环磷酰胺。

[0562] 本发明化合物还可以与如下治疗剂中的任一者联合用于治疗癌症:阿巴瑞克(Plenaxis depot®);阿地白介素(Prokine®);阿地白介素(Proleukin®);阿仑单抗(Campath®);阿利维A酸(Panretin®);别嘌呤醇(Zyloprim®);六甲蜜胺(Hexalen®);氨磷汀(Ethyol®);阿那曲唑(Arimidex®);三氧化二砷(Trisenox®);天门冬酰胺酶(Elspar®);阿扎胞苷(Vidaza®);贝伐单抗(Avastin®);蓓萨罗丁胶囊(Targretin®);蓓萨罗丁凝胶剂(Targretin®);博来霉素(Blenoxane®);硼替佐米(Velcade®);静脉用白消安(Busulfex®);口服用白消安(Myleran®);卡普睾酮(Methosarb®);卡培他滨(Xeloda®);卡铂(Paraplatin®);卡莫司汀(BCNU®, BiCNU®);卡莫司汀(Gliadel®);使用聚苯丙生20植入物的卡莫司汀(Gliadel Wafer®);塞来考昔(Celebrex®);西妥昔单抗(Erbitux®);苯丁酸氮芥(Leukeran®);顺铂(Platinol®);克拉屈滨(Leustatin®, 2-CdA®);氯法拉滨(Clolar®);环磷酰胺(Cytoxan®, Neosar®);环磷酰胺(Cytoxan Injection®);环磷酰胺(Cytoxan Tablet®);阿糖胞苷(Cytosar-U®);阿糖胞苷脂质体(DepoCyt®);达卡巴嗪(DTIC-Dome®);更生霉素、放线菌素D(Cosmegen®);达依泊汀α(Aranesp®);柔毛霉素脂质体(DanuoXome®);柔毛霉素、柔红霉素(Daunorubicin®);柔毛霉素、柔红霉素(Cerubidine®);地尼白介素(Ontak®);右雷佐生(Zinecard®);多烯紫杉醇(Taxotere®);多柔比星(Adriamycin PFS®);多柔比星(Adriamycin®, Rubex®);多柔比星(Adriamycin PFS Injection®);多柔比星脂质体(Doxil®);丙酸屈他雄酮(dromostanolone®);丙酸屈他雄酮(masterone injection®);Elliott's B溶液(Elliott's B Solution®);表柔比星(Ellence®);阿法依泊汀(epogen®);埃罗替尼(Tarceva®);雌莫司汀(Emcyt®);磷酸依托泊苷(Etopophos®);依托泊苷、VP-16(Vepesid®);依西美坦(Aromasin®);非格司亭(Neupogen®);氟尿苷(**动脉内**)(FUDR®);氟达拉滨(Fludara®);氟尿嘧啶、5-FU(Adrucil®);氟维司群(Faslodex®);吉

非替尼(Iressa®)；吉西他滨(Gemzar®)；吉妥珠单抗奥佐米星(Mylotarg®)；醋酸戈舍瑞林(Zoladex Implant®)；醋酸戈舍瑞林(Zoladex®)；醋酸组胺瑞林(Histrelin implant®)；羟基脲(Hydrea®)；替伊莫单抗(Zevalin®)；伊达比星(Idamycin®)；异环磷酰胺(IFEX®)；甲磺酸伊马替尼(Gleevec®)；干扰素α2a(Roferon A®)；干扰素α-2b(Intron A®)；伊立替康(Camptosar®)；来那度胺(Revlimid®)；来曲唑(Femara®)；亚叶酸(Wellcovorin®，Leucovorin®)；醋酸亮丙瑞林(Eligard®)；左旋咪唑(Ergamisol®)；环己亚硝脲、CCNU(CeeBU®)；双氯乙基甲胺、氮芥(Mustargen®)；醋酸甲地孕酮(Megace®)；美法仑、L-PAM(Alkeran®)；巯嘌呤、6-MP(Purinethol®)；美司钠(Mesnex®)；美司钠(Mesnex tabs®)；甲氨蝶呤(Methotrexate®)；甲氧沙林(Uvadex®)；丝裂霉素C(Mutamycin®)；米托坦(Lysodren®)；米托蒽醌(Novantrone®)；苯丙酸诺龙(Durabolin-50®)；奈拉滨(Arranon®)；诺莫单抗(Verluma®)；奥普瑞白介素(Neumega®)；奥沙利铂(Eloxatin®)；紫杉醇(Paxene®)；紫杉醇(Taxol®)；紫杉醇蛋白结合粒子(Abraxane®)；帕利夫明(Kepivance®)；帕米膦酸盐(Aredia®)；培加酶(Adagen (Pegademase Bovine)®)；培门冬酶(Oncaspar®)；培非格司亭(Neulasta®)；培美曲塞二钠(Alimta®)；喷司他丁(Nipent®)；哌泊溴烷(Vercyte®)；普卡霉素、光辉霉素(Mithracin®)；卟吩姆钠(Photofrin®)；丙卡巴肼(Matulane®)；奎纳克林(Atabrine®)；拉布立酶(Elitek®)；利妥昔单抗(Rituxan®)；沙格司亭(Leukine®)；沙格司亭(Prokine®)；索拉非尼(Nexavar®)；链佐星(Zanosar®)；顺丁烯二酸舒尼替尼(Sutent®)；滑石(Sclerosol®)；他莫昔芬(Nolvadex®)；替莫唑胺(Temodar®)；替尼泊苷、VM-26(Vumon®)；睾内酯(Teslac®)；硫鸟嘌呤，6-TG(Thioguanine®)；噻替派(Thioplex®)；托泊替康(Hycamtin®)；托瑞米芬(Fareston®)；托西莫单抗(Bexxar®)；托西莫单抗/I-131托西莫单抗(Bexxar®)；曲妥珠单抗(Herceptin®)；维甲酸、ATRA(Vesanoid®)；尿嘧啶氮芥(Uracil Mustard Capsules®)；戊柔比星(Valstar®)；长春花碱(Velban®)；

长春新碱(Oncovin®);长春瑞滨(Navelbine®);唑来膦酸盐(Zometa®);和伏立诺他(Zolinza®)。

[0563] 关于最新癌症疗法的综合性论述,参见 http://www.nci.nih.gov/, http://www.fda.gov/cder/cancer/druglistframe.htm 上的 FDA 批准的肿瘤药物的列表,以及 The Merck Manual, Seventeenth Ed. 1999(《默克诊疗手册》,第十七版,1999 年),这些文献的全部内容据此以引用方式并入。

[0564] 用于施用至受试者体内的组合物

[0565] 可以将 ATR 激酶抑制剂或其药用盐配制成用于施用给动物或人的药物组合物。包含有效治疗或预防本申请中所述的疾病或病症的量的 ATR 抑制剂和药学上可接受的载体的这些药物组合物是本发明的另一个实施方案。

[0566] 治疗所需的化合物的确切量将在受试者之间有所不同,这取决于受试者的物种、年龄和一般状况、病症的严重性、具体的药剂、其施用模式等。优选将本发明化合物配制成单位剂型以易于施用和保持剂量均匀。本申请中所用的表达"单位剂型"是指适合于待治疗的患者的药剂的物理离散单元。然而,应当理解,本发明的化合物和组合物的总每日用量将由主治医师在合理的医学判断范围内决定。用于任何特定患者或生物体的具体有效剂量水平将取决于包括如下各项在内的多种因素:所治疗的病症和该病症的严重性;所使用的具体化合物的活性;所使用的具体组合物;患者的年龄、体重、总体健康情况、性别和饮食;所使用的具体化合物的施用时间、施用途径以及排泄速率;治疗持续时间;与所使用的具体化合物联合或同时使用的药物,以及医学领域熟知的类似因素。本申请中所用的术语"患者"意指动物,优选哺乳动物,并且最优选人。

[0567] 在一些实施方案中,这些组合物任选还包含一种或多种另外的治疗剂。例如,化学治疗剂或其它抗增殖剂可以与本发明化合物联合用于治疗增殖性疾病和癌症。可以与这些组合物联合的已知药剂的实例在上文中列于"联合疗法"部分中并且还贯穿于整个说明书中。一些实施方案提供了同时、单独或依次使用组合制剂。

[0568] 给药模式和剂型

[0569] 本发明的药学上可接受的组合物可通过经口、经直肠、肠胃外、脑池内、阴道内、腹膜内、局部(如通过散剂、软膏剂或滴剂)、经颊、以口腔或鼻喷雾剂形式等方式施用给人和其它动物,这取决于所治疗的感染的严重性。在某些实施方案中,本发明化合物可以约 0.01mg/kg 至约 50mg/kg 且优选约 1mg/kg 至约 25mg/kg 受试者体重/天的剂量水平经口或肠胃外施用,每天一次或多次,以获得所需的治疗效果。或者,本发明化合物的给药方案可变。

[0570] 供口服施用的液体剂型包括但不限于药学上可接受的乳剂、微乳剂、溶液剂、混悬剂、糖浆剂和酏剂。除了活性化合物之外,液体剂型还可含有本领域常用的惰性稀释剂,例如水或其它溶剂,增溶剂和乳化剂例如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苄醇、苯甲酸苄酯、丙二醇、1,3-丁二醇、二甲基甲酰胺、油(尤其是棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油和芝麻油)、甘油、四氢糠醇、聚乙二醇和脱水山梨糖醇的脂肪酸酯,以及它们的混合物。除惰性稀释剂外,口服组合物还可包含助剂,例如湿润剂、乳化剂和助悬剂、甜味剂、调味剂和芳香剂。

[0571] 可根据已知技术使用适合的分散剂或润湿剂和助悬剂配制可注射的制剂，例如无菌可注射水性或油性混悬剂。无菌注射剂也可能是在无毒的肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液、混悬液或乳液，例如作为在 1,3- 丁二醇中的溶液。可采用的可接受的介质和溶剂有水，林格氏溶液，U.S.P. 和等渗氯化钠溶液。另外，常规上将无菌不挥发性油用作溶剂或助悬介质。为此目的，可采用任何温和的不挥发性油，包括合成的甘油单脂或甘油二酯。另外，将脂肪酸例如油酸用于制备注射剂。

[0572] 可对注射制剂进行灭菌，例如通过滤过截留细菌的过滤器进行灭菌，或通过掺入无菌固体组合物形式的灭菌剂进行灭菌，在使用之前可将该灭菌剂溶于或分散于无菌水或其它无菌可注射介质中。

[0573] 为延长本发明化合物的效果，常常希望减缓化合物从皮下或肌肉注射的吸收。这可通过使用水溶性差的晶体或无定形物质的液体混悬剂来实现。化合物的吸收速率于是取决于其溶解速率，而溶解速率又可取决于晶体大小和晶体形式。或者，通过将化合物溶解或悬浮于油介质中来实现经肠胃外施用的化合物的延迟吸收。通过在可生物降解的聚合物例如聚丙交酯 - 聚乙交酯中形成化合物的微胶囊基质来制成可注射的储库形式。根据化合物与聚合物之比以及所采用的特定聚合物的性质，可控制化合物发释放速率。其它可生物降解的聚合物的实例包括聚（原酸酯）和聚（酸酐）。也可通过将化合物截留在与身体组织相容的脂质体或微乳剂中来制备储库型注射制剂。

[0574] 供直肠或阴道施用的组合物优选为栓剂，其可通过将本发明化合物与适合的非刺激性赋形剂或载体例如可可脂、聚乙二醇或栓剂蜡混合来制备，所述赋形剂或载体在环境温度下为固体但在体温下为液体并因而在直肠或阴道腔内融化并释放活性化合物。

[0575] 口服固体剂型包括胶囊剂、片剂、丸剂、散剂和颗粒剂。在这种固体剂型中，活性化合物混有至少一种惰性的药学上可接受的赋形剂或载体例如柠檬酸钠或磷酸二钙和 / 或 a) 填料或增量剂，例如淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸，b) 粘合剂，例如羧基甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和阿拉伯树胶，c) 保湿剂，例如甘油，d) 崩解剂，例如琼脂、碳酸钙、马铃薯或木薯淀粉、藻酸、某些硅酸盐和碳酸钠，e) 溶液阻滞剂，例如石蜡，f) 吸收加速剂，例如季铵化合物，g) 润湿剂，例如鲸蜡醇和单硬脂酸甘油酯，h) 吸收剂，例如高岭土和膨润土，和 i) 润滑剂，例如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠，以及它们的混合物。就胶囊剂、片剂和丸剂而言，剂型也可包含缓冲剂。

[0576] 也可采用类似类型的固体组合物作为软和硬填充明胶胶囊中的填料，所述胶囊使用例如乳糖或奶糖以及高分子量聚乙二醇等赋形剂。片剂、糖锭剂、胶囊剂、丸剂和颗粒剂的固体剂型可制备有包衣和外壳，例如肠溶衣和药物配制领域众所周知的其它包衣。它们可任选含有遮光剂并且还可具有这样的组成，该组成使得它们仅仅或优先地在肠道的某一部分中释放活性成分，任选地以延迟的方式释放。可使用的包埋组合物的实例包括聚合物和蜡。也可采用类似类型的固体组合物作为软和硬填充明胶胶囊中的填料，所述胶囊使用例如乳糖或奶糖以及高分子量聚乙二醇等赋形剂。

[0577] 活性化合物也可为具有一种或多种上述赋形剂的微胶囊形式。片剂、糖锭剂、胶囊剂、丸剂和颗粒剂的固体剂型可制备有包衣和外壳，例如肠溶衣、控释包衣以及药物配制领域众所周知的其它包衣。在这种固体剂型中，活性化合物可与至少一种惰性稀释剂例如蔗糖、乳糖或淀粉混合。如一般的做法，这种剂型还可包含非惰性稀释剂的另外的物质，例如

压片润滑剂和其它压片辅助剂如硬脂酸镁和微晶纤维素。就胶囊剂、片剂和丸剂而言，剂型也可包含缓冲剂。它们可任选含有遮光剂并且还可具有这样的组成，该组成使得它们仅仅或优先地在肠道的某一部分中释放活性成分，任选地以延迟的方式释放。可使用的包埋组合物的实例包括聚合物和蜡。

[0578] 本发明化合物的局部或经皮施用剂型包括软膏剂、糊剂、霜剂、洗剂、凝胶剂、散剂、溶液剂、喷剂、吸入剂或贴片剂。将活性化合物在无菌条件下与药学上可接受的载体和任何需要的防腐剂或可能需要的缓冲剂相混合。眼科制剂、滴耳剂和滴眼剂也被设想到本发明的范围之内。另外，本发明设想使用透皮贴片剂，其具有使化合物控制递送至身体的附加优点。可通过将化合物溶解或分散于恰当的介质中来制备这种剂型。吸收促进剂也可用于提高化合物穿过皮肤的通量。可通过提供速率控制膜或通过将化合物分散于聚合物基质或凝胶中来控制速率。

[0579] 也可以经口、肠胃外的方式、通过吸入喷剂、以局部、直肠、鼻、颊面、阴道的方式或通过植入的贮器施用本发明组合物。本申请中所用的术语“肠胃外”包括但不限于皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。优选地，以经口、腹膜内或静脉内的方式施用组合物。

[0580] 本发明所述组合物的无菌可注射形式可为水性或油性混悬剂。这些混悬剂可根据本领域已知的技术使用适合的分散或润湿剂和助悬剂配制。无菌注射剂也可以是在无毒的肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液剂或混悬剂，例如作为在 1,3- 丁二醇中的溶液。可采用的可接受的介质和溶剂是水、林格氏溶液和等渗氯化钠溶液。另外，常规上将无菌不挥发性油用作溶剂或助悬介质。为此目的，可采用任何温和的不挥发性油，包括合成的甘油单脂或甘油二酯。脂肪酸例如油酸及其甘油酯衍生物可用于制备注射剂，同样的是天然的药学上可接受的油，例如橄榄油或蓖麻油，尤其是以它们的聚氧乙烯化形式。这些油溶液剂或混悬剂也可含有长链醇稀释剂或分散剂，例如羧甲基纤维素或在配制药学上可接受的剂型（包括乳剂和混悬剂）中常用的类似分散剂。其它常用的表面活性剂，例如吐温、司盘和在生产药学上可接受的固体、液体或其它剂型中常用的其它乳化剂或生物利用度增强剂也可用于配制目的。

[0581] 可以任何口服可接受的剂型，包括但不限于胶囊剂、片剂、水混悬剂或溶液剂，来经口施用本发明药物组合物。就供口服使用的片剂而言，常用载体包括但不限于乳糖和玉米淀粉。通常还加入润滑剂，例如硬脂酸镁。对于以胶囊剂形式口服，可用的稀释剂包括乳糖和干玉米淀粉。当需要水混悬剂进行口服时，将活性成分与乳化剂和助悬剂组合。如果需要，还可加入某些甜味剂、调味剂或着色剂。

[0582] 或者，可以供直肠施用的栓剂形式施用本发明药物组合物。可通过将该药剂与适合的非刺激性赋形剂混合来制备这些药物组合物，所述赋形剂在室温下为固体，但在直肠温度下为液体，因此将在直肠内融化而释放药物。这种物质包括但不限于可可脂、蜂蜡和聚乙二醇。

[0583] 本发明的药物组合物还可局部施用，尤其是当治疗目标包括局部施用易于接近的区域或器官（包括眼部、皮肤或下肠道疾病）时。容易制备用于这些区域或器官中的每一者的合适局部用制剂。

[0584] 对下肠道的局部施加可以直肠栓剂制剂（见上文）或以适合的灌肠制剂来实现。

也可使用局部透皮贴片剂。

[0585] 对于局部施用而言，可将药物组合物配制为含有悬浮或溶于一种或多种载体中的活性组分的合适软膏剂。用于局部施用本发明化合物的载体包括但不限于矿物油、液体石蜡、白凡士林、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡和水。或者，可将药物组合物配制为含有悬浮或溶于一种或多种药学上可接受的载体中的活性成分的适合洗剂或霜剂。适合的载体包括但不限于矿物油、一硬脂酸脱水山梨醇酯、聚山梨醇酯 60、十六醇酯蜡、鲸蜡硬脂醇、2- 辛基十二醇、苄醇和水。

[0586] 对于眼科使用，可使用或不用例如苯扎氯铵的防腐剂，将药物组合物配制为在等渗、经 pH 调节的无菌盐水中的微粉化混悬剂，或者优选地，制备为在等渗、经 pH 调节的无菌盐水中的溶液剂。或者，对于眼科使用，可将药物组合物配制在软膏例如凡士林中。

[0587] 本发明的药物组合物还可以通过鼻用气溶胶或吸入施用。这种组合物根据药物配制领域中众所周知的技术制备，并且可采用苄醇或其它适合的防腐剂、增强生物利用度的吸收促进剂、碳氟化合物和 / 或其它常规增溶剂或分散剂制备成在盐水中的溶液剂。

[0588] 可以与载体物质组合以产生单个剂型的蛋白激酶抑制剂的量将根据所治疗的宿主、特定施用模式而变化。优选地，组合物应经过配制以使得可以给接受这些组合物的患者施用 0.01-100mg/kg 体重 / 天之间的剂量的抑制剂。或者，可以给接受这些化合物的患者施用 0.01 - 50mg/kg 体重 / 剂量的抑制剂。

[0589] 还应当理解，用于任何特定患者的具体剂量和治疗方案将取决于多种因素，包括所使用的具体化合物的活性、年龄、体重、总体健康情况、性别、饮食、施用时间、排泄速率、药物组合和治疗医师的判断以及所治疗的特定疾病的严重性。抑制剂的量还将取决于组合物中的特定化合物。

[0590] 与另外的药剂一起施用

[0591] 取决于有待治疗或预防的特定蛋白激酶介导的病症，可以将通常施用来治疗或预防该病症的另外的药物连同本发明化合物一起施用。

[0592] 那些另外的药剂可以作为多重给药方案的一部分与含有该蛋白激酶抑制剂的化合物或组合物分开施用。或者，那些药剂可以是单个剂型的一部分，与所述蛋白激酶抑制剂一起混合于单个组合物中。

[0593] 本发明的另一个方面涉及在有需要的受试者中治疗癌症的方法，该方法包括依次或共同施用本发明化合物或其药学上可接受的盐和抗癌剂。在一些实施方案中，所述抗癌剂选自铂化剂，例如顺铂、奥沙利铂、卡铂、奈达铂或沙铂和其它衍生物；Topo I 抑制剂，例如喜树碱、托泊替康、伊立替康 /SN38、鲁比替康和其它衍生物；抗代谢物，例如叶酸家族（甲氨蝶呤、培美曲塞 (Pemetrexed) 及相关物）；嘌呤家族（硫鸟嘌呤、氟达拉滨、克拉屈滨、6- 巯嘌呤及相关物）；嘧啶家族（阿糖胞苷、吉西他滨、5- 氟尿嘧啶及相关物）；烷化剂，例如氮芥类（环磷酰胺、美法仑、苯丁酸氮芥、双氯乙基甲胺、异环磷酰胺及相关物）；亚硝基脲类（例如卡莫司汀）；三氮烯类（达卡巴嗪、替莫唑胺）；烷基磺酸酯类（例如白消安）；丙卡巴肼和氮丙啶类；抗生素，例如羟基脲；蒽环类（多柔比星、柔红霉素、表柔比星和其它衍生物）；蒽二酮类（米托蒽醌及相关物）；链霉菌科（博来霉素、丝裂霉素 C、放线菌素）和紫外光。

[0594] 另一个实施方案提供了将本发明化合物与抑制或调节碱基切除修复蛋白的另外

的治疗剂一起施用。在一些实施方案中，碱基切除修复蛋白选自 UNG、SMUG1、MBD4、TDG、OGG1、MYH、NTH1、MPG、NEIL1、NEIL2、NEIL3(DNA 糖基化酶）；APE1、APEX2(AP 核酸内切酶）；LIG1、LIG3(DNA 连接酶 I 和 III)；XRCC1(LIG3 辅助因子）；PNK、PNKP(多核苷酸激酶和磷酸酶）；PARP1、PARP2(多聚 (ADP- 核糖）聚合酶）；PolB、PolG(聚合酶）；FEN1(内切酶）或 Aprataxin。在其它实施方案中，碱基切除修复蛋白选自 PARP1、PARP2 或 PolB。在其它实施方案中，碱基切除修复蛋白选自 PARP1 或 PARP2。在一些实施方案中，所述药剂选自奥拉帕尼 (Olaparib)(也被称为 AZD2281 或 KU-0059436)、Iniparib(也被称为 BSI-201 或 SAR240550)、Veliparib(也被称为 ABT-888)、Rucaparib(也被称为 PF-01367338)、CEP-9722、INO-1001、MK-4827、E7016、BMN673 或 AZD2461。

[0595] 生物样品

[0596] 作为 ATR 激酶的抑制剂，本发明的化合物和组合物还可用于生物样品中。本发明的一个方面涉及抑制生物样品中的 ATR 激酶活性，该方法包括使所述生物样品与本申请中所述的化合物或包含所述化合物的组合物接触。本申请中所用的术语“生物样品”意指体外或离体样品，包括但不限于细胞培养物或其提取物；从哺乳动物获得的活组织检查材料或其提取物；以及血液、唾液、尿、粪便、精液、泪液或其它体液或它们的提取物。术语“本申请中所述的化合物”包括式 I、I-A、I-A-1 和 I-B 的化合物。

[0597] 生物样品中 ATR 激酶活性的抑制可用于本领域技术人员公知的各种目的。这样的目的的实例包括，但不限于输血、器官移植和生物样本储存。

[0598] 蛋白激酶的研究

[0599] 本发明的另一个方面涉及对生物学和病理学现象中的蛋白激酶进行研究；对由这些蛋白激酶介导的细胞内信号转导途径进行研究；以及对新的蛋白激酶抑制剂进行对比评价。这些用途的实例包括但不限于生物测定法，例如酶测定法和基于细胞的测定法。

[0600] 可以在体外、体内或在细胞系中对化合物作为蛋白激酶抑制剂的活性进行测定。体外测定法包括测定对活化激酶的激酶活性或 ATP 酶活性的抑制作用的测定法。备选的体外测定法可定量抑制剂结合蛋白激酶的能力并且可以通过在结合之前对抑制剂进行放射性标记、分离抑制剂 / 激酶复合体并且测定所结合的放射性标记的量，或者通过进行竞争实验来测量，在所述竞争实验中，将新的抑制剂与结合至已知放射性配体的激酶一起温育。用于测定在本发明中用作 ATR 抑制剂的化合物的详细条件在下文实施例中示出。

[0601] 本发明的另一个方面提供了通过使本申请中所述的化合物与 ATR 激酶接触来调节酶活性的方法。

[0602] 治疗方法

[0603] 在一个方面，本发明提供了用于治疗疾病、病症或障碍或减轻其严重性的方法，所述疾病、病症或障碍中牵涉 ATR 激酶。在另一个方面，本发明提供了用于治疗 ATR 激酶疾病、病症或障碍或减轻其严重性的方法，其中在所述疾病的治疗中牵涉对酶活性的抑制。在另一个方面，本发明提供了使用通过与 ATR 激酶结合来抑制酶活性的化合物治疗疾病、病症或障碍或减轻其严重性的方法。另一个方面提供了通过用 ATR 激酶抑制剂抑制 ATR 激酶的酶活性来治疗激酶疾病、病症或障碍或减轻其严重性的方法。

[0604] 本发明的一个方面涉及抑制患者中的 ATR 激酶活性的方法，该方法包括对所述患者施用本申请中所述的化合物或包含所述化合物的组合物。在一些实施方案中，所述方法

用于治疗或预防选自增殖性和过度增殖性疾病（例如癌症）的病症。

[0605] 本发明的另一个方面提供了用于治疗、预防增殖性或过度增殖性疾病或减轻增殖性或过度增殖性疾病的严重性的方法，该方法包括给有需要的受试者施用有效量的化合物或包含化合物的药学上可接受的组合物。在一些实施方案中，所述方法用于治疗或预防癌症。在一些实施方案中，所述方法用于治疗或预防具有实体瘤的一种类型的癌症。在另一个实施方案中，所述癌症选自如下癌症：口部癌症：口腔癌、唇癌、舌癌、嘴癌、咽癌；心脏癌症：肉瘤（血管肉瘤、纤维肉瘤、横纹肌肉瘤、脂肪肉瘤）、粘液瘤、横纹肌瘤、纤维瘤、脂肪瘤和畸胎瘤；肺部癌症：支气管癌症（鳞状细胞癌或表皮样癌、未分化小细胞癌、未分化大细胞癌、腺癌）、肺泡（细支气管）癌、支气管腺瘤、肉瘤、淋巴瘤、软骨瘤性错构瘤、间皮瘤；胃肠癌症：食道癌症（鳞状细胞癌、喉癌、腺癌、平滑肌肉瘤、淋巴瘤）、胃癌（上皮细胞癌、淋巴瘤、平滑肌肉瘤）、胰腺癌症（导管腺癌、胰岛素瘤、胰高血糖素瘤、胃泌素瘤、类癌瘤、血管活性肠肽瘤）、小肠癌症（腺癌、淋巴瘤、类癌瘤、卡波西氏肉瘤、平滑肌瘤、血管瘤、脂肪瘤、纤维神经瘤、纤维瘤）、大肠癌症（腺癌、管状腺瘤、绒毛状腺瘤、错构瘤、平滑肌瘤）、结肠癌、结肠-直肠癌、结肠直肠癌；直肠癌；泌尿生殖道癌症：肾癌症（腺癌、维耳姆斯瘤［肾胚细胞瘤］、淋巴瘤）、膀胱和尿道癌症（鳞状细胞癌、移行细胞癌、腺癌）、前列腺癌症（腺癌、肉瘤）、睾丸癌症（精原细胞瘤、畸胎瘤、胚胎性癌、畸胎上皮细胞癌、绒毛膜癌、肉瘤、间质细胞癌、纤维瘤、纤维腺瘤、腺瘤样瘤、脂肪瘤）；肝脏癌症：肝细胞瘤（肝细胞癌）、胆管癌、肝胚细胞瘤、血管肉瘤、肝细胞性腺瘤、血管瘤、胆道癌；骨癌症：成骨肉瘤（骨肉瘤）、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤文氏肉瘤、恶性淋巴瘤（网状细胞肉瘤）、多发性骨髓瘤、恶性巨细胞瘤、脊索瘤、骨软骨纤维瘤（骨软骨性外生骨疣）、良性软骨瘤、成软骨细胞瘤、软骨粘液纤维瘤、骨样骨瘤和巨细胞瘤；神经系统癌症：颅骨癌症（骨瘤、血管瘤、肉芽肿、黄瘤、畸形性骨炎）、脑膜癌（脑膜瘤、脑膜肉瘤、神经胶质瘤病）、脑癌（星形细胞瘤、成神经管细胞瘤、神经胶质瘤、室管膜瘤、生殖细胞瘤［松果体瘤］、多形性成胶质细胞瘤、少突神经胶质瘤、神经鞘瘤、成视网膜细胞瘤、先天性肿瘤）、脊髓神经纤维瘤、脑膜瘤、神经胶质瘤、肉瘤）；妇科癌症：子宫癌症（子宫内膜癌）、宫颈癌症（宫颈癌、肿瘤前宫颈非典型增生）、卵巢癌症（卵巢癌［浆液性囊腺癌、粘液性囊腺癌、未分类癌瘤］、粒层-卵泡膜细胞瘤、塞-莱二氏细胞瘤、无性细胞瘤、恶性畸胎瘤）、外阴癌症（鳞状细胞癌、上皮内癌、腺癌、纤维肉瘤、黑素瘤）、阴道癌症（透明细胞癌、鳞状细胞癌、葡萄样肉瘤（胚胎性横纹肌肉瘤）、输卵管癌症（癌瘤）、乳腺癌；皮肤癌症：恶性黑素瘤、基底细胞癌、鳞状细胞癌、卡波西氏肉瘤、角化棘皮瘤、发育不良痣、脂肪瘤、血管瘤、皮肤纤维瘤、瘢痕瘤、牛皮癣；甲状腺癌症：乳头状甲状腺癌、滤泡性甲状腺癌、髓样甲状腺癌、2A 型多发性内分泌腺瘤、2B 型多发性内分泌腺瘤、家族性髓样甲状腺癌、嗜铬细胞瘤、副神经节瘤；以及肾上腺癌症：成神经细胞瘤。

[0606] 在一些实施方案中，所述癌症选自本申请中所述的癌症。在一些实施方案中，所述癌症是肺癌、头颈部癌、胰腺癌、胃癌或脑癌。在其它实施方案中，所述癌症选自肺癌或胰腺癌。

[0607] 在其它实施方案中，所述癌症选自非小细胞肺癌、小细胞肺癌、胰腺癌、胆道癌、头颈部癌、膀胱癌、结肠直肠癌、成胶质细胞瘤、食道癌、乳腺癌、肝细胞癌或卵巢癌。

[0608] 在一些实施方案中，所述肺癌是小细胞肺癌，且所述另外的治疗剂是顺铂和依托

泊苷。在其它实例中，所述肺癌是非小细胞非癌，且所述另外的治疗剂是吉西他滨和顺铂。在其它实施方案中，所述非小细胞肺癌是鳞状非小细胞肺癌。在另一个实施方案中，所述癌症是乳腺癌，且所述另外的治疗剂是顺铂。在其它实施方案中，所述癌症是三阴性乳腺癌。

[0609] 在一些实施方案中，化合物或药学上可接受的组合物的“有效量”是有效治疗所述疾病的量。根据本发明方法，可以使用有效治疗所述疾病或减轻所述疾病的严重性的任何量和任何施用途径来施用所述化合物和组合物。

[0610] 一个方面提供了用于抑制患者中的ATR的方法，该方法包括如本文所述地施用本申请中所述的化合物。另一个实施方案提供了治疗癌症的方法，该方法包括给患者施用本申请中所述的化合物，其中变量是如本申请中所定义的。

[0611] 一些实施方案包括给所述患者施用选自DNA损伤剂的另外的治疗剂；其中所述另外的治疗剂适用于所治疗的疾病；并且所述另外的治疗剂与所述化合物作为单剂量形式一起施用或者作为多剂量形式的部分与所述化合物分开施用。

[0612] 在一些实施方案中，所述DNA损伤剂选自电离辐射、拟辐射新制癌菌素、铂化剂、Topo I抑制剂、Topo II抑制剂、抗代谢物、烷化剂、烷基磺酸酯、抗代谢物或抗生素。在其它实施方案中，所述DNA损伤剂选自电离辐射、铂化剂、Topo I抑制剂、Topo II抑制剂或抗生素。

[0613] 铂化剂的实例包括顺铂、奥沙利铂、卡铂、奈达铂、沙铂和其它衍生物。其它铂化剂包括洛铂(Lobaplatin)和三铂(Triplatin)。其它铂化剂包括四硝酸盐、吡铂(Picoplatin)、沙铂、ProLindac和Aroplatin。

[0614] Topo I抑制剂的实例包括喜树碱、托泊替康、伊立替康/SN38、鲁比替康和其它衍生物。其它Topo I抑制剂包括贝洛替康(Belotecan)。

[0615] Topo II抑制剂的实例包括依托泊苷、柔红霉素、多柔比星、阿柔比星(Aclarubicin)、表柔比星、伊达比星、氨柔比星(Amrubicin)、吡柔比星(Pirarubicin)、戊柔比星、佐柔比星(Zorubicin)和替尼泊苷。

[0616] 抗代谢物的实例包括叶酸家族、嘌呤家族（嘌呤拮抗剂）或嘧啶家族（嘧啶拮抗剂）的成员。叶酸家族的实例包括甲氨蝶呤、培美曲塞及相关物；嘌呤家族的实例包括硫鸟嘌呤、氟达拉滨、克拉屈滨、6-巯嘌呤及相关物；嘧啶家族的实例包括阿糖胞苷、吉西他滨、5-氟尿嘧啶(5FU)及相关物。

[0617] 抗代谢物的一些其它具体实例包括氨基蝶呤、甲氨蝶呤、培美曲塞、雷替曲塞、喷司他丁、克拉屈滨、氯法拉滨、氟达拉滨、硫鸟嘌呤、巯嘌呤、氟尿嘧啶、卡培他滨、替加氟、卡莫氟、氟尿苷、阿糖胞苷、吉西他滨、阿扎胞苷和羟基脲。

[0618] 烷化剂的实例包括氮芥类、三氮烯类、烷基磺酸酯类、丙卡巴肼和氮丙啶类。氮芥类的实例包括环磷酰胺、美法仑、苯丁酸氮芥及相关物；亚硝基脲类的实例包括卡莫司汀；三氮烯类的实例包括达卡巴嗪和替莫唑胺；烷基磺酸酯类的实例包括白消安。

[0619] 烷化剂的其它具体实例包括双氯乙基甲胺、环磷酰胺、异环磷酰胺、曲洛磷胺(Trofosfamide)、苯丁酸氮芥、美法仑、泼尼莫司汀(Prednimustine)、苯达莫司汀(Bendamustine)、乌拉莫司汀(Uramustine)、雌莫司汀、卡莫司汀、洛莫司汀、司莫司汀(Semustine)、福莫司汀(Fotemustine)、尼莫司汀(Nimustine)、雷莫司汀(Ranimustine)、链佐星、白消安、甘露舒凡(Mannosulfan)、苏消安(Treosulfan)、卡波醌(Carboquone)、

噻替派、三亚胺醌 (Triaziquone)、曲他胺 (Triethyllamine)、丙卡巴肼、达卡巴嗪、替莫唑胺、六甲蜜胺、二溴甘露醇 (Mitobronitol)、放线菌素、博来霉素、丝裂霉素和普卡霉素。

[0620] 抗生素的实例包括丝裂霉素、羟基脲；蒽环类、蒽二酮类、链霉菌科。蒽环类的实例包括多柔比星、柔红霉素、表柔比星及其它衍生物；蒽二酮类的实例包括米托蒽醌及相关物；链霉菌科的实例包括博来霉素、丝裂霉素 C 和放线菌素。

[0621] 在某些实施方案中，所述铂化剂是顺铂或奥沙利铂；所述 Topo I 抑制剂是喜树碱；所述 Topo II 抑制剂是依托泊苷；并且所述抗生素是丝裂霉素。在其它实施方案中，所述铂化剂选自顺铂、奥沙利铂、卡铂、奈达铂或沙铂；所述 Topo I 抑制剂选自喜树碱、托泊替康、伊立替康 /SN38、鲁比替康；所述 Topo II 抑制剂选自依托泊苷；所述抗代谢物选自叶酸家族、嘌呤家族或嘧啶家族的成员；所述烷化剂选自氮芥类、亚硝基脲类、三氮烯类、烷基磺酸酯类、丙卡巴肼或氮丙啶类；并且所述抗生素选自羟基脲、蒽环类、蒽二酮类或链霉菌科。

[0622] 在一些实施方案中，另外的治疗剂是电离辐射。在其它实施方案中，另外的治疗剂是顺铂或卡铂。在另外的实施方案中，另外的治疗剂是依托泊苷。在另外的实施方案中，另外的治疗剂是替莫唑胺。

[0623] 在一些实施方案中，另外的治疗剂选自如下的一种或多种：顺铂、卡铂、吉西他滨、依托泊苷、替莫唑胺或电离辐射。

[0624] 另一个实施方案提供了通过与另一种已知的胰腺癌治疗组合施用本申请中所述的化合物来治疗胰腺癌的方法。本发明的一个方面包括与吉西他滨组合施用本申请中所述的化合物。在一些实施方案中，胰腺癌包含如下细胞系之一：PSN-1、MiaPaCa-2 或 Panc-1。根据另一个方面，癌症包含如下原发性肿瘤细胞系中的一种：Panc-M 或 MRC5。

[0625] 本发明的另一个方面包括与放射疗法组合施用本申请中所述的化合物。另一个方面提供了通过与放射治疗组合施用本申请中所述的化合物来消除放射诱导的 G2/M 关卡的方法。

[0626] 另一个方面提供了通过与一种或多种癌症疗法的组合将本申请中所述的化合物施用给胰腺癌细胞来治疗胰腺癌的方法。在一些实施方案中，将所述化合物与化学放射疗法、化学疗法和 / 或放射疗法组合。本领域技术人员将会了解，化学放射治疗是指包括化学疗法（例如吉西他滨）和放射疗法二者在内的治疗方案。在一些实施方案中，化学疗法是吉西他滨。

[0627] 另一个方面提供了通过与所述癌症疗法组合施用本申请中所述的化合物来增加胰腺癌细胞对选自吉西他滨或放射疗法的癌症疗法的敏感性的方法。

[0628] 在一些实施方案中，所述癌症疗法是吉西他滨。在其它实施方案中，所述癌症疗法是放射疗法。在又另一个实施方案中，所述癌症疗法是化学放射疗法。

[0629] 另一个方面提供了抑制胰腺癌细胞中的 Chk1(Ser345) 磷酸化的方法，该方法包括在用吉西他滨 (100nM) 和 / 或放射 (6Gy) 治疗后给胰腺癌细胞施用本申请中所述的化合物。

[0630] 另一个方面提供了通过与放射疗法组合给肿瘤细胞施用本申请中所述的化合物来使缺氧性 PSN-1、MiaPaCa-2 或 PancM 肿瘤细胞对放射敏感的方法。

[0631] 另一个方面提供了通过与吉西他滨组合给肿瘤细胞施用本申请中所述的化合物

来使缺氧性 PSN-1、MiaPaCa-2 或 PancM 肿瘤细胞敏感的方法。

[0632] 另一个方面提供了通过与化学放射疗法组合给肿瘤细胞施用本申请中所述的化合物来使 PSN-1 和 MiaPaCa-2 肿瘤细胞对化学放射疗法敏感的方法。

[0633] 另一个方面提供了通过与放射疗法的组合给胰腺癌细胞施用本申请中所述的化合物来破坏由损伤所诱导的细胞周期关卡的方法。

[0634] 另一个方面提供了通过与如下治疗中的一者或多者组合施用本申请中所述的化合物来抑制胰腺癌细胞中通过同源性重组对 DNA 损伤进行的修复的方法：化学放射疗法、化学疗法和放射疗法。

[0635] 在一些实施方案中，化学疗法是吉西他滨。

[0636] 另一个方面提供了通过与吉西他滨和放射疗法组合施用本申请中所述的化合物来抑制胰腺癌细胞中通过同源性重组对 DNA 损伤进行的修复的方法。

[0637] 在一些实施方案中，所述胰腺癌细胞源自选自 PSN-1、MiaPaCa-2 或 Panc-1 的胰腺细胞系。

[0638] 在其它实施方案中，所述胰腺癌细胞处于癌症患者中。

[0639] 本发明的另一个方面提供治疗非小细胞肺癌的方法，该方法包括与如下另外的治疗剂中的一者或多者组合对患者施用本申请中所述的化合物：顺铂或卡铂、依托泊苷和电离辐射。一些实施方案包括给患者施用本申请中所述的化合物与顺铂或卡铂、依托泊苷和电离辐射的组合。在一些实施方案中，所述组合是顺铂、依托泊苷和电离辐射。在其它实施方案中，所述组合是卡铂、依托泊苷和电离辐射。

[0640] 另一个实施方案提供了促进癌细胞发生细胞死亡的方法，该方法包括给患者施用本申请中所述的化合物或包含所述化合物的组合物。

[0641] 另一个实施方案提供了防止癌细胞中 DNA 损伤的细胞修复的方法，该方法包括给患者施用本申请中所述的化合物或包含所述化合物的组合物。另一个实施方案提供了防止癌细胞中由 DNA 损伤所引起的细胞修复的方法，该方法包括给患者施用本申请中所述的化合物或包含所述化合物的组合物。

[0642] 另一个实施方案提供了使细胞对 DNA 损伤剂敏感的方法，该方法包括给患者施用本申请中所述的化合物或包含所述化合物的组合物。

[0643] 在一些实施方案中，将所述方法用于在 ATM 信号级联放大方面具有缺陷的癌细胞。在一些实施方案中，所述缺陷是如下一种或多种的表达或活性发生改变：ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1、H2AX、MCPH1/BRIT1、CTIP 或 SMC1。在其它实施方案中，所述缺陷是如下一种或多种的表达或活性发生改变：ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1 或 H2AX。根据另一个实施方案，将所述方法用于表达 DNA 损伤致癌基因的癌症、癌细胞或细胞。

[0644] 在另一个实施方案中，所述细胞是表达 DNA 损伤致癌基因的癌细胞。在一些实施方案中，所述癌细胞的如下一种或多种的表达或活性发生改变：K-Ras、N-Ras、H-Ras、Raf、Myc、Mos、E2F、Cdc25A、CDC4、CDK2、细胞周期蛋白 E、细胞周期蛋白 A 和 Rb。

[0645] 根据另一个实施方案，将所述方法用于在涉及碱基切除修复的蛋白质（“碱基切除修复蛋白”）中具有缺陷的癌症、癌细胞或细胞。存在多种本领域已知用于测定肿瘤是否在碱基切除修复方面具有缺陷的方法。例如，可以对肿瘤样品中每个碱基切除修复基因（例

如 UNG、PARP1 或 LIG1）的基因组 DNA 或 mRNA 产物进行测序以确定是否存在预期会调节基因产物的功能或表达的突变（Wang 等人，Cancer Research 52:4824(1992)（Wang 等人，《癌症研究》，第 52 卷，第 4824 页，1992 年））。除突变失活之外，肿瘤细胞还可以通过使 DNA 修复基因的启动子区超甲基化，从而使得基因表达减少来调节 DNA 修复基因。这最常使用甲基化特异性聚合酶链反应（PCR）来进行评估以对所关注的碱基切除修复基因启动子的甲基化水平进行定量。对碱基切除修复基因启动子甲基化的分析可商购获得（http://www.sabiosciences.com/dna_methylation_product/HTML/MEAH-421A.html）。

[0646] 最后，可以通过分别使用例如定量逆转录酶偶联聚合酶链反应（RT-PCR）和免疫组织化学法（IHC）的标准技术对每个基因的 mRNA 和蛋白质产物的水平直接进行定量来评估碱基切除修复基因的表达水平（Shinmura 等人，Carcinogenesis 25:2311(2004)（Shinmura 等人，《癌发生》，第 25 卷，第 2311 页，2004 年）；Shinmura 等人，Journal of Pathology 225:414(2011)（Shinmura 等人，《病理学杂志》，第 225 卷，第 414 页，2011 年））。

[0647] 在一些实施方案中，碱基切除修复蛋白是 UNG、SMUG1、MBD4、TDG、OGG1、MYH、NTH1、MPG、NEIL1、NEIL2、NEIL3（DNA 糖基化酶）；APE1、APEX2（AP 核酸内切酶）；LIG1、LIG3（DNA 连接酶 I 和 III）；XRCC1（LIG3 辅助因子）；PNK、PNKP（多核苷酸激酶和磷酸酶）；PARP1、PARP2（多聚（ADP- 核糖）聚合酶）；PolB、PolG（聚合酶）；FEN1（核酸内切酶）或 Aprataxin。

[0648] 在一些实施方案中，碱基切除修复蛋白是 PARP1、PARP2 或 PolB。在其它实施方案中，碱基切除修复蛋白是 PARP1 或 PARP2。

[0649] 上述方法（基因序列、启动子甲基化和 mRNA 表达）还可以用于表征所关注的其它基因或蛋白质的状态（例如表达或突变），如肿瘤所表达的 DNA 损伤致癌基因或细胞 ATM 信号级联放大中的缺陷。

[0650] 另一个实施方案提供了本申请中所述的化合物作为放射增敏剂或化学增敏剂的用途。

[0651] 其它实施方案提供了式 I 的化合物作为用于治疗癌症的单一药剂（单一疗法）的用途。在一些实施方案中，式 I 的化合物用于治疗患有具有 DNA 损伤应答（DDR）缺陷的癌症的患者。在其它实施方案中，所述缺陷是 ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1 或 H2AX 的突变或缺失。

[0652] 供使用的化合物和组合物

[0653] 一个实施方案提供了如本申请中所述的用作放射增敏剂或化学增敏剂的化合物或组合物。另一个实施方案提供了如本申请中所述的用作用于治疗癌症的单一药剂（单一疗法）的化合物或组合物。

[0654] 另一个实施方案提供了如本申请中所述的用于治疗患有具有 DNA 损伤应答（DDR）缺陷的癌症的患者的化合物或组合物。在一些实施方案中，所述缺陷是 ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1 或 H2AX 的突变或缺失。在其它实施方案中，所述缺陷是 ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1、H2AX、MCPH1/BRIT1、CTIP 或 SMC1 的突变或缺失。

[0655] 另一个实施方案提供了本申请中所述的用于治疗癌症的化合物或组合物。在一些实施方案中，还将所述化合物或组合物与本申请中所述的另外的治疗剂组合。在一些实施

方案中，还将所述化合物或组合物与本申请中所述的 DNA 损伤剂组合。

[0656] 在一些实施方案中，所述癌症在本申请中所述的途径方面具有缺陷。

[0657] 药物的制造

[0658] 一个实施方案提供了本申请中所述的化合物或组合物用于制造用作放射增敏剂或化学增敏剂的药物的用途。另一个实施方案提供了本申请中所述的化合物或组合物用于制造用作用于治疗癌症的单一药剂（单一疗法）的药物的用途。

[0659] 另一个实施方案提供了本申请中所述的化合物或组合物用于制造用于治疗患有具有 DNA 损伤应答 (DDR) 缺陷的癌症的患者的药物的用途。

[0660] 在一些实施方案中，所述缺陷是 ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1 或 H2AX 的突变或缺失。在其它实施方案中，所述缺陷是 ATM、p53、CHK2、MRE11、RAD50、NBS1、53BP1、MDC1、H2AX、MCPH1/BRIT1、CTIP 或 SMC1 的突变或缺失。

[0661] 另一个实施方案提供了本申请中所述的化合物或组合物用于制造用于治疗癌症的药物的用途。在一些实施方案中，将所述化合物或组合物与本申请中所述的例如 DNA 损伤剂的另外的治疗剂组合。在另一个实施方案中，所述癌症在本申请中所述的途径方面具有缺陷。

[0662] 实验材料和方法

[0663] 所有可商购的溶剂和试剂均以收到时的形式使用。使用 CEMDiscovery 微波进行微波反应。例如，使用ISCO© Combiflash® Companion™系统进行急骤色谱法，用 0－100% EtOAc/ 石油醚梯度洗脱。本领域中公知的其它方法也用于进行急骤色谱法。将样品应用预吸附在硅胶上。如所述的，使用 Berger Minigram SFC 机器进行超临界流体色谱法 (SFC)。使用 Bruker Avance III 500 仪器在 500MHz 记录全部 ^{1}H NMR 光谱。使用 Waters SQD 质谱仪与以正和负离子模式操作的电喷雾电离分析 MS 样品。使用色谱法将样品导入质谱仪。除非在实验详细描述部分另有指定，否则全部终产物具有≥ 95% 的纯度。使用带有 Waters SQD MS 仪器的 Waters Acquity UPLC 系统测定 HPLC 纯度，所述 Waters SQD MS 仪器安装有 Waters UPLC BEH C81.7 μm，2.1x 50mm 柱和 a Vanguard BEH C81.7 μm，2.1x 5mm 保护柱。

[0664] 本申请中所用的术语“Rt(min)”是指以分钟计的与化合物相关的 HPLC 保留时间。除非另有指示，否则用于得到报道的保留时间的 HPLC 方法如下所述：

[0665] HPLC 方法 A

[0666] 仪器：Waters Acquity UPLC-MS；

[0667] 柱：Waters UPLC BEH C81.7 μm，2.1x 50mm，带有 Vanguard BEH C81.7 μm，2.1x 5mm 保护柱；

[0668] 柱温：45℃；

[0669] 流动相 A：10mM 甲酸铵的水：乙腈 95：5 的溶液，pH 9；

[0670] 流动相 B：乙腈；

[0671] 检测：210-400nm

[0672] 梯度：起始：2% B，0-1.15min：2% B － 98% B，1.15-1.35min：保持在 98% B，1.35-1.40min：98% B － 2% B，1.40-1.50min：保持在 2% B；

[0673] 流速：1.0 毫升 / 分钟；

[0674] HPLC 方法 B

[0675] 仪器 :Waters Acquity UPLC-MS ;

[0676] 柱 :Waters UPLC BEH C81.7 μ m,2.1x 50mm,带有 Vanguard BEH C81.7 μ m,2.1x 5mm 保护柱 ;

[0677] 柱温 :45℃ ;

[0678] 流动相 A :10mM 甲酸铵的水 :乙腈 95 :5 的溶液,pH 9 ;

[0679] 流动相 B :乙腈 ;

[0680] 检测 :210-400nm ;

[0681] 梯度 :0-0.40min :2% B,0.40-4.85min :2% B — 98% B,4.85-4.90min :98% B — 2% B,4.90-5.00min :保持在 2% B ;

[0682] 流速 :0.6 毫升 / 分钟。

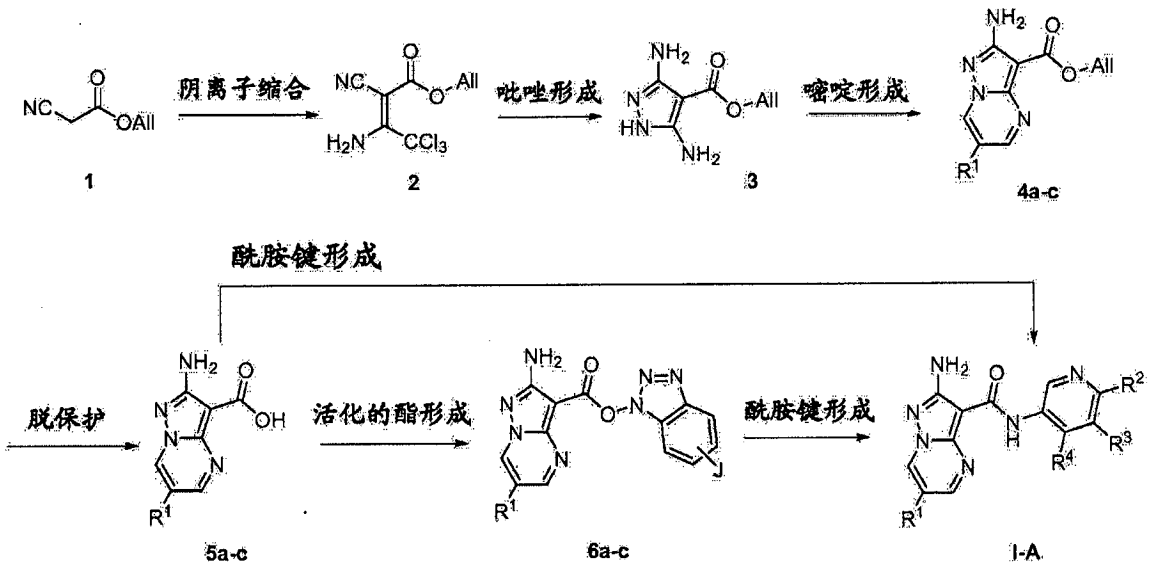
[0683] 实施例和方案

[0684] 可以根据本说明书,使用本领域技术人员一般公知的步骤制备本申请中公开的化合物。可以通过已知方法分析那些化合物,包括,但不限于 LCMS(液相色谱法质谱法) 和 NMR(核磁共振)。下列一般方案和实施例举例说明如何制备本申请中公开的化合物。实施例仅用于举例说明的目的,而不应被以任何方式解释为限制本发明的范围。

[0685] 可以理解,当本申请中提供的化学结构与相应的名称存在不一致时,以化学结构为准。

[0686] 方案 1 :制备化合物 I-A 的通用方法

[0687]



[0688] 可以根据与方案 1 中所述类似的方法合成本发明的化合物。

[0689] 可以使商购的氰乙酸烯丙酯 1 的阴离子与三氯乙腈反应,得到中间体 2。在阴离子缩合步骤中,可以使用碱例如乙酸钾在适合的溶剂例如醇 (例如异丙醇) 中生成商购的氰乙酸烯丙酯 1 的阴离子。然后使该阴离子与三氯乙腈在室温下反应 (具体详细描述在下文的制备例 1 步骤 1 中)。

[0690] 然后使中间体 2 与肼反应,形成二氨基吡唑 3。在吡唑形成步骤中,使中间体 2 与

肼（或其水合物）在非质子溶剂例如 DMF 中反应，得到二氨基吡唑 3。该反应在碱性条件下（例如在乙酸钾或 AcONa 的存在下）使用加热（例如 110℃）进行，以确保完全环化（具体详细描述在下文的制备例 1 步骤 2 中）。

[0691] 可以使中间体 3 与二亲电性偶合配偶体进一步缩合，形成嘧啶 4a-c。在嘧啶形成步骤中，使中间体 3 与 1,3- 二亲电类物质（例如 1,3- 二醛或 3-（二烷基氨基）- 丙 -2- 烯醛）在不同类型的溶剂（例如 DMF 或 DMSO/ 水）中反应，得到双环核 4a-c。当亲电中心的一个或两个被保护 / 掩蔽时（例如醛被掩蔽为缩酮），需要引入磺酸（例如 PTSA）以释放反应性官能团（具体详细描述在下文的制备例 4 步骤 1 中）。

[0692] 所述烯丙酯例如通过水解脱保护，得到羧酸 5a-c。在脱保护步骤中，使化合物 4a-c 经受本领域技术人员公知的水解条件。例如，用苯基硅烷或 4- 甲基苯亚磺酸酯在催化量的钯（例如 $Pd(PPh_3)_4$）的存在下处理 4a-c，导致相应的羧酸 5a-c 形成。或者，可以用碱金属水溶液（例如 NaOH、KOH）处理化合物 4a-c，产生酸 5a-c（具体详细描述在下文的制备例 4 步骤 2 中）。

[0693] 在活化酯形成步骤中，使羧酸 5a-c 与本领域技术人员公知的酰胺偶合剂反应。当适当选择偶合剂时，反应可以在室温下在有机碱（例如三乙胺、DIPEA）的存在下快速地进行（～ 1h），得到活化酯类 6a-c。例如，当使用酰胺偶合剂 TBTU[J = H] 或 TCTU[J = Cl] 时，易于通过过滤该反应混合物得到化合物 6a-c（具体详细描述在下文的制备例 4 步骤 3 中）。

[0694] 一般优选在酰胺键形成前形成活化酯类 6a-c 以制备 I-A，尽管将 5a-c 直接转化成本发明式 I-A 的化合物也是可能的。还可以使用可替代的活化酯类（分离或在原位形成），且它们是本领域技术人员公知的（例如使用 TBTU、TCTU、HATU、T3P、COMU 偶合剂。）

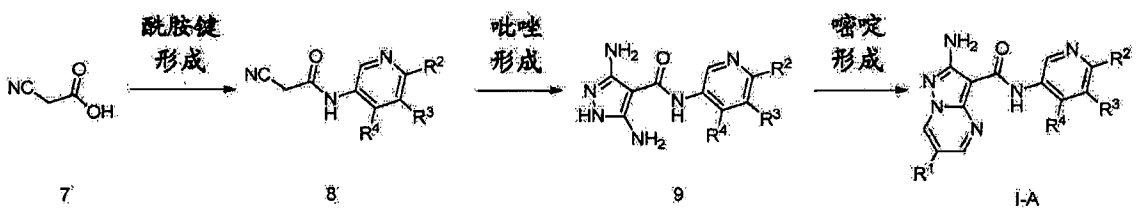
[0695] 在酰胺键形成步骤中，可以使活化酯类 6a-c 与取代的 3- 氨基吡啶反应，得到本发明式 I-A 的化合物。用于酰胺偶合的反应条件一般是在非质子溶剂（例如 NMP、吡啶、DMF 等）中使用加热（例如，≥ 90℃）（具体详细描述在下文实施例 1 中）。可以在酰胺键形成后进一步使 3- 氨基吡啶官能化。

[0696] 或者，可以合并上述两个步骤：羧酸 5a-c 可以用作用于酰胺键形成的起点，使用与如上所述相同的酰胺偶合剂在原位生成活化酯类。按照与如上所述类似的方式分离本发明的化合物 I-A（具体详细描述在下文的实施例 3a 中）。

[0697] 还可以使用类似方法制备式 I、I-A-1 和 I-B 的化合物。

[0698] 方案 2：制备化合物 I-A 的可替代方法

[0699]



[0700] 或者，可以根据与方案 2 中所述类似的方法制备本申请中公开的化合物。

[0701] 可以轻易地由商购氰基乙酸 7 制备酰胺 8。在酰胺键形成步骤中，可以使氰基乙酸 7 与取代的 3- 氨基吡啶反应，得到本发明的化合物 8。用于酰胺偶合的反应条件一般是在

非质子溶剂（例如 DCM、NMP、DMF 等）中，在有机碱例如脂族胺（例如三乙胺或 DIPEA）和本领域技术人员公知的酰胺偶合剂的存在下：例如 EDCI、TBTU、COMU、T3P 等（具体详细描述在下文的实施例 3e 步骤 1 中）。

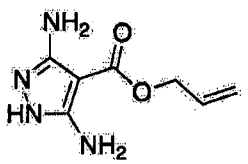
[0702] 在吡唑形成步骤中，可以使用碱（例如乙酸钾或乙酸钠）在适合的溶剂例如醇（例如乙醇）中生成氰基酰胺 8 的阴离子。然后使该阴离子与三氯乙腈在室温下反应（具体详细描述在下文实施例 3e 步骤 2 中）。然后可以使可通过过滤采集的得到的固体与肼（或其水合物）在非质子溶剂例如 DMF 或 NMP 中反应，得到二氨基吡唑 9，后者进一步与二亲电性偶合配偶体缩合，形成本发明式 I-A 的化合物的嘧啶部分。

[0703] 在嘧啶形成步骤中，使中间体 9 与 1,3- 二亲电类物质（例如 1,3- 二醛或 3-（二烷基氨基）- 丙 -2- 烯醛）在不同类型的溶剂（例如 iPrOH/ 水、DMF 或 DMSO/ 水）中反应，得到期望的产物 I-A。当亲电中心的一个或两个被保护 / 掩蔽时（例如醛被掩蔽为缩酮），需要引入磺酸（例如 PTSA）以释放反应性官能团（具体详细描述在下文的实施例 3e 步骤 3 中）。

[0704] 还可以使用类似方法制备式 I、I-A-1 和 I-B 的化合物。

[0705] 制备例 1：3,5- 二氨基 -1H- 吡唑 -4- 甲酸烯丙酯

[0706]



3

[0707] 步骤 1：3- 氨基 -4,4,4- 三氯 -2- 氰基丁 -2- 烯酸烯丙酯 2

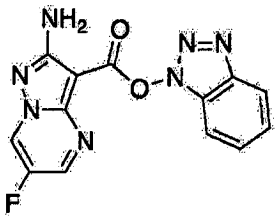
[0708] 向 KOAc(589.4g,6.006mol) 在异丙醇 (3L) 中的溶液中加入氰乙酸烯丙酯 (429.4g,403.2mL,3.432mol)，将该反应混合物冷却至 5℃。分 50mL 的部分加入三氯乙腈 (495.5g,3.432mol)，维持温度低于 15℃。然后将该反应混合物温至 20℃，搅拌 3h。加入水（～ 4L）以溶解无机物，沉淀出期望的产物。将该混合物搅拌 20 分钟，通过真空过滤分离固体。过滤该固体，用水 (2x 0.5L) 洗涤，在 40℃真空烘箱干燥过夜，得到 3- 氨基 -4,4,4- 三氯 -2- 氰基丁 -2- 烯酸烯丙酯 2，为灰白色粉末 (787g,85％）。

[0709] 步骤 2：3,5- 二氨基 -1H- 吡唑 -4- 甲酸烯丙酯 3

[0710] 在 0℃在 15min 内向 3- 氨基 -4,4,4- 三氯 -2- 氰基 - 丁 -2- 烯酸烯丙酯 2(619g,2.297mol) 和 KOAc(676.3g,6.891mol) 在 DMF(2.476L) 中的混悬液中缓慢地加入水合肼 (172.5g,167.6mL,3.446mol)。然后将该反应混合物在环境温度搅拌 2h，在该阶段 ^{1}H NMR 显示原料完全耗尽。然后将反应混合物在 110℃加热过夜，此后冷却至环境，再搅拌 48h。通过垂熔玻璃漏斗过滤该混合物，以除去沉淀的固体，减压蒸发滤液，得到浓稠液体。加入 DCM（约 2L），再过滤该混合物，以除去沉淀的另外固体。通过 1kg 硅胶柱纯化滤液 (DCM/MeOH 梯度作为洗脱剂），除去溶剂，得到橙色固体，将其混悬于乙腈，在约 70℃加热直至全部固体溶入溶液，此时让该溶液冷却至环境温度，然后冷却至 2℃。通过真空过滤分离形成的沉淀，用冷 MeCN（～ 50mL）洗涤，在真空烘箱内干燥至质量恒定，得到标题化合物，为灰白色粉末 (171.2g,41％）。

[0711] 制备例 2a :2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酸 1H- 苯并 [d][1,2,3] 三唑 -1- 基酯

[0712]



6a

[0713] 步骤 1 :2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4a

[0714] 向 3,5- 二氨基 -1H- 吡唑 -4- 甲酸烯丙酯 3(42.72g,234.5mmol) 在 DMSO(270.8mL)/ 水 (270.8mL) 中的混悬液中加入 p-TsOH 水合物 (46.72g,245.6mmol) 和 3-(二异丙基氨基)-2- 氟 - 丙 -2- 烯醛 (描述在 Tetrahedron Letters,33(3),357-60 ; 1992 中)(38.69g,223.3mmol)。将该反应混合物加热至 100℃ 3h,在此过程中,固体缓慢地从溶液中沉淀出来。将橙色混悬液冷却至 RT 过夜。过滤固体,用水洗涤,真空干燥,得到 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4a,为砂样固体 (45.05g,85% 收率)。

[0715] 步骤 2 :2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5a

[0716] 向 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4a(45g,190.5mmol) 在 DCM(1.35L) 中的混悬液中加入苯基硅烷 (41.23g,46.96mL,381.0mmol),然后加入 $Pd(PPh_3)_4$(8.805g,7.620mmol)。将该反应体系在室温搅拌 2h 30min。过滤该反应混合物,用 DCM 洗涤固体,得到淡黄色固体 (43.2g)。再将该固体在 RT 在 DCM(225mL) 中研磨 45min,然后过滤,真空干燥过夜,得到 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5a,为淡黄色固体 (37.77g,100% 收率)。

[0717] 在可替代的方法中,将 4- 甲基苯亚磺酸酯 (无水,1.2eqv,22.6g,127mmol) 混悬于干 DMSO(20vol,500ml)。将搅拌的混合物在氮气气氛中温至 30℃。在完全溶解时,加入 $Pd(PPh_3)_4$(2mol%,2.4g,2.1mmol)。将该混合物在 25-30℃搅拌 10min,此后,出现浑浊黄色溶液。逐步加入 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 (25g,105.8mmol),维持温度在 25-30℃。一旦添加完成,则将浑浊溶液搅拌至通过 HPLC 证明反应完成 (2-3hrs)。在添加底物后的 15 分钟后,形成大量沉淀。当反应进行时,该混合物变成浓稠物。用水 (125ml) 稀释该反应混合物,缓慢地添加 2M HCl(66ml),维持温度在 25-30℃。将该淤浆搅拌 30 分钟,然后过滤。过滤缓慢 (2hrs)。用水洗涤得到的固体,然后用烧结物干燥。将固体在 DCM(8vol) 中搅拌成淤浆 1hr。过滤固体 (快速过滤),用 DCM 洗涤。将固体在氯仿 (8vol) 中再搅拌成淤浆 1hr。过滤酸,用烧结物干燥。再在真空烘箱中在 50℃干燥 24hrs。得到产物,为灰白色固体 (18.6g,85%) ;1H NMR(500MHz,DMSO-d6) δ 12.14(1H,brs),9.31(1H,dd),8.69(1H,m),6.47(2H,brS) ;19F NMR(500MHz,DMSO-d6) δ -153.65 ;MS(ES+) 197.1。

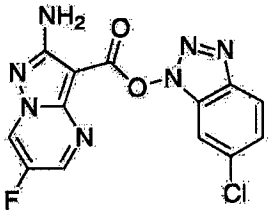
[0718] 步骤 3 :2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酸 1H- 苯并 [d][1,2,3] 三唑 -1- 基酯 6a

[0719] 向 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5a(20g,102.0mmol) 在氯仿 (300mL) 中的溶液中加入 Et_3N(11.35g,15.63mL,112.2mmol)。将该混悬液搅拌～ 5mins,

然后加入（苯并三唑-1-基氧基-二甲基氨基-亚甲基）-二甲基-铵四氟化硼（32.75g，102.0mmol）。将该混悬液加热至60℃ 1h，然后使浓稠混悬液冷却至RT。过滤得到的混悬液，用氯仿（200mL）洗涤，真空干燥过夜，得到标题化合物6a，为淡黄色粉末（32.5g，88%）。

[0720] 制备例2b：(6-氯苯并三唑-1-基)-2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-甲酸酯6a*

[0721]



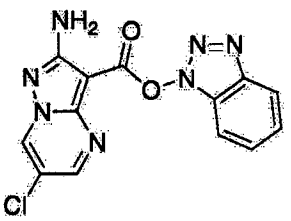
6a*

[0722] 在安装了搅拌棒、冷凝器、氮气管和Hanna温度探头的2.5L 3-颈烧瓶中加入2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-甲酸5a(60g，305.9mmol)、氯仿（900.0mL）和三乙胺（32.44g，44.68mL，320.6mmol）。在5mins内逐步加入[(6-氯苯并三唑-1-基）氧基-(二甲基氨基）亚甲基]-二甲基-铵（四氟化硼离子（1））(87.00g，244.7mmol)（添加完成时内部从22.7降至21.5℃）。混合物在60℃（内部温度）加热2H，仍然是乳膏状混悬液。将混合物冷却至室温，然后通过过滤采集固体，用氯仿充分洗涤（直到滤液基本上呈无色为止），通过抽吸干燥，得到产物6a*，为乳膏状固体（82.2g，77%收率）。^{1}H NMR(500MHz，DMSO-d_6) δ 9.55(dd，1H)，8.91(d，1H)，8.22(dd，1H)，8.09(dd，1H)，7.57(dd，1H) 和6.87(s，2H)。MS(ES+)348.1。

[0723] 在可替代的方法中，将2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酸5a(30g，153mmol)在乙腈（540ml）中搅拌成淤浆。加入三乙胺（22.5ml，153mmol)，然后加入[(6-氯苯并三唑-1基）氧基-(二甲基氨基）亚甲基]-二甲基铵四氟硼酸盐（TCTU，54.4g，153mmol)。将该混合物在室温搅拌2hrs。通过过滤分离产物-用乙腈（2x60ml）洗涤滤饼（49.3g，93%）；^{1}H NMR(500MHz，DMSO-d_6) δ 9.55(dd，1H)，8.91(d，1H)，8.22(dd，1H)，8.09(dd，1H)，7.57(dd，1H) 和 6.87(s，2H)；19F NMR(500MHz，DMSO-d6) δ -150.1；MS(ES+)348.1。

[0724] 制备例3：2-氨基-6-氯吡唑并[1,5-a]嘧啶-3-甲酸1H-苯并[d][1,2,3]三唑-1-基酯

[0725]



6b

[0726] 步骤1：2-氨基-6-氯-吡唑并[1,5-a]嘧啶-3-甲酸酯4b

[0727] 向 3,5- 二氨基 -1H- 吡唑 -4- 甲酸烯丙酯 3(1g,5.489mmol) 在 DMF(5mL) 中的混悬液中加入 (Z)-2- 氯 -3- 二甲基氨基 - 丙 -2- 亚烯基]- 二甲基 - 铵六氟磷酸盐 (1.683g,5.489mmol),然后加入三乙胺 (722.1mg,994.6μL,7.136mmol)。将该反应混合物加热至 60℃ 4h,在此过程中,固体缓慢地从溶液中沉淀出来。将棕色混悬液冷却至 RT。过滤固体,用水洗涤,真空干燥,得到 2- 氨基 -6- 氯 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4b,为棕色固体 (1.092g,72% 收率)。

[0728] 步骤 2 :2- 氨基 -6- 氯 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5b

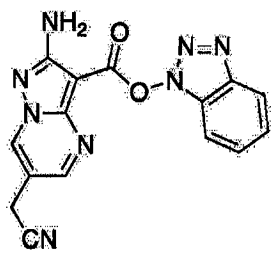
[0729] 向 2- 氨基 -6- 氯 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4b(1g,3.96mmol) 在 DCM(15mL) 中的混悬液中加入苯基硅烷 (856.6mg,0.9756mL,7.916mmol),然后加入 $Pd(PPh_3)_4$(182.9mg,0.1583mmol)。将该反应体系在室温搅拌 7h。过滤该反应混合物,用 DCM 洗涤固体,得到淡黄色固体 (43.2g)。将该固体再在 DCM(225mL) 中在 RT 研磨 45min,然后过滤,真空干燥过夜,得到 2- 氨基 -6- 氯 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5b,为黄色固体 (791m,94% 收率)。

[0730] 步骤 3 :2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酸 1H- 苯并 [d][1,2,3] 三唑 -1- 基酯 6b

[0731] 向 2- 氨基 -6- 氯 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5b(1.51g,7.103mmol) 在氯仿 (15.1mL) 中的溶液中加入 TBTU 四氟化硼 (2.737g,8.524mmol) 和 TEA(862.5mg,1.188mL,8.524mmol)。将该反应混合物在 50℃ 搅拌 1 小时。过滤得到的混悬液,在乙酸乙酯中研磨固体,得到标题化合物 6b,为黄色固体 (2.05g,88%)。

[0732] 制备例 4 :2- 氨基 -6-(氰基甲基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 1H- 苯并 [d][1,2,3] 三唑 -1- 基酯

[0733]



6c

[0734] 步骤 1 :2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4c

[0735] 向 3,5- 二氨基 -1H- 吡唑 -4- 甲酸烯丙酯 3(63.49g,348.5mmol) 在 DMSO(340mL) 和水 (340mL) 的混合物中的混悬液中加入 3-(二甲氧基甲基)-4,4- 二甲氧基 - 丁腈 (如下方案 3)(85g,418.2mmol),然后加入对甲苯磺酸水合物 (1)(11.27g,59.24mmol)。将该反应混合物加热至 85℃,搅拌过夜。用冰冷却该反应混合物。用 EtOAc(680mL) 和饱和 $NaHCO_3$ 水溶液 (1.36L) 稀释该混合物。过滤沉淀,用水冲洗,然后用水和 EtOAc 的混合物冲洗。真空干燥棕色固体,得到 2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4c,为棕色固体 (55.94g,62% 收率)。

[0736] 步骤 2 :2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5c

[0737] 向 2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸烯丙酯 4c(10.2g,

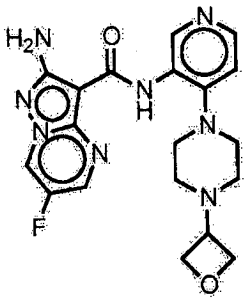
39.65mmol) 在 DCM(350mL) 中的混悬液中加入苯基硅烷 (8.581g,9.773mL,79.3mmol),然后加入 $Pd(PPh_3)_4$(1.5g,1.298mmol)。将该反应体系在室温搅拌 2h。过滤该反应混合物,用 DCM 洗涤固体,真空干燥,得到 2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5c,为黄色固体 (8.61g,100% 收率)。

[0738] 步骤 3 :2- 氨基 -6-(氰基甲基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 1H- 苯并 [d][1,2,3] 三唑 -1- 基酯 6c

[0739] 向 2- 氨基 -6-(氰基甲基)- 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5c(5.11g,23.53mmol) 在 DCM(51mL) 中的溶液中加入 TBTU 四氟化硼 (9.067g,28.24mmol) 和 TEA(2.858g,3.937mL,28.24mmol)。将该反应化合物在室温搅拌 1 小时。过滤得到的混悬液,在热氯仿中研磨固体,得到标题化合物 6c,为黄褐色固体 (6.59g,84%)。

[0740] 实施例 1 :2- 氨基 -6- 氟 -N-(4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-1)

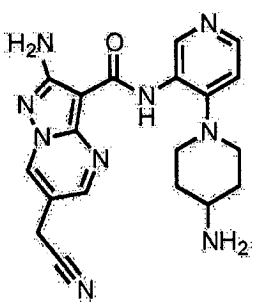
[0741]



[0742] 向 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸苯并三唑 -1- 基酯 6a(根据制备例 2a 中所述类似的方法制备)(5g,15.62mmol) 在 NMP(78.27mL) 中的混悬液中加入 4-[4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基] 吡啶 -3- 胺 (根据与下述制备例 N-1 中所述类似的方法制备)(3.660g,15.62mmol),将得到的混合物在 100℃加热 18 小时。将该反应混合物冷却至 RT,然后通过预湿润的 SCX 柱 (2x 50g 柱),用甲醇洗涤柱。用 2M 氨的甲醇溶液洗脱产物,真空浓缩洗脱液,得到深色固体,通过硅胶柱色谱法、使用 ISCO 柱 companion 纯化,用 DCM 和 90 :10 :1DCM :MeOH :NH_3(0-100% 梯度,40g 柱) 洗脱。合并产物级分,真空浓缩,得到产物,为黄色固体,然后使其从甲醇中重结晶,得到纯产物,为黄色固体。MS(ES+)413.2。

[0743] 实施例 2 :2- 氨基 -N-(4-(4- 氨基哌啶 -1- 基) 吡啶 -3- 基)-6-(氰基甲基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-2)

[0744]

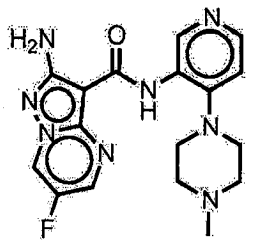


[0745] 向根据与实施例 1 中所述类似的方法制备的 N-[1-[3-[[2- 氨基 -6-(氰基甲基)

吡唑并[1,5-a]嘧啶-3-羰基]氨基]-4-吡啶基]-4-哌啶基]氨基甲酸叔丁酯(70mg,0.1424mmol)在DCM(4mL)中的溶液中加入TFA(1mL,12.98mmol),将该混合物在环境温度搅拌1.5小时。将该反应混合物蒸发至干,通过HPLC:10-90%CAN的水溶液(TFA调节剂)纯化,冷冻干燥级分。将固体残余物溶于甲醇(1mL),上预湿润的(15mL甲醇)2g SCX-2柱。用甲醇(2x15mL)洗涤柱,然后使用2M氨的甲醇溶液(3x15mL)洗脱作为游离碱的产物。将包含产物的级分蒸发至干,再溶于水/甲醇,冷冻干燥,得到期望的产物,为黄色固体(17mg,31%)。MS(ES+)391.1。

[0746] 实施例3a:2-氨基-6-氟-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-3)

[0747]



[0748] 将4-(4-甲基哌嗪-1-基)吡啶-3-胺(根据与下述制备例N-1中所述类似的方法制备)(588.1mg,3.059mmol)、2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-甲酸5a(根据与制备例2a顺序步骤1-步骤2中所述类似的方法制备)(500mg,2.549mmol)、TBTU(1.146g,3.569mmol)和Et_3N(515.9mg,710.6μL,5.098mmol)在NMP(7mL)中的混合物在110℃在密封试管中搅拌20h。用EtOAc稀释该反应混合物,用饱和碳酸氢钠水溶液和盐水洗涤。用$MgSO_4$干燥有机层,过滤后浓缩。将固体在DCM中研磨,然后过滤出来。再Fractionlynx HPLC通过纯化,得到标题化合物,为无色固体。MS(ES+)371.3。

[0749] 或者,可以根据方案2、使用实施例3b中所述的方法制备化合物I-N-3。

[0750] 实施例3b:2-氨基-6-氟-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-3)

[0751] 步骤1:2-氰基-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)乙酰胺8

[0752] 向冰冷的2-氰基乙酸7(1.15g,13.52mmol)在DCM(40mL)中的溶液中滴加草酰氯(1.3mL,14.90mmol),然后加入催化量的DMF。将该反应混合物在室温搅拌3h,然后真空浓缩,以除去溶剂。将残余物加入到在THF(40mL)中的4-(4-甲基哌嗪-1-基)吡啶-3-胺(根据与下述制备例N-1中所述类似的方法制备)(1.3g,6.762mmol)和Et_3N(1.026g,1.413mL,10.14mmol)中,将该反应混合物在室温搅拌18h。用EtOAc稀释该混合物,用饱和碳酸氢钠水溶液和盐水洗涤。再用DCM(20mL x 2)萃取水层。用Na_2SO_4干燥合并的有机层,浓缩,得到2-氰基-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)乙酰胺8,为黄色油状物。MS(ES+)260.1.

[0753] 步骤2:3,5-二氨基-N-[4-(4-甲基哌嗪-1-基)-3-吡啶基]-1H-吡唑-4-甲酰胺9

[0754] 向2-氰基-N-[4-(4-甲基哌嗪-1-基)-3-吡啶基]乙酰胺8(1.6g,6.170mmol)在乙醇(40mL)中的混悬液中加入乙酸钠(1.052g,12.83mmol),然后滴加三氯乙腈(1.042g,733.8μL,7.219mmol)。将不均匀混合物在室温在氮气气氛中搅拌18h。真空浓缩该反应

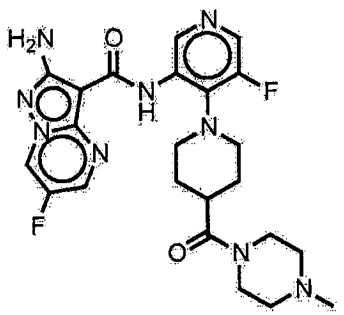
混合物，将残余物溶于 NMP(30mL)。加入水合肼 (803mg,780.4 μL,16.04mmol)，将该反应混合物在室温搅拌 3h。真空除去溶剂，将残余物在 DCM 中研磨，形成棕色固体，通过过滤分离，得到 3,5- 二氨基 -N-[4-(4- 甲基哌嗪 -1- 基)-3- 吡啶基]-1H- 吡唑 -4- 甲酰胺 9(1g,51%)。MS(ES+)317.1.

[0755] 步骤 3 :2- 氨基 -6- 氟 -N-(4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺

[0756] 将 (Z)-3-(二异丙基氨基)-2- 氟 - 丙 -2- 烯醛 (Tetrahedron Letters(1992),33(3),357-60)(22.81mg,0.1317mmol)、4- 甲基苯磺酸 (水 (1))(30.05mg,0.1580mmol)、3,5- 二氨基 -N-[4-(4- 甲基哌嗪 -1- 基)-3- 吡啶基]-1H- 吡唑 -4- 甲酰胺 (50mg,0.1580mmol) 在 DMSO(1mL)/H2O(0.5mL) 中的混合物在 140℃搅拌 25min。通过 Fractionlynx HPLC 纯化粗混合物。合并水性级分，冻干，得到 2- 氨基 -6- 氟 -N-(4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (10mg,21%)。

[0757] 实施例 3c :2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-4)

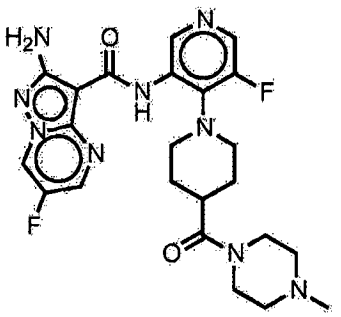
[0758]



[0759] 将苯并三唑 -1- 基 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸酯 6a(6.271g,20.02mmol)、[1-(3- 氨基 -5- 氟 -4- 吡啶基)-4- 哌啶基]-(4- 甲基哌嗪 -1- 基) 甲酮氢溴酸盐 17a(6.98g,16.68mmol) 和 DIPEA(2.802g,3.776mL,21.68mmol) 在吡啶 (63mL) 中的混悬液放入密封试管，在 100℃加热 24h。将该混合物冷却至室温，然后真空浓缩。使得到的固体上硅胶，通过色谱法纯化 (330g SiO_2,0.5-7.5% MeOH(包含 10% 氢氧化铵)/DCM)。将残余物在乙醇中搅拌 5mins，通过过滤采集形成的固体，用少量乙醇洗涤，通过抽吸干燥 2h，得到期望的产物，为淡黄色固体 (4.71g,56.5%)。MS(ES+)500.2 ;^{1}H NMR(DMSO-d6) δ 10.63(s,1H),9.67(s,1H),9.47(dd,J = 4.8,2.5Hz,1H),9.25(dd,J = 2.6,0.7Hz,1H),8.25(d,J = 2.4Hz,1H),6.79(s,2H),3.60(t,J = 5.0Hz,2H),3.55(t,J = 4.9Hz,2H),3.19(m,2H),3.03(m,2H),2.95(tt,J = 11.7,3.6Hz,1H),2.34(t,J = 5.0Hz,2H),2.29(t,J = 5.1Hz,2H),2.20(s,3H),2.13(qd,J = 12.4,3.9Hz,2H),1.75-1.72(m,2H)。

[0760] 实施例 3d :2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-4)

[0761]

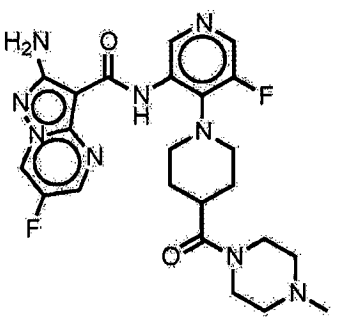


[0762] 在实施例 3c 中报道的方法的可替代的方法中，可以如下制备化合物 I-G-4：

[0763] 向安装了高架搅拌器、空气冷凝器、温度计和氮气管的 2L 烧瓶中加入 2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸 5a(14.19g,72.36mmol)，然后加入吡啶 (353mL)，随后加入 [(6- 氯苯并三唑 -1- 基）氧基 -（二甲基氨基）亚甲基]- 二甲基 - 铵三氟硼酸盐 (22.14g,65.78mmol)，同时在环境温度下搅拌。将该混悬液在 0℃加热 1h 以上期间。然后加入 DIPEA(17.85g,24.06mL,138.1mmol)，接着加入 [1-(3- 氨基 -5- 氟 -4- 吡啶基)-4- 哌啶基]-(4- 甲基哌嗪 -1- 基）甲酮盐酸盐 17b（根据制备例 N-14 制备）(23.54g,65.78mmol)。使内部温度升至 90℃，将该反应混合物在该温度下搅拌 13h。然后缓慢地冷却该混合物，真空蒸发溶剂。将残余物在 DCM(250ml) 中搅拌成淤浆，使橙色固体分配在 DCM(1L) 和 2M 碳酸钠 (200mL) 之间。分离有机层，用 2M 碳酸钠 (200mL) 洗涤，干燥 ($MgSO_4$)，过滤，真空浓缩，得到橙色固体。将该固体残余物再在 EtOH(115mL) 中搅拌成淤浆 10mins，然后通过过滤采集，再用乙醇（约 100mL）洗涤，通过抽吸干燥，得到产物，为淡黄色固体，18.75g,57%）。

[0764] 实施例 3e :2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-G-4)

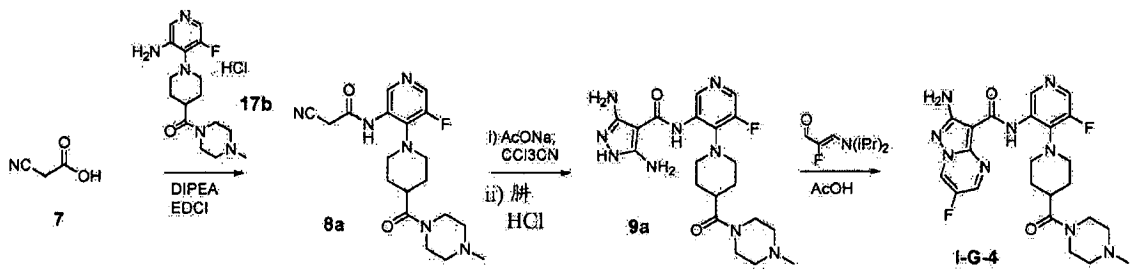
[0765]



[0766] 在实施例 3c 和 3d 中报道的方法的可替代的方法中，可以如下制备化合物 I-G-4：

[0767] 方案 2a：

[0768]



[0769] 步骤 1 :2- 氰基 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 乙酰胺 8a

[0770] 向 [1-(3- 氨基 -5- 氟 -4- 吡啶基)-4- 哌啶基]-(4- 甲基哌嗪 -1- 基) 甲酮盐酸 盐 17b(300mg,0.8383mmol) 和 DIPEA(541.8mg,730.2μL,4.192mmol) 在 DCM(8mL) 中的溶液中加入氰基乙酸 7(106.9mg,1.257mmol)。用冰浴冷却该反应混合物,然后加入 EDCI(241.0mg,1.257mmol)。将该混合物在室温搅拌过夜,然后回流加热 4h。将该反应混合物冷却至室温,用 DCM(30mL) 稀释,用水 (2x 10ml) 洗涤,然后用饱和碳酸氢钠溶液 (10mL) 洗涤。干燥有机层 ($MgSO_4$),过滤,真空浓缩,得到期望的产物 8a,为橙色泡沫体 (292mg,90%)。MS(ES+)389.2.

[0771] 步骤 2 :3,5- 二氨基 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-1H- 吡唑 -4- 甲酰胺 9a

[0772] 将 2- 氰基 -N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基] 乙酰胺 8a(290mg,0.7466mmol) 在乙醇 (3.3mL) 中搅拌成淤浆。加入乙酸钠 (127.4mg,1.553mmol),然后加入三氯乙腈 (129.4mg,91.13μL,0.8959mmol),将该反应混合物在室温搅拌 1hr,此后,灰白色沉淀形成。通过过滤采集固体,用少量乙醇、然后用少量水洗涤,通过抽吸干燥,得到白色固体 (155mg)。真空浓缩滤液,以除去乙醇,然 EtOAc(3x) 后用萃取残留的水溶液。干燥合并的有机层 ($MgSO_4$),过滤,真空浓缩至干,得到粘性油状物,将其在 EtOAc(5mL) 中研磨,形成灰白色沉淀,通过过滤采集,用少量 EtOAc 洗涤,通过抽吸干燥,得到第二批固体 (49mg)。总计分离 204mg(51%)3- 氨基 -4,4,4- 三氟 -2- 氰基 -N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基] 丁 -2- 烯酰胺 ; MS(ES+)532.0.

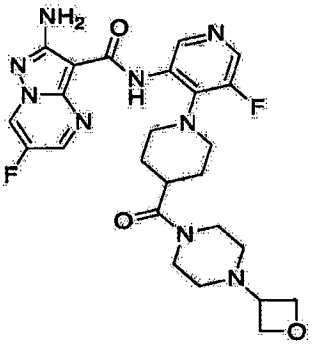
[0773] 将 3- 氨基 -4,4,4- 三氟 -2- 氰基 -N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基] 丁 -2- 烯酰胺 (4.1g,7.695mmol) 溶于 N- 甲基吡咯烷酮 (40mL)。加入水合肼 (1.002g,973.8μL,20.01mmol),将该反应混合物在室温搅拌 10mins,然后在 80℃加热 3.5h。真空浓缩该混合物,然后使残余物分配在 EtOAc/ 水之间。用水 (2x)、盐水 (1x) 洗涤有机层,干燥 (MgSO4),过滤,真空浓缩,得到期望的化合物,为白色固体。(64%)。MS(ES+)446.1,^{1}H NMR(500MHz, DMSO)11.03(s,1H),9.45(s,1H),8.69(s,1H),8.52(d, J = 4.7Hz,1H),7.36(br s,4H),4.47-4.43(m,1H),4.23-4.21(m,1H),3.50-3.47(m,2H),3.41-3.39(m,2H),3.24-3.15(m,2H)3.05-2.98(m,2H),2.93-2.88(m,2H),2.77-2.76(m,4H),1.73-1.71(m,4H)。

[0774] 步骤 3 :2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 I-G-4

[0775] 向 3,5- 二氨基 -N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基]-1H- 吡唑 -4- 甲酰胺 9a(106mg,1.19mmol) 在 IPA/ 水 (1 :1,1mL) 和乙酸 (71.46mg,67.67μL,0.1078mmol) 中的混悬液中加入 3-(二异丙基氨基)-2- 氟 - 丙 -2- 烯醛 (41.21mg,0.2379mmol)。将该反应混合物回流加热 6h,然后冷却至室温过夜。真空除去 IPA,使得到的水溶液分配在 DCM 与 2M 碳酸钠溶液之间。用 1 :1 盐水 / 水洗涤有机层,干燥 ($MgSO_4$),过滤,真空浓缩,得到黄色固体,将其在乙醇 (0.5mL) 中搅拌成混悬液 2h。通过过滤采集固体,得到期望的化合物 I-G-4(63mg,53%)。

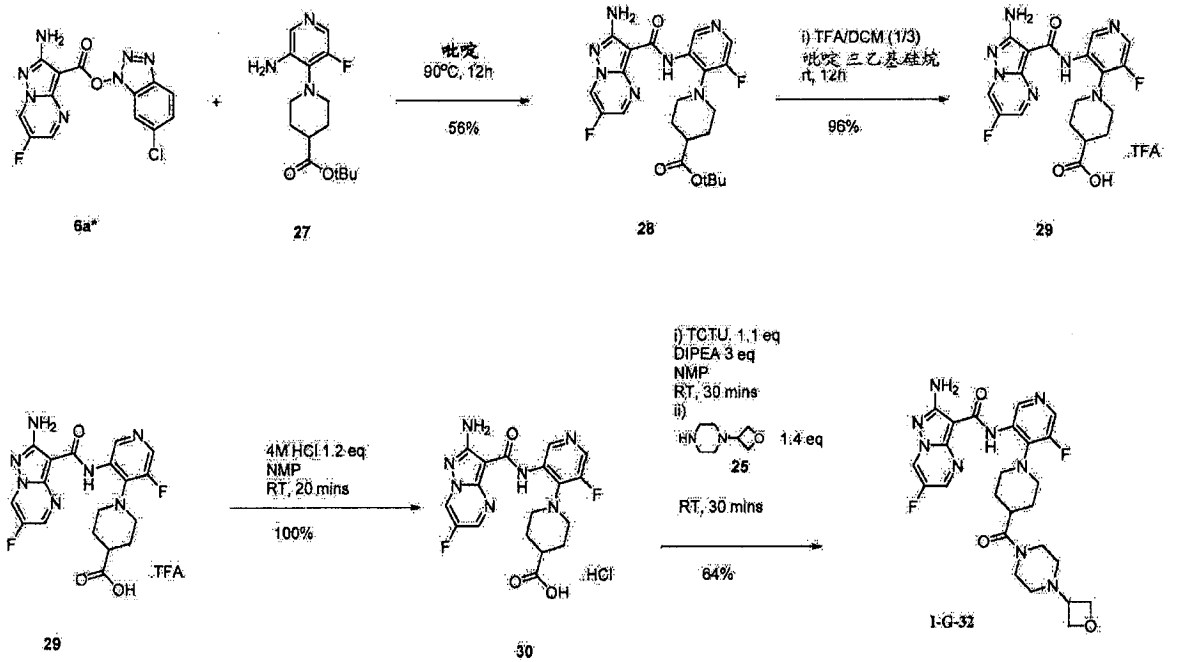
[0776] 实施例 3f :2- 氨基 -6- 氟 -N-[5- 氟 -4-[4-[4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 羰基]-1- 哌啶基]-3- 吡啶基] 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-32)

[0777]



[0778] 方案 2b :化合物 I-G-32 的制备

[0779]



[0780] 步骤 1 :1-[3-[(2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 羰基) 氨基]-5- 氟 -4- 吡啶基] 哌啶 -4- 甲酸叔丁酯 28

[0781] 将 (6- 氯苯并三唑 -1- 基)2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 甲酸酯 6a*(44.02g,126.6mmol) 和 1-(3- 氨基 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯 27(根据制备例 N-15 制备)(34g,115.1mmol) 在吡啶 (510.0mL) 中的混合物在内部 95℃下加热过夜 (18h)。将混合物冷却至室温 (产物沉淀),然后加入乙醇 (340.0mL),在室温搅拌 10mins。通过过滤采集黄色固体,用乙醇充分洗涤,通过抽吸干燥,然后用高度真空管线干燥 1h,得到产物 28,为黄色固体 (32.5g 56% 收率)。^{1}H NMR(500MHz,DMSO-d6) δ 10.45(s,1H),9.58(s,1H),9.51(dd,1H),8.72(dd,1H),8.25(d,1H),6.81(s,2H),3.15-2.93(m,4H),2.55 - 2.47(掩蔽的信号,1H),2.02 - 1.91(m,4H),1.47(s,9H)。MS(ES+)474.2.

[0782] 步骤 2 :1-[3-[(2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 羰基) 氨基]-5- 氟 -4- 吡

啶基]哌啶-4-甲酸三氟乙酸盐29

[0783] 向1-[3-[(2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-羰基)氨基]-5-氟-4-吡啶基]哌啶-4-甲酸叔丁酯28(69.7g,147.2mmol)在DCM(348.5mL)和三乙基硅烷(18.83g,25.87mL,161.9mmol)中的混悬液中加入TFA(151.1g,102.1mL,1.325mol)(混合物在最初添加TFA时使固体凝固,然后在完全添加后形成溶液)。将得到的橙色溶液在室温搅拌过夜。再加入TFA(16.78g,11.34mL,147.2mmol),将该混合物在室温搅拌2h。然后在40℃将混合物加热20mins以促使反应完成。真空浓缩混合物,加入氯仿(300mL),将混合物再真空浓缩,得到橙色固体混悬液。将混合物在DCM(约200mL)中研磨,搅拌20mins,通过过滤采集固体,用少量DCM洗涤,通过抽吸干燥,得到黄色固体。真空浓缩滤液,将残余物再在DCM(约50mL)中搅拌成淤浆,搅拌20mins,然后通过过滤采集固体,用少量DCM洗涤,通过抽吸干燥,得到黄色固体,与第一批固体合并。真空干燥固体过夜,得到期望的产物29,为黄色固体(82.8g,96%)。^{1}H NMR(500MHz,DMSO-d6)δ10.44(s,1H),9.59(s,1H),9.50(dd,1H),8.84(dd,1H),8.33(d,1H),3.13-3.10(m,4H),2.57-2.47(掩蔽的信号,1H)和2.08-1.93(m,4H)。MS(ES+)418.1.

[0784] 步骤3:1-[3-[(2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-羰基)氨基]-5-氟-4-吡啶基]哌啶-4-甲酸盐酸盐30

[0785] 向1-[3-[(2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-羰基)氨基]-5-氟-4-吡啶基]哌啶-4-甲酸(三氟乙酸)29(73g,124.7mmol)在NMP(662.7mL)中的溶液中加入氯化氢(4M的1,4-二噁烷溶液)(37.40mL的4M,149.6mmol)。几秒钟后,形成黄色沉淀。将混合物在室温搅拌20mins,然后通过过滤采集固体,用少量NMP、然后用MTBE洗涤,通过抽吸干燥,得到纯产物30,为淡黄色固体(59.7g,定量收率)。MS(ES+)418.1.

[0786] 步骤4:2-氨基-6-氟-N-[5-氟-4-[4-[4-(氧杂环丁烷-3-基)哌嗪-1-羰基]-1-哌啶基]-3-吡啶基]吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-32)

[0787] 向黄色1-[3-[(2-氨基-6-氟-吡唑并[1,5-a]嘧啶-3-羰基)氨基]-5-氟-4-吡啶基]哌啶-4-甲酸(盐酸)30(59.7g,131.5mmol)在NMP(477.6mL)中的混悬液中加入DIPEA(50.99g,68.72mL,394.5mmol),然后加入[(6-氯苯并三唑-1-基)氧基-(二甲基氨基)亚甲基]-二甲基-铵(四氟化硼离子(1))(51.44g,144.7mmol)。几分钟后黄色混悬液形成。将该混合物在室温搅拌30mins,然后加入1-(氧杂环丁烷-3-基)哌嗪25(根据如下制备例N-32制备)(26.18g,184.1mmol)。乳膏状/黄褐色混悬液变成橙色溶液(放热23.9—29.4℃)。将烧瓶置于冰/水浴上,直到内部温度在24℃为止,然后除去冰浴,此后内部温度稳定在24℃。

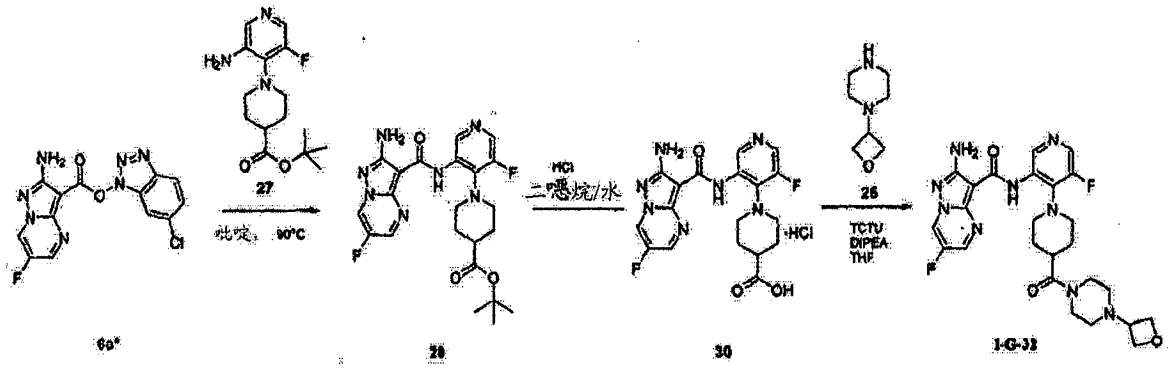
[0788] 将该溶液在室温搅拌30mins,然后用冰/盐/水浴冷却至10℃,然后分100mL部分添加水(1.015L)。添加下一个100mL水前,等待放热至17℃—20℃(内部),然后允许冷却至10—15℃。重复至全部水添加完成。一旦放热停止,则除去冰/盐/水浴,将混合物在环境温度搅拌20mins(浓稠黄色/乳膏状混悬液形成)。通过垂熔漏斗过滤采集固体,用水充分洗涤,然后通过抽吸干燥10mins。除去真空,用垂熔漏斗将固体在水中搅拌成淤浆,然后再施加真空,通过抽吸将固体干燥过夜,然后在40℃<10mBar真空烘箱干燥24h。

[0789] 将固体(54.5g)混悬于乙醇(545mL,10vol eq.),回流加热2h,然后在2h内冷却至室温。通过过滤采集固体,用少量乙醇洗涤,通过抽吸干燥1h,得到产物,为淡黄色固

体。将固体在23.5℃和<10mBar放入真空烘箱过夜，得到产物I-G-32，为淡黄色固体（51g，64%收率）。^{1}HNMR(500MHz，DMSO-d6) δ 10.64(s,1H)，9.67(s,1H)，9.48(dd,1H)，9.26(dd,1H)，8.26(d,1H)，6.79(s,2H)，4.55(t,2H)，4.47(t,2H)，4.34(t,0.7H)，3.61(dt,4H)，3.48-3.41(m,2.5H)，3.22-3.17(m,2H)，3.05-3.03(m,2H)，3.99-2.93(m,1H)，2.28(dt,4H)，2.17-2.10(m,2H)，1.74(d,2H)，1.07(t,2H)。MS(ES+)542.3.

[0790] 方案2c：制备化合物I-G-32的可替代方法

[0791]



[0792] 步骤1：1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸叔丁酯28

[0793] 将2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酸6-氯-1H-苯并[d][1,2,3]三唑-1-酯6a*(45g,129.4mmol)和1-(3-氨基-5-氟吡啶-4-基)哌啶-4-甲酸叔丁酯27(40.1g,135.9mmol)在吡啶(675ml)中搅拌成淤浆。将该混合物在95℃在氮气气氛中加热至反应完成（通过HPLC分析测定）。冷却该混合物，滴加乙醇(450ml)。过滤该混合物，用乙醇(2x70ml)洗涤滤饼。干燥潮湿饼状物，得到产物28，为黄色结晶固体(47.7g，78%)；^{1}H NMR(500MHz，DMSO-d_6) δ 10.45(s,1H)，9.58(s,1H)，9.51(dd,1H)，8.72(dd,1H)，8.25(d,1H)，6.81(s,2H)，3.15-2.93(m,4H)，2.55 - 2.47(掩蔽的信号，1H)，2.02 - 1.91(m,4H)，1.47(s,9H)；19FNMR(500MHz，DMSO-d6) δ - 153.5、-136.3；MS(ES+)474.2.

[0794] 步骤2：1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸盐酸盐30

[0795] 将1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸叔丁酯28(36g,76mmol)混悬于HCl的1,4-二噁烷溶液(4M,670ml)。向快速搅拌的淤浆中滴加水(36ml)。将该混合物在氮气气氛中搅拌至反应完成（通过HPLC分析测定）。用1,4-二噁烷(180ml)稀释该混合物，过滤。用TBME(2x72ml)洗涤滤饼。干燥潮湿饼状物，得到浅棕色固体（盐酸盐，32.7g，95%）；^{1}H NMR(500MHz，DMSO-d_6) δ 10.34(s,1H)，9.53-9.49(m,2H)，8.82(m,1H)，8.50(m,1H)，3.13 - 3.22(m,4H)，2.57 - 2.47(掩蔽的信号，1H)和2.08-1.93(m,4H)；19F NMR(500MHz，DMSO-d6) δ - 152.9、-133.8；MS(ES+)418.1.

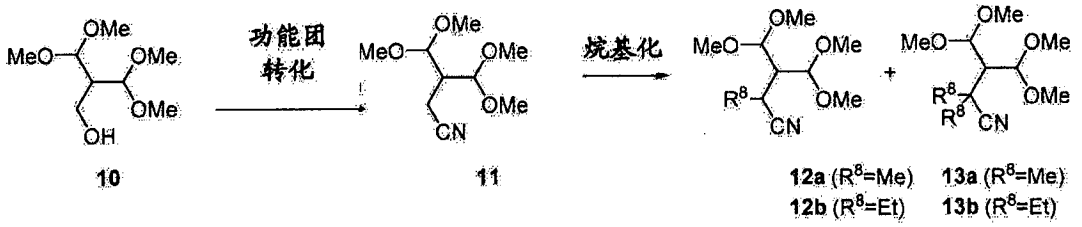
[0796] 步骤3：2-氨基-6-氟-N-(5-氟-4-(4-(4-(氧杂环丁烷-3-基)哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物I-G-32）

[0797] 向1-(氧杂环丁烷-3-基)哌嗪(525mg,3.69mmol)在THF(12ml)中的溶液中加入DIPEA(1.72ml,9.91mmol)，然后加入1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲

酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸(盐酸盐,1.5g,3.3mmol)。加入[(6-氯苯并三唑-1-基)氧基-(二甲基氨基)亚甲基]-二甲基-铵四氟硼酸盐(TCTU,1.29g,3.64mmol),将该混合物在氮气气氛中搅拌至反应完成(通过HPLC分析测定)。冷却该混合物,滴加水(24ml)。将该混合物温至环境,搅拌3hrs,然后过滤。用(3x3ml)洗涤滤饼。在40℃真空干燥潮湿饼状物(用氮气流)。得到产物,为黄色固体(1.54g,86%);^{1}H NMR(500MHz,DMSO-d6)δ 10.64(s,1H),9.67(s,1H),9.48(dd,1H),9.26(dd,1H),8.26(d,1H),6.79(s,2H),4.55(t,2H),4.47(t,2H),4.34(t,0.7H),3.61(dt,4H),3.48-3.41(m,2.5H),3.22-3.17(m,2H),3.05-3.03(m,2H),3.99-2.93(m,1H),2.28(dt,4H),2.17-2.10(m,2H),1.74(d,2H),1.07(t,2H);19F NMR(500MHz,DMSO-d6)δ -152.8、-136.1;MS(ES+)542.3。

[0798] 方案3—丁腈中间体的制备

[0799]



[0800] 步骤1:3-(二甲氧基甲基)-4,4-二甲氧基丁腈11

[0801] 将2-(二甲氧基甲基)-3,3-二甲氧基-丙-1-醇10(Journal of the American Chemical Society(1973),95(26),8741)(92g,473.7mmol)溶于干THF(920mL),用冰浴冷却该混合物。一次加入三乙胺(143.8g,198.1mL,1.421mol),然后在1h内滴加甲磺酰氯(59.69g,40.33mL,521.1mmol),保持内部温度低于5℃。将该反应混合物搅拌1h,然后温至室温。用乙酸乙酯(920mL)和水(920mL)稀释该混合物。分离各层,分离有机层,用饱和$NaHCO_3$溶液、然后用盐水洗涤。用$MgSO_4$干燥有机层,过滤,蒸发,得到[2-(二甲氧基甲基)-3,3-二甲氧基丙基]甲磺酸酯,为橙色油状物(125.31g,97%),未经进一步纯化直接使用。

[0802] 在10分钟内将氰化四乙基铵(142.3g,910.8mmol)逐步加入到[2-(二甲氧基甲基)-3,3-二甲氧基丙基]甲磺酸酯(124g,455.4mmol)在MeCN(1.24L)中的溶液中。将该反应混合物在室温搅拌72H,然后分配在乙酸乙酯(1.24L)与水(1.24L)之间。分离各层,分离有机层,用盐水洗涤。用$MgSO_4$干燥有机层,过滤,蒸发,得到3-(二甲氧基甲基)-4,4-二甲氧基丁腈11,为深棕色油状物(86.1g)。

[0803] 步骤2:3-(二甲氧基甲基)-4,4-二甲氧基-2-甲基丁腈12a和3-(二甲氧基甲基)-4,4-二甲氧基-2,2-二甲基丁腈13a

[0804] 在-75℃向3-(二甲氧基甲基)-4,4-二甲氧基-丁腈11(250mg,1.205mmol)在THF(3mL)中的溶液中加入碘甲烷(513.1mg,225.0μL,3.615mmol)在THF(1ml)中的溶液。然后加入(双(三甲基甲硅烷基)氨基)钠的THF溶液(1.808mL的2M,3.615mmol),保持温度低于-60℃。添加后,将该反应混合物在-75℃搅拌2hrs,然后缓慢地用饱和NH_4Cl水溶液(5ml)猝灭。用水用乙醚稀释该混合物,分离各层。用盐水洗涤有机层,干燥(Na_2SO_4),真空浓缩,得到黄色油状物,通过硅胶色谱法纯化,用石油醚洗脱:100:0—80:20EtOAc梯度。真空浓缩溶剂,得到澄清油状物(194mg)。NMR证实该油状物为80%一甲基化合物12a

与和 20%双甲基化合物 13a 的混合物。将该混合物在直接用于随后的步骤中。

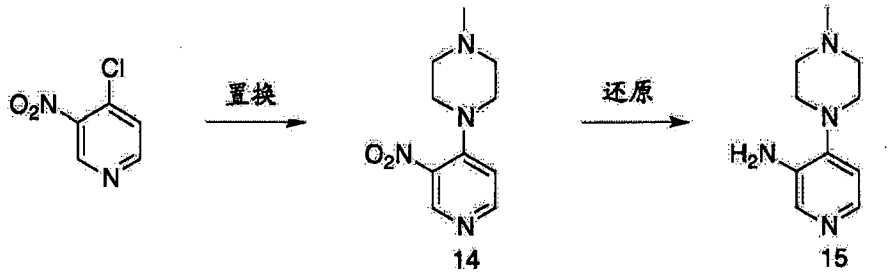
[0805] 步骤 3 :3-(二甲氧基甲基)-2- 乙基 -4,4- 二甲氧基丁腈 12b 和 3-(二甲氧基甲基)-2- 二乙基 -4,4- 二甲氧基丁腈 13b

[0806] 当按照与上述方案 3 步骤 2 类似的方法用碘乙烷梯度碘甲烷使用时,分离单取代的化合物 12b 和二取代的化合物 13b 的混合物,直接用于随后的步骤。

[0807] 制备例 N-1 :4-(4- 甲基哌嗪 -1- 基)吡啶 -3- 胺 15

[0808] 方案 4

[0809]



[0810] 步骤 1 :1- 甲基 -4-(3- 硝基 -4- 吡啶基)哌嗪 14

[0811] 用 1- 甲基哌嗪 (1.515g,1.678mL,15.13mmol) 和 DIPEA(2.445g,3.295mL,18.92mmol) 处理在二噁烷 (15mL) 中的 4- 氯 -3- 硝基 - 吡啶 (2g,12.61mmol)。将该混合物在 80℃搅拌 1 小时,冷却至 RT。使该混合物分配在 EtOAc 与饱和 $NaHCO_3$ 水溶液 (40ml) 之间。用 $MgSO_4$ 干燥合并的有机萃取物,减压浓缩,得到橙色油状物,通过硅胶色谱法纯化,用 5-10% MeOH/EtOAc/0.5-1% NH_4OH 洗脱,得到 1- 甲基 -4-(3- 硝基 -4- 吡啶基)哌嗪 14,为深黄色油状物,静置时结晶 (2.56g,11.52mmol,91.36%)。MS(ES+)223.4.

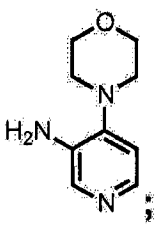
[0812] 步骤 2 :4-(4- 甲基哌嗪 -1- 基)吡啶 -3- 胺 15

[0813] 用批钯碳 (10 % wt % Degussa)(300mg) 处理在甲醇 (200mL) 中的 1- 甲基 -4-(3- 硝基 -4- 吡啶基)哌嗪 14(2.56g,11.52mmol),在 RT 在气囊压力下氢化 3 小时。过滤出催化剂,减压浓缩滤液,得到 4-(4- 甲基哌嗪 -1- 基)吡啶 -3- 胺 15,为无色固体 (2.124g,11.05mmol,95.89%)。MS(ES+)193.1.

[0814] 使用制备例 N-1 制备了如下 3- 氨基吡啶中间体 :

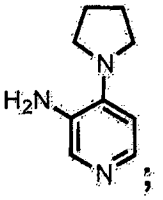
[0815] 4- 吗啉代吡啶 -3- 胺 ;

[0816]



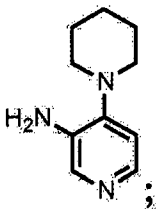
[0817] 4-(吡咯烷 -1- 基)吡啶 -3- 胺 :

[0818]



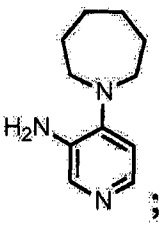
[0819] 4-(哌啶-1-基)吡啶-3-胺：

[0820]



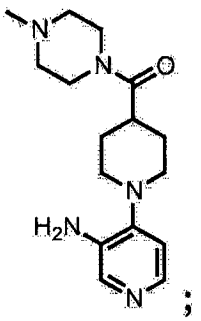
[0821] 4-(氮杂庚环-1-基)吡啶-3-胺：

[0822]



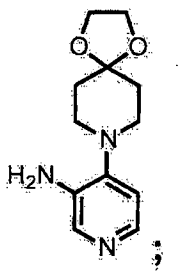
[0823] (1-(3-氨基吡啶-4-基)哌啶-4-基)(4-甲基哌嗪-1-基)甲酮：

[0824]



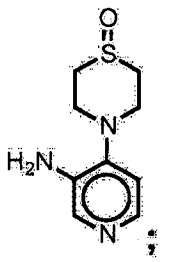
[0825] 4-(1,4-二氧杂-8-氮杂螺[4.5]癸-8-基)吡啶-3-胺：

[0826]



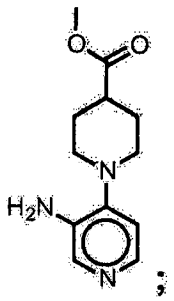
[0827] 4-(3-氨基吡啶-4-基)硫吗啉1-氧化物：

[0828]



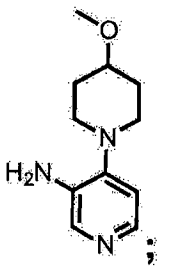
[0829] 1-(3-氨基吡啶-4-基)哌啶-4-甲酸甲酯：

[0830]



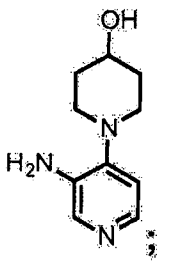
[0831] 4-(4-甲氧基哌啶-1-基)吡啶-3-胺：

[0832]



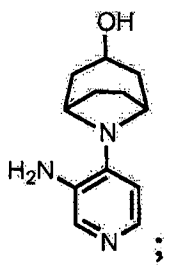
[0833] 1-(3-氨基吡啶-4-基)哌啶-4-醇：

[0834]



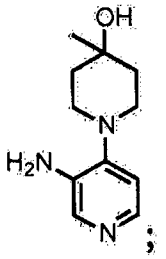
[0835] 8-(3-氨基吡啶-4-基)-8-氮杂双环[3.2.1]辛-3-醇：

[0836]



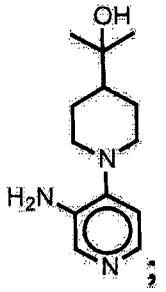
[0837] 1-(3-氨基吡啶-4-基)-4-甲基哌啶-4-醇：

[0838]



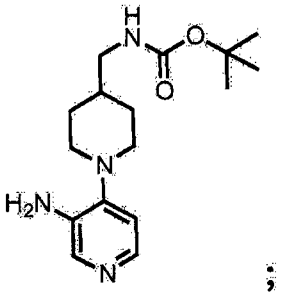
[0839] 2-(1-(3-氨基吡啶-4-基)哌啶-4-基)丙-2-醇：

[0840]



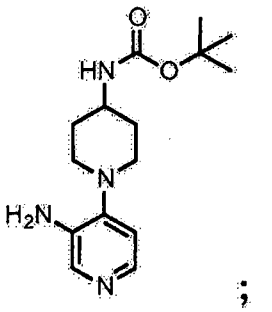
[0841] ((1-(3-氨基吡啶-4-基)哌啶-4-基)甲基)氨基甲酸叔丁酯：

[0842]



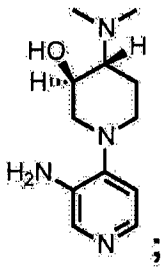
[0843] (1-(3-氨基吡啶-4-基)哌啶-4-基)氨基甲酸叔丁酯：

[0844]



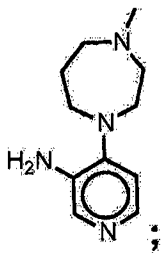
[0845] (3R,4R)-1-(3-氨基吡啶-4-基)-4-(二甲基氨基)哌啶-3-醇：

[0846]



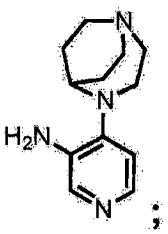
[0847] 4-(4-甲基-1,4-二氮杂庚环-1-基)吡啶-3-胺：

[0848]



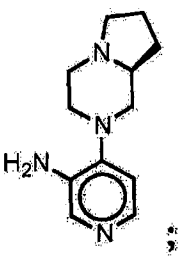
[0849] 4-(1,4-二氮杂双环[3.2.2]壬-4-基)吡啶-3-胺：

[0850]



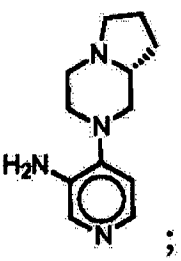
[0851] (S)-4-(六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-胺：

[0852]



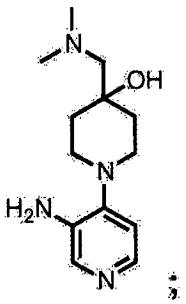
[0853] (R)-4-(六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-胺：

[0854]



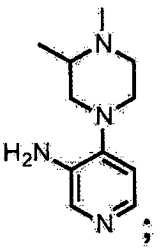
[0855] 1-(3-氨基吡啶-4-基)-4-((二甲基氨基)甲基)哌啶-4-醇：

[0856]



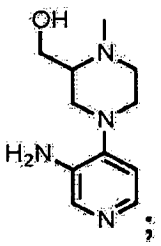
[0857] 4-(3,4-二甲基哌嗪-1-基)吡啶-3-胺：

[0858]



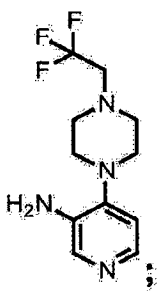
[0859] (4-(3-氨基吡啶-4-基)-1-甲基哌嗪-2-基)甲醇：

[0860]



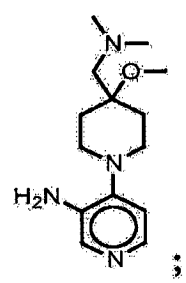
[0861] 4-(4-(2,2,2-三氟乙基)哌嗪-1-基)吡啶-3-胺：

[0862]



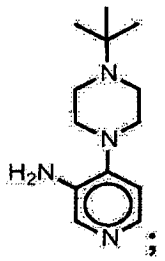
[0863] 4-(4-((二甲基氨基)甲基)-4-甲氧基哌啶-1-基)吡啶-3-胺：

[0864]



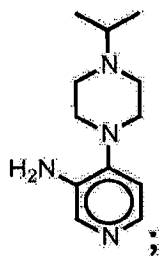
[0865] 4-(4-(叔丁基)哌嗪-1-基)吡啶-3-胺：

[0866]



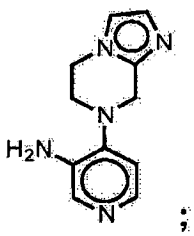
[0867] 4-(4-异丙基哌嗪-1-基)吡啶-3-胺：

[0868]



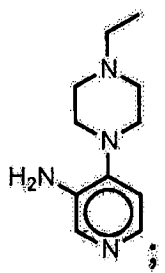
[0869] 4-(5,6-二氢咪唑并[1,2-a]吡嗪-7(8H)-基)吡啶-3-胺：

[0870]



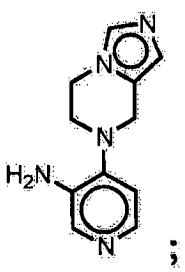
[0871] 4-(4-乙基哌嗪-1-基)吡啶-3-胺：

[0872]



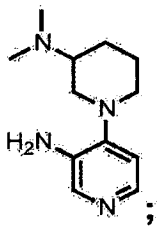
[0873] 4-(5,6-二氢咪唑并[1,5-a]吡嗪-7(8H)-基)吡啶-3-胺：

[0874]



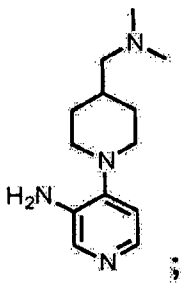
[0875] 4-(3-(二甲基氨基)哌啶-1-基)吡啶-3-胺：

[0876]



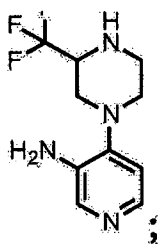
[0877] 4-(4-((二甲基氨基)甲基)哌啶-1-基)吡啶-3-胺：

[0878]



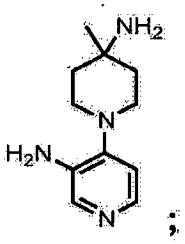
[0879] 4-(3-(三氟甲基)哌嗪-1-基)吡啶-3-胺：

[0880]



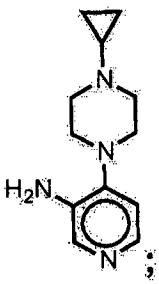
[0881] 4-(4-氨基-4-甲基哌啶-1-基)吡啶-3-胺：

[0882]



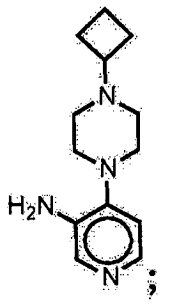
[0883] 4-(4-环丙基哌嗪-1-基)吡啶-3-胺：

[0884]



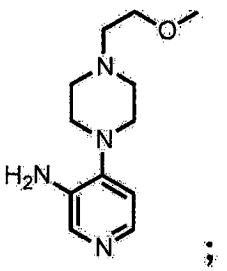
[0885] 4-(4-环丁基哌嗪-1-基)吡啶-3-胺：

[0886]



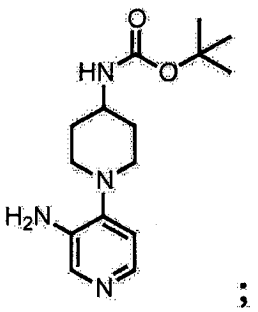
[0887] 4-(4-(2-甲氧基乙基)哌嗪-1-基)吡啶-3-胺：

[0888]



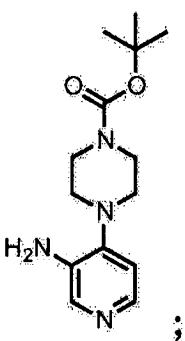
[0889] (1-(3-氨基吡啶-4-基)哌啶-4-基)氨基甲酸叔丁酯：

[0890]



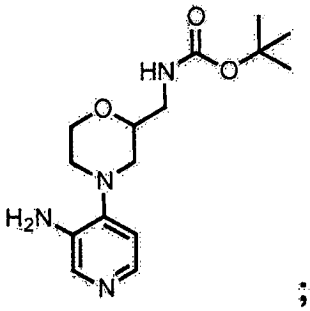
[0891] 4-(3-氨基吡啶-4-基)哌嗪-1-甲酸叔丁酯：

[0892]



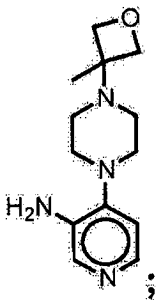
[0893] ((4-(3-氨基吡啶-4-基)吗啉-2-基)甲基)氨基甲酸叔丁酯：

[0894]



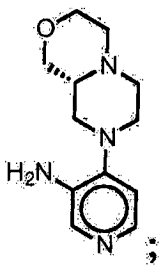
[0895] 4-(4-(3-甲基氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-胺:

[0896]



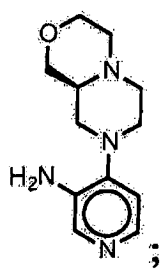
[0897] (R)-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-胺:

[0898]



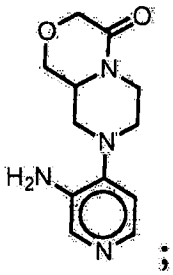
[0899] (S)-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-胺:

[0900]



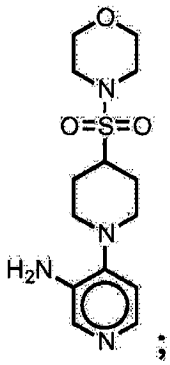
[0901] 8-(3-氨基吡啶-4-基)六氢吡嗪并[2,1-c][1,4]噁嗪-4(3H)-酮:

[0902]



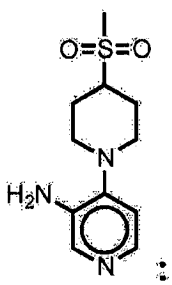
[0903] 4-(4-(吗啉代磺酰基)哌啶-1-基)吡啶-3-胺:

[0904]



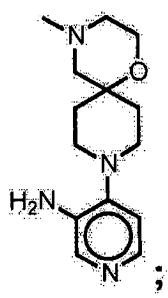
[0905] 4-(4-(甲基磺酰基)哌啶-1-基)吡啶-3-胺:

[0906]



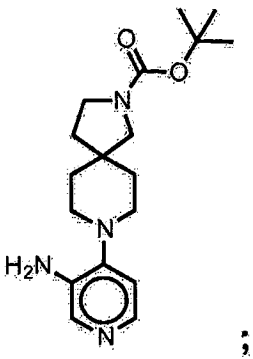
[0907] 4-(4-甲基-1-氧杂-4,9-二氮杂螺[5.5]十一烷-9-基)吡啶-3-胺:

[0908]



[0909] 8-(3-氨基吡啶-4-基)-2,8-二氮杂螺[4.5]癸烷-2-甲酸叔丁酯:

[0910]



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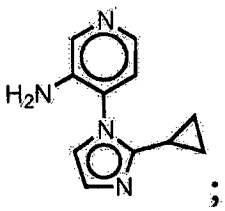
[0911] 4-(2-环丙基-1H-咪唑-1-基)吡啶-3-胺：

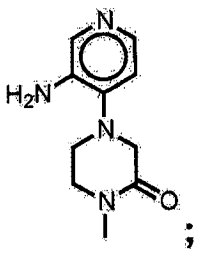
[0912]



;

[0913] 4-(3-氨基吡啶-4-基)-1-甲基哌嗪-2-酮：

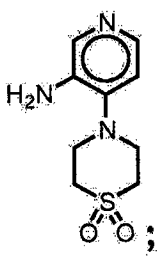
[0914]



;

[0915] 4-(3-氨基吡啶-4-基)硫吗啉1,1-二氧化物：

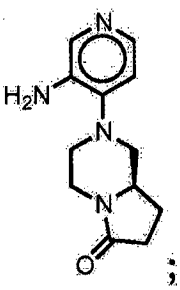
[0916]



;

[0917] (R)-2-(3-氨基吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-6(2H)-酮：

[0918]



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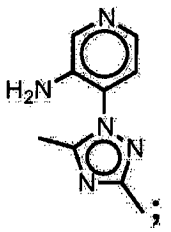
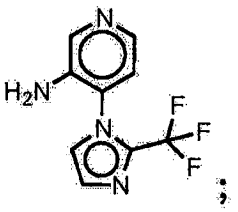
[0919] 4-(3,5-二甲基-1H-1,2,4-三唑-1-基)吡啶-3-胺：

[0920]



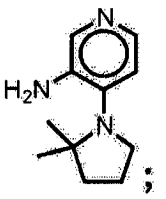
[0921] 4-(2-(三氟甲基)-1H-咪唑-1-基)吡啶-3-胺：

[0922]



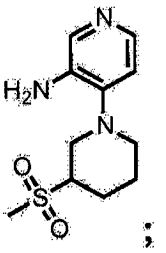
[0923] 4-(2,2-二甲基吡咯烷-1-基)吡啶-3-胺：

[0924]



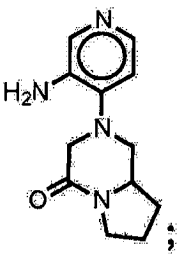
[0925] 4-(3-(甲基磺酰基)哌啶-1-基)吡啶-3-胺：

[0926]



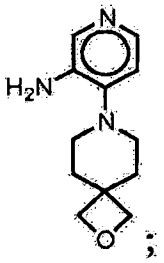
[0927] 2-(3-氨基吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-4(1H)-酮：

[0928]



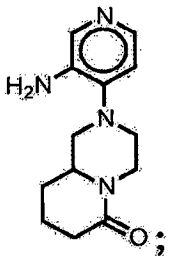
[0929] 4-(2-氧杂-7-氮杂螺[3.5]壬-7-基)吡啶-3-胺：

[0930]



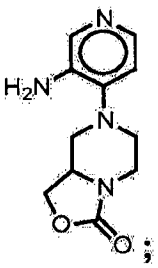
[0931] 2-(3-氨基吡啶-4-基)六氢-1H-吡啶并[1,2-a]吡嗪-6(2H)-酮：

[0932]



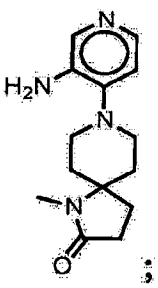
[0933] 7-(3-氨基吡啶-4-基)四氢-1H-噁唑并[3,4-a]吡嗪-3(5H)-酮：

[0934]



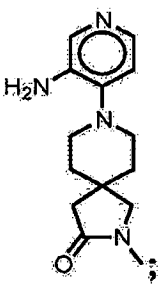
[0935] 8-(3-氨基吡啶-4-基)-1-甲基-1,8-二氮杂螺[4.5]癸-2-酮：

[0936]



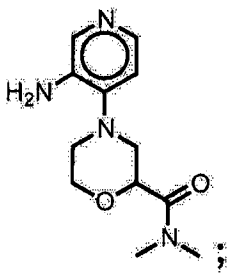
[0937] 8-(3-氨基吡啶-4-基)-2-甲基-2,8-二氮杂螺[4.5]癸-3-酮：

[0938]



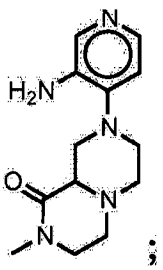
[0939] 4-(3-氨基吡啶-4-基)-N,N-二甲基吗啉-2-甲酰胺：

[0940]



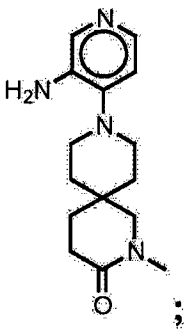
[0941] 8-(3-氨基吡啶-4-基)-2-甲基八氢-1H-吡嗪并[1,2-a]吡嗪-1-酮：

[0942]



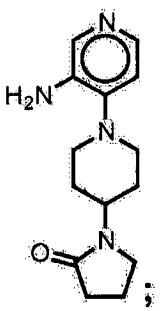
[0943] 9-(3-氨基吡啶-4-基)-2-甲基-2,9-二氮杂螺[5.5]十一烷-3-酮：

[0944]



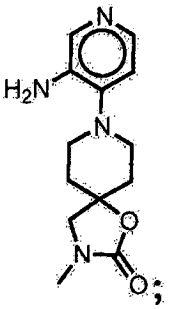
[0945] 1-(1-(3-氨基吡啶-4-基)哌啶-4-基)吡咯烷-2-酮：

[0946]



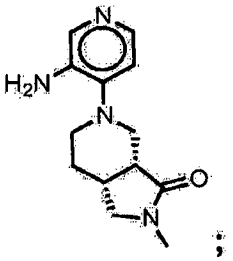
[0947] 8-(3-氨基吡啶-4-基)-3-甲基-1-氧杂-3,8-二氮杂螺[4.5]癸-2-酮：

[0948]



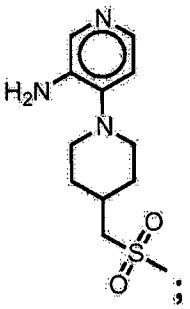
[0949] (3aS,7aS)-5-(3-氨基吡啶-4-基)-2-甲基六氢-1H-吡咯并[3,4-c]吡啶-3(2H)-酮：

[0950]



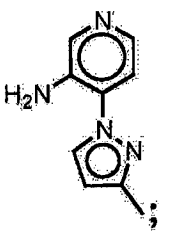
[0951] 4-(4-((甲基磺酰基)甲基)哌啶-1-基)吡啶-3-胺：

[0952]



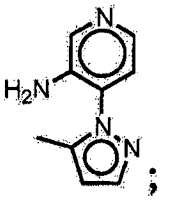
[0953] 4-(3-甲基-1H-吡唑-1-基)吡啶-3-胺：

[0954]



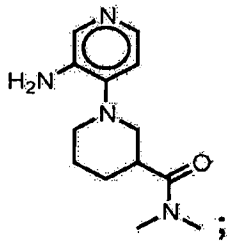
[0955] 4-(5-甲基-1H-吡唑-1-基)吡啶-3-胺：

[0956]



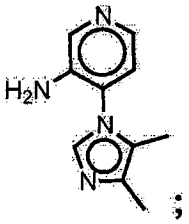
[0957] 1-(3-氨基吡啶-4-基)-N,N-二甲基哌啶-3-甲酰胺：

[0958]



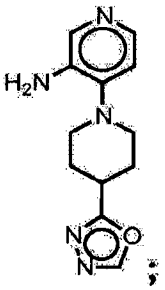
[0959] 4-(4,5-二甲基-1H-咪唑-1-基)吡啶-3-胺：

[0960]



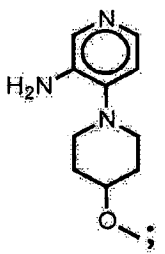
[0961] 4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)吡啶-3-胺：

[0962]



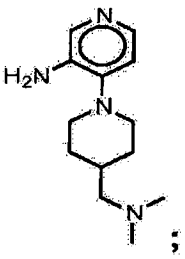
[0963] 4-(4-甲氧基哌啶-1-基)吡啶-3-胺：

[0964]



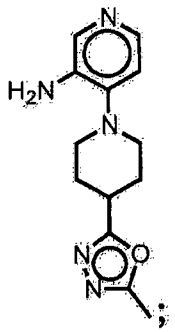
[0965] 4-(4-((二甲基氨基)甲基)哌啶-1-基)吡啶-3-胺：

[0966]



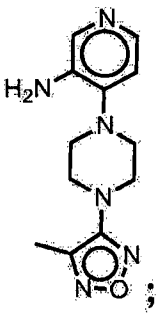
[0967] 4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)吡啶-3-胺：

[0968]



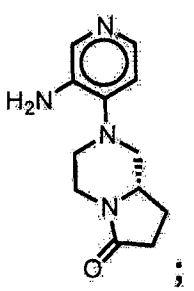
[0969] 4-(4-(4-甲基-1,2,5-噁二唑-3-基)哌嗪-1-基)吡啶-3-胺：

[0970]



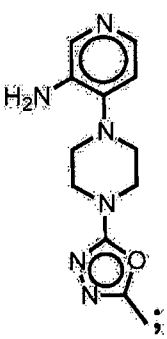
[0971] (S)-2-(3-氨基吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-6(2H)-酮：

[0972]



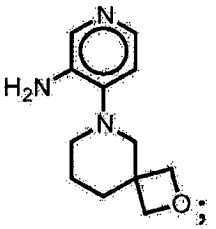
[0973] 4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)吡啶-3-胺：

[0974]



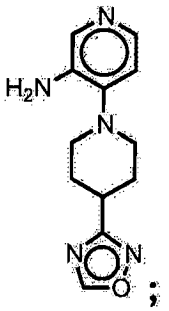
[0975] 4-(2-氧杂-6-氮杂螺[3.5]壬-6-基)吡啶-3-胺：

[0976]

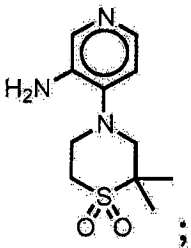


[0977] 4-(4-(1,2,4-噁二唑-3-基)哌啶-1-基)吡啶-3-胺：

[0978]

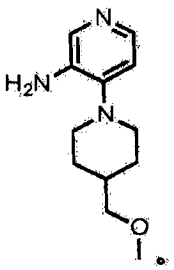


[0979] 4-(3-氨基吡啶-4-基)-2,2-二甲基硫吗啉1,1-二氧化物：

[0980]  以及

[0981] 4-(4-(甲氧基甲基)哌啶-1-基)吡啶-3-胺：

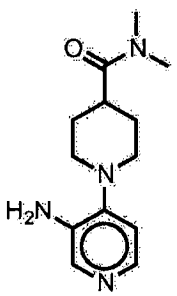
[0982]



[0983] 氨基吡啶类的其它制备

[0984] 制备例N-2：1-(3-氨基吡啶-4-基)-N,N-二甲基哌啶-4-甲酰胺

[0985]



[0986] 步骤 1 :1-(3- 氨基 -4- 吡啶基) 哌啶 -4- 甲酸

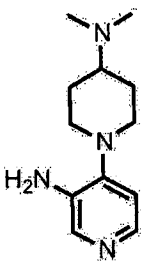
[0987] 向微波小瓶中加入 1-(3- 氨基 -4- 吡啶基) 哌啶 -4- 甲酸甲酯 (根据与制备例 N-1 中所述类似的方法制备) (176mg,0.7106mmol)、MeOH(3mL) 和 H_2O(0.1mL)。加入 LiOH(51.06mg,2.132mmol),将该混合物在 50℃搅拌过夜。通过添加 HCl 水溶液至达到 pH = 3-4 使反应停止。然后减压浓缩该反应混合物,得到 1-(3- 氨基 -4- 吡啶基) 哌啶 -4- 甲酸,不经进一步纯化使用。MS(ES+)222.1.

[0988] 步骤 2 :1-(3- 氨基吡啶 -4- 基)-N,N- 二甲基哌啶 -4- 甲酰胺

[0989] 向微波小瓶中加入 1-(3- 氨基 -4- 吡啶基) 哌啶 -4- 甲酸 (125mg,0.197mmol)、TBTU(200mg,0.62mmol) 和 N- 甲基甲胺 (3.5mL,2M in MeOH)。密封试管,将该混合物在 120℃搅拌 3h。将粗产物再溶于 MeOH,上 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗,用甲醇的氨溶液释放产物。减压浓缩氨萃取物,得到 1-(3- 氨基吡啶 -4- 基)-N,N- 二甲基哌啶 -4- 甲酰胺。MS(ES+)249.2.

[0990] 制备例 N-3 :4-(4-(二甲基氨基) 哌啶 -1- 基) 吡啶 -3- 胺

[0991]



[0992] 步骤 1 :(1-(3- 氨基吡啶 -4- 基) 哌啶 -4- 基)(甲基) 氨基甲酸叔丁酯

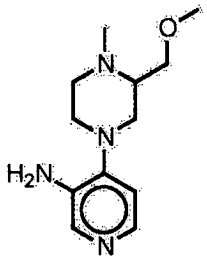
[0993] 在 0℃向 N-[1-(3- 硝基 -4- 吡啶基)-4- 哌啶基] 氨基甲酸叔丁酯 (2100mg,6.514mmol)(根据与制备例 N-1 步骤 1 中所述类似的方法制备) 和碘甲烷 (4.623g,2.028mL,32.57mmol) 在 DMF 中的溶液中逐步加入氢化钠 (312.7mg,7.817mmol)。将该反应体系在 0℃搅拌 1h,在室温搅拌 1h。通过将该反应混合物倾倒在饱和氯化铵水溶液上使反应停止,然后用乙酸乙酯 (2x 50mL) 萃取。用盐水 (2x 50mL) 洗涤合并的有机层,干燥,蒸发,得到橙色固体。向溶于 MeOH(50mL) 的粗固体中加入 Pd/C(10%)(346mg),将该混合物在氢气气氛中搅拌 4h。通过 C 盐过滤该反应体系,蒸发,得到 (1-(3- 氨基吡啶 -4- 基) 哌啶 -4- 基)(甲基) 氨基甲酸叔丁酯,为黄色油状物 (600mg,20%)MS(ES+-tBu)251.1.

[0994] 步骤 2 :4-(4-(二甲基氨基) 哌啶 -1- 基) 吡啶 -3- 胺

[0995] 在室温将 $LiAlH_4$(49.57mg,1.306mmol) 滴加倒 N-[1-(3- 氨基 -4- 吡啶基)-4- 哌啶基]-N- 甲基 - 氨基甲酸叔丁酯 (100mg,0.3264mmol) 在 THF 中的溶液中。将该反应体系在 50℃搅拌 3h,然后在室温搅拌,通过滴加湿 THF 使该反应混合物猝灭。使该反应混合物分配在 1N NaOH(50mL) 与乙醚 (50mL) 之间。干燥合并的有机层 ($MgSO_4$),蒸发,得到 4-(4-(二甲基氨基) 哌啶 -1- 基) 吡啶 -3- 胺,为黄色油状物。MS(ES+)221.1.

[0996] 制备例 N-4 :4-(3-(甲氧基甲基)-4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[0997]



[0998] 步骤 1 :2-(甲氧基甲基)-1- 甲基 -4-(3- 硝基吡啶 -4- 基) 哌嗪

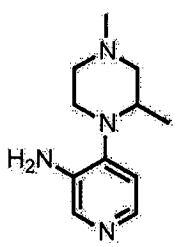
[0999] 在 0℃向在 DMF(2mL) 中的 (1- 甲基 -4-(3- 硝基吡啶 -4- 基) 哌嗪 -2- 基) 甲醇 (根据与制备例 N-1 步骤 1 中所述类似的方法制备) (250mg,0.9910mmol) 中加入 NaH(59.43mg,1.486mmol)。将该反应混合物搅拌 10min,然后滴加 MeI(281.3mg,123.4μL,1.982mmol)。将该反应混合物温至 RT,搅拌 2 小时。使该反应混合物上预洗涤的 SCX 柱,用 MeOH 冲洗,使用甲醇的氨溶液释放产物。减压浓缩氨萃取物。通过硅胶柱色谱法纯化残余物,用 1-15% MeOH :DCM 洗脱,得到 2-(甲氧基甲基)-1- 甲基 -4-(3- 硝基吡啶 -4- 基) 哌嗪 (84mg,32%)。MS(ES+)237.1.

[1000] 步骤 2 :4-(3-(甲氧基甲基)-4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1001] 向 2-(甲氧基甲基)-1- 甲基 -4-(3- 硝基吡啶 -4- 基) 哌嗪 (84mg,0.31mmol) 在甲醇中的溶液中加入批 Pd C(10%,湿的,Degussa)(10mg),将该反应混合物在室温在氢气气囊中搅拌过夜。过滤出催化剂,减压浓缩滤液,得到 4-(3-(甲氧基甲基)-4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺,为薄膜状物 (72mg,96%)。MS(ES+)267.1.

[1002] 制备例 N-5 :4-(2,4- 二甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1003]



[1004] 步骤 1 :2- 甲基 -1-(3- 硝基 -4- 吡啶基) 哌嗪

[1005] 向 3- 甲基 -4-(3- 硝基吡啶 -4- 基) 哌嗪 -1- 甲酸叔丁酯 (根据与制备例 N-1 步骤 1 中所述类似的方法制备) 在 DCM(5mL) 中的溶液中加入 TFA(1.445g,976.4μL,12.67mmol)。将该反应混合物在 RT 搅拌 48h,然后减压除去溶剂。将粗产物再溶于 MeOH,上 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗,用甲醇的氨溶液释放产物。减压浓缩氨萃取物,得到 2- 甲基 -1-(3- 硝基 -4- 吡啶基) 哌嗪 (334mg,71%)。MS(ES+)223.1.

[1006] 步骤 2 :2,4- 二甲基 -1-(3- 硝基吡啶 -4- 基) 哌嗪

[1007] 在 0℃向在 DMF 中的 2- 甲基 -1-(3- 硝基 -4- 吡啶基) 哌嗪 (1.5mL 的 0.3M,0.4500mmol) 中加入 NaH(18.00mg,0.4500mmol)。将该反应体系搅拌 10mins,然后加入 MeI(60.68mg,26.61μL,0.4275mmol)。将该反应混合物在 RT 搅拌 4 小时,通过添加水猝灭。使粗产物上 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗,用甲醇的氨溶液释放产物。减压浓缩氨萃取物。通过柱色谱法纯化残余物,用 1-15% MeOH :DCM 洗脱,得到 2,4- 二甲基 -1-(3- 硝基

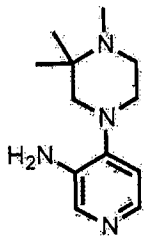
吡啶 -4- 基) 哌嗪。MS(ES+)237.2.

[1008] 步骤 3 :4-(2,4- 二甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1009] 将 2,4-二甲基 -1-(3- 硝基 -4- 吡啶基) 哌嗪 (89mg,0.3767mmol) 在甲醇 (4mL) 和批 Pd C(10%,湿的, Degussa)(20mg) 中的溶液在 RT 在氢气气氛中 (气囊) 氢化过夜。通过 C 盐柱过滤出催化剂,用甲醇洗涤。减压浓缩滤液,得到 4-(2,4- 二甲基哌嗪 -1- 基) 吡啶 -3- 胺 (71mg,91%)。MS(ES+)207.2.

[1010] 制备例 N-6 :4-(3,3,4- 三甲基哌嗪 -1- 基) 吡啶 -3- 胺

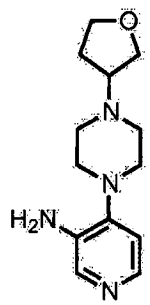
[1011]



[1012] 在 0℃向在 DMF(2mL) 中的 4-(3,3- 二甲基哌嗪 -1- 基) 吡啶 -3- 胺 (根据与制备例 N-1 中所述类似的方法制备)(120mg,0.5817mmol) 中加入 NaH(20.94mg,0.5235mmol)。将该反应混合物在 0℃搅拌 10mins,然后加入 MeI(276.3uL,0.5526mmol,2M 的 TBDME 溶液)。将该反应混合物温至 RT,在 RT 搅拌 2 小时。使粗产物上 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗,用甲醇的氨溶液释放产物。减压浓缩氨萃取物,得到 4-(3,3,4- 三甲基哌嗪 -1- 基) 吡啶 -3- 胺 (128mg,73%)。MS(ES+)221.1.

[1013] 制备例 N-7 :4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 胺

[1014]



[1015] 步骤 1 :1-(3- 硝基吡啶 -4- 基)-4-(四氢呋喃 -3- 基) 哌嗪

[1016] 向圆底烧瓶中加入在 MeCN(4mL) 中的 1-(3- 硝基 -4- 吡啶基) 哌嗪 (根据与制备例 N-1 步骤 1 中所述类似的方法制备)、二氢呋喃 -3(2H)- 酮 (98mg,1.13mmol) 和乙酸 (129uL,2.27mmol)。加入 $Na(OAc)_3BH$(482.4mg,2.27mmol),将该反应混合物在 RT 搅拌 1h。使该反应混合物分配在 EtOAC 与饱和 Na_2CO_3 水溶液之间。用 $MgSO_4$ 干燥有机萃取物,减压浓缩,得到 1-(3- 硝基吡啶 -4- 基)-4-(四氢呋喃 -3- 基) 哌嗪,为黄色固体。MS(ES+)279.1.

[1017] 步骤 2 :4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 胺

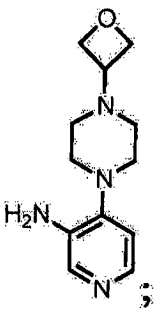
[1018] 将 1-(3- 硝基吡啶 -4- 基)-4-(四氢呋喃 -3- 基) 哌嗪 (316mg,1.13mmol) 在 MeOH(15mL)、批 Pd C(10%,湿的, Degussa)(120mg) 中的溶液在 RT 在氢气气氛中 (气囊) 搅拌过夜。通过 C 盐垫过滤该混合物,减压浓缩。将粗产物再溶于 MeOH,上 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗,用甲醇的氨溶液释放产物。减压浓缩氨萃取物,得到 4-(4-(四氢呋

喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 胺,为固体,将其不经进一步纯化用于下一步 (300mg,纯度 77%, 收率 82%)。MS(ES+)249.2.

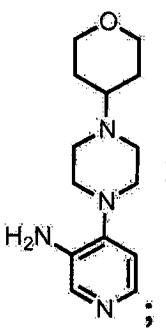
[1019] 根据与制备例 N-7 中所述类似的方法制备了如下氨基吡啶 :

[1020] 4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 胺 :

[1021]

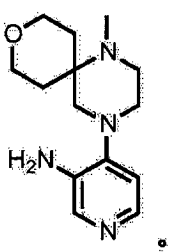


[1022] 4-(4-(四氢 -2H- 吡喃 -4- 基) 哌嗪 -1- 基) 吡啶 -3- 胺 :

[1023]  以及

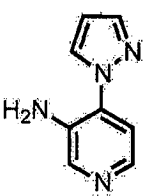
[1024] 4-(1- 甲基 -9- 氧杂 -1,4- 二氮杂螺 [5.5] 十一烷 -4- 基) 吡啶 -3- 胺 :

[1025]



[1026] 制备例 N-8 :4-(1H- 吡唑 -1- 基) 吡啶 -3- 胺

[1027]



[1028] 步骤 1 :3- 硝基 -4-(1H- 吡唑 -1- 基) 吡啶

[1029] 将吡唑 (150mg,2.2mmol) 和 Cs_2CO_3(526mg,1.6mmol) 在无水 MeCN(3.5mL) 中的混悬液在惰性气氛中搅拌 20min。然后加入 4- 氯 -3- 硝基 - 吡啶 (233mg,1.47mmol),在 75℃ 搅拌过夜。过滤出不溶物,减压浓缩滤液,得到 3- 硝基 -4-(1H- 吡唑 -1- 基) 吡啶,将其不

经进一步纯化使用 (410mg,98%)。MS(ES+)191.1.

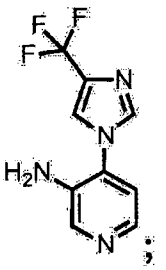
[1030] 步骤 2 :4-(1H- 吡唑 -1- 基) 吡啶 -3- 胺

[1031] 向 3- 硝基 -4-(1H- 吡唑 -1- 基) 吡啶 (410mg,2.15mmol) 在 MeOH(15mL) 中的溶液中加入批 Pd C(10%,湿的, Degussa)(129mg),将该反应混合物在 RT 在氢气气氛中 (气囊) 剧烈搅拌过夜。过滤出催化剂,减压浓缩滤液,得到 4-(1H- 吡唑 -1- 基) 吡啶 -3- 胺。(285mg,82%)。MS(ES+)161.1.

[1032] 根据与制备例 N-8 中所述类似的方法制备了如下氨基吡啶 :

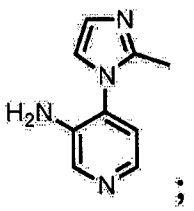
[1033] 4-(4-(三氟甲基)-1H- 咪唑 -1- 基) 吡啶 -3- 胺 :

[1034]



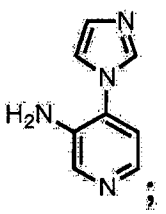
[1035] 4-(2- 甲基 -1H- 咪唑 -1- 基) 吡啶 -3- 胺 :

[1036]



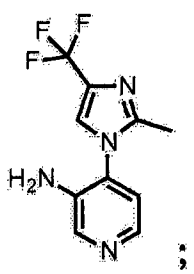
[1037] 4-(1H- 咪唑 -1- 基) 吡啶 -3- 胺 :

[1038]

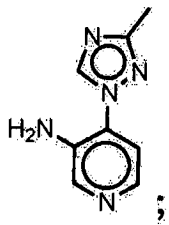


[1039] 4-(2- 甲基 -4-(三氟甲基)-1H- 咪唑 -1- 基) 吡啶 -3- 胺 :

[1040]



[1041] 4-(3- 甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶 -3- 胺 :

[1042]  以及

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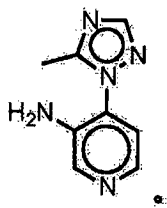
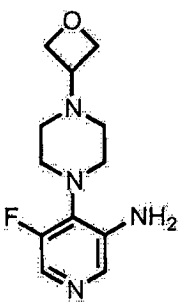
[1043] 4-(5-甲基-1H-1,2,4-三唑-1-基)吡啶-3-胺:

[1044]



[1045] 制备例 N-9:5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-胺

[1046]



[1047] 步骤 1:1-(3-氯-5-氟吡啶-4-基)哌嗪

[1048] 在 100mL 密封反应容器/瓶中,将 3-氯-5-氟-4-碘-吡啶 (5600mg,21.75mmol) 溶于 NMP(12mL)。向得到的澄清棕色溶液中加入 DIPEA(3.373g,4.546mL,26.10mmol),然后加入哌嗪 (2.810g,32.62mmol)。密封容器,在 120℃加热 18hrs。将该混合物冷却至 RT,真空浓缩,得到棕色树胶状物,通过根据色谱法纯化,用 DCM-DCM:MeOH:NH_3(90:10:1)100-0 — 0:100 梯度洗脱。采集包含澄清产物的级分,真空浓缩,得到 1-(3-氯-5-氟吡啶-4-基)哌嗪,为乳膏状固体 (3.52g,75%)。MS(ES+)216.0.

[1049] 步骤 2:1-(3-氯-5-氟-4-吡啶基)-4-(氧杂环丁烷-3-基)哌嗪

[1050] 向 1-(3-氯-5-氟吡啶-4-基)哌嗪 (900mg,4.173mmol) 在 THF(9.000mL) 中的混悬液中加入 3-氧杂环丁酮 (601.4mg,8.346mmol)。在 N_2 气氛中向该混合物中在 5min 内逐步加入三乙酰氧基硼氢化钠 (2.034g,9.598mmol),将该反应混合物在 RT 搅拌过夜。将 MeOH(2ml) 加入到烧瓶中,然后真空浓缩该混合物。使残余物分配在水 (50ml) 与 EtAOc(50ml) 之间。用 NH_4OH 将水相碱化至 pH 7-8。用盐水 (30ml) 洗涤合并的有机层,用 Na_2SO_4 干燥,过滤,真空浓缩,得到 1-(3-氯-5-氟-4-吡啶基)-4-(氧杂环丁烷-3-基)哌嗪,为乳膏状固体,将其不经进一步纯化用于下一步。MS(ES+)272.1.

[1051] 步骤 3:5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-胺

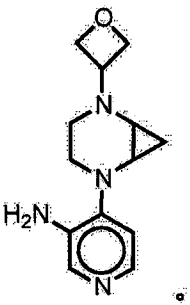
[1052] 在包含 1-(3-氯-5-氟-4-吡啶基)-4-(氧杂环丁烷-3-基)哌嗪 (800mg, 2.944mmol) 的压力试管中加入二噁烷 (6mL)。向该溶液中加入氨基甲酸叔丁酯 (517.3mg,

4.416mmol)、Cs_2CO_3(1.918g,5.888mmol)、xantphos(85.17mg,0.1472mmol)，然后加入$Pd_2(dba)_3$(134.8mg,0.1472mmol)。密封试管，在115℃加热60h。将该反应混合物冷却至RT，用C盐垫过滤。用EtOAc洗涤饼状物，真空浓缩合并的滤液，得到黑色油状物。将残余物溶于DCM(2ml)，加入TFA(3ml)。将得到的深棕色澄清溶液在RT搅拌2h，然后真空浓缩。使残余物上SCX-2(10g)柱。用MeOH(x3,CV)冲洗，然后用2M NH_3的MeOH溶液(x3CV)洗脱期望的产物。真空浓缩碱性洗脱液，得到深棕色油状物，通过硅胶色谱法纯化，用100-0—30:70梯度的DCM-DCM:MeOH:NH_3(90:10:1)洗脱。采集包含产物的级分，真空浓缩，得到5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-胺，为浅棕色固体。295mg：MS(ES+)253.2.

[1053] 根据与制备例N-9中所述类似的方法制备了如下氨基吡啶类：

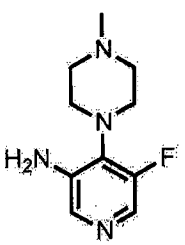
[1054] 4-(5-(氧杂环丁烷-3-基)-2,5-二氮杂双环[4.1.0]庚-2-基)吡啶-3-胺：

[1055]



[1056] 制备例N-10:5-氟-4-(4-甲基哌嗪-1-基)吡啶-3-胺

[1057]



[1058] 步骤1:1-(3-氯-5-氟吡啶-4-基)-4-甲基哌嗪

[1059] 将3-氯-5-氟-4-碘-吡啶(2.18g,8.468mmol)、1-甲基哌嗪(1.272g,1.409mL,12.70mmol)和DIPEA(2.189g,2.950mL,16.94mmol)在MeCN(13.08mL)中的溶液在130℃在微波中加热300min。真空浓缩该反应混合物，通过硅胶柱色谱法纯化，用0-10% MeOH/DCM洗脱。合并产物级分，真空浓缩，得到1-(3-氯-5-氟吡啶-4-基)-4-甲基哌嗪，为黄色/棕色油状物(1.16g,59%)。MS(ES+)230.0.

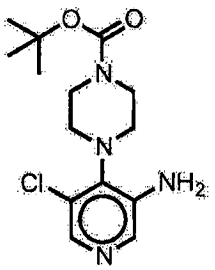
[1060] 步骤2:5-氟-4-(4-甲基哌嗪-1-基)吡啶-3-胺

[1061] 将氨基甲酸叔丁酯(709.9mg,6.060mmol)、Cs_2CO_3(3.291g,10.10mmol)、xantphos(146.1mg,0.2525mmol)、$Pd_2(dba)_3$(231.2mg,0.2525mmol)和1-(3-氯-5-氟-4-吡啶基)-4-甲基-哌嗪(1.16g,5.050mmol)在二噁烷(11.60mL)中的混合物在110℃加热1h。在室温加入氨基甲酸叔丁酯(709.9mg,6.060mmol)、xantphos(146.1mg,0.2525mmol)和$Pd_2(dba)_3$(231.2mg,0.2525mmol)，将该混合物在120℃

在微波中再加热 1h。然后通过 C 盐垫过滤该反应混合物，用甲醇洗涤，真空浓缩滤液。通过硅胶柱色谱法、使用 ISCO 柱 companion 系统纯化残余物，用 0-10％ MeOH/DCM 洗脱。合并产物级分，真空浓缩，得到 5- 氟 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 胺，为浅棕色粘性油状物 (642mg,60％）。MS(ES+)211.1.

[1062] 制备例 N-11 :4-(3- 氨基 -5- 氯吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯

[1063]



[1064] 步骤 1 :4-(3- 氯 -5- 硝基吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯

[1065] 将 4- 溴 -3- 氯 -5- 硝基 - 吡啶 (700mg,2.948mmol)、哌嗪 -1- 甲酸叔丁酯 (823.6mg,4.422mmol) 和 DIPEA(762.0mg,1.027mL,5.896mmol) 在 NMP(2.5mL) 中的混合物在 RT 搅拌过夜。使该反应混合物分配在 EtOAc 与水之间。用盐水洗涤合并的有机萃取物，用 $MgSO_4$ 干燥，减压浓缩，得到 4-(3- 氯 -5- 硝基吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯，将其不经进一步纯化用于下一步 (1g,99％）。MS(ES+)343.1.

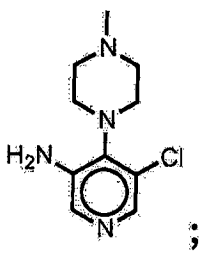
[1066] 步骤 2 :4-(3- 氨基 -5- 氯吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯

[1067] 向 4-(3- 氯 -5- 硝基吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯 (900mg,2.626mmol) 和 $ZnBr_2$(118.3mg,28.16μL,0.5252mmol) 在甲醇 (27.00mL) 中的溶液中加入批 Pd C(10％，湿的，Degussa)(300mg)。将该反应混合物在 RT 在氢气气氛中（气囊）搅拌 4h。过滤出催化剂，真空浓缩滤液，得到 4-(3- 氨基 -5- 氯吡啶 -4- 基）哌嗪 -1- 甲酸叔丁酯，将其不经进一步纯化使用 (820mg,99％）。MS(ES+)313.2.

[1068] 根据与制备例 N-11 中所述类似的方法制备了如下氨基吡啶类：

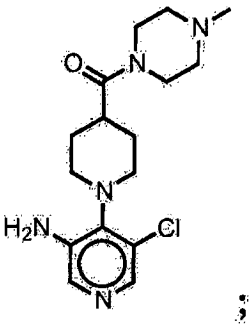
[1069] 5- 氯 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 胺：

[1070]



[1071] (1-(3- 氨基 -5- 氯吡啶 -4- 基）哌啶 -4- 基）(4- 甲基哌嗪 -1- 基）甲酮：

[1072]



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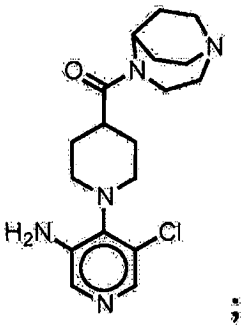
[1073] (1-(3-氨基-5-氯吡啶-4-基)哌啶-4-基)(1,4-二氮杂双环[3.2.2]壬-4-基)甲酮：

[1074]



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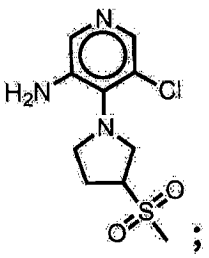
[1075] 5-氯-4-(3-(甲基磺酰基)吡咯烷-1-基)吡啶-3-胺：

[1076]



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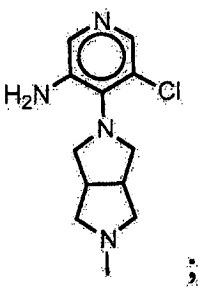
[1077] 5-氯-4-(5-甲基六氢吡咯并[3,4-c]吡咯-2(1H)-基)吡啶-3-胺：

[1078]



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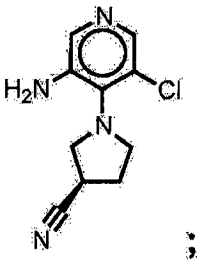
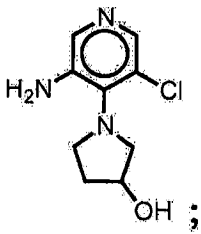
[1079] (R)-1-(3-氨基-5-氯吡啶-4-基)吡咯烷-3-甲腈：

[1080]



；

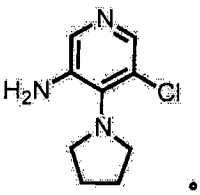
[1081] 1-(3-氨基-5-氯吡啶-4-基)吡咯烷-3-醇：

[1082]  以及

；

[1083] 5-氯-4-(吡咯烷-1-基)吡啶-3-胺：

[1084]



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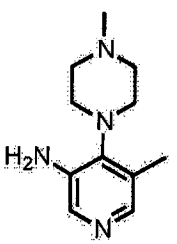
[1085] 制备例 N-12：1-甲基-4-(3-甲基-5-硝基吡啶-4-基)哌嗪

[1086]



[1087] 步骤 1：1-甲基-4-(3-甲基-5-硝基-4-吡啶基)哌嗪

[1088] 在氮气气氛中向烘干的烧瓶中加入 1-(3-溴-5-硝基-4-吡啶基)-4-甲基-哌嗪(根据与制备例 N-1 步骤 1 中所述类似的方法由 3-溴-4-氯-5-硝基吡啶合成 (750mg, 2.491mmol)、Pd_2dba_3(34.21mg,0.03736mmol) 和 X-Phos(35.62mg,0.07473mmol)。加入无水 THF(37.50mL),然后加入 1,4-二氮杂双环 [2.2.2] 辛烷三甲基 alumane(638.6mg, 2.491mmol)。将该反应体系回流加热 2 小时,然后冷却至环境温度。使该反应混合物分配在水与 EtOAc 之间。用盐水洗涤合并的有机萃取物,干燥 ($MgSO_4$),真空浓缩。通过硅胶柱色谱法、使用 ISCO 柱 companion 系统 (24g 柱,乙酸乙酯 / 石油醚 (0-100% EtOAc)) 纯化残余物,得到 1-甲基-4-(3-甲基-5-硝基-4-吡啶基)哌嗪,为黄色油状物 (290mg,49%)。MS(ES+)237.1.

[1089] 步骤 2：5-甲基-4-(4-甲基哌嗪-1-基)吡啶-3-胺

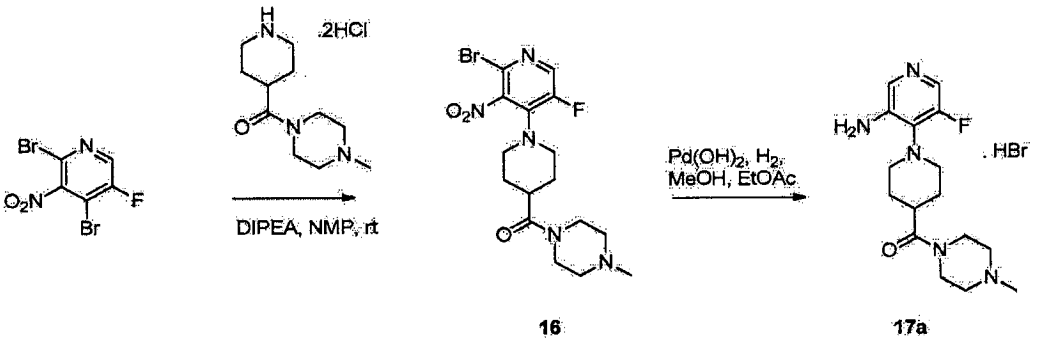
[1090] 将批 Pd C,(10%,湿的,Degussa)(130.6mg,0.1227mmol) 与 1-甲基-4-(3-甲

基 -5- 硝基 -4- 吡啶基) 哌嗪 (290mg,1.227mmol) 在甲醇 (5.800mL) 中的混悬液在 rt 在氢气气氛中 (气囊) 搅拌过夜。通过 C 盐垫过滤该反应混合物,用甲醇和乙酸乙酯洗涤,真空浓缩滤液,得到 5- 甲基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺,为黄色油状物 (243mg,96%)。MS(ES+)207.1.

[1091] 制备例 N-13 :(1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 基)(4- 甲基哌嗪 -1- 基) 甲酮 (氢溴酸盐)17a

[1092] 方案 5

[1093]



[1094] 步骤 1 :(1-(2- 溴 -5- 氟 -3- 硝基吡啶 -4- 基) 哌啶 -4- 基)(4- 甲基哌嗪 -1- 基) 甲酮 16

[1095] 向圆底烧瓶中加入在 NMP(160mL) 中的 (4- 甲基哌嗪 -1- 基)-(4- 哌啶基) 甲酮二盐酸盐 (16.45g,57.89mmol) 和 DIPEA(23.20g,31.27mL,179.5mmol)。加入 2,4- 二溴 -5- 氟 -3- 硝基 - 吡啶 (17.36g,57.89mmol),将该反应混合物在室温在氮气气氛中搅拌过夜。再加入 (4- 甲基哌嗪 -1- 基)-(4- 哌啶基) 甲酮二盐酸盐 (1.65g,0.1eq) 和 DIPEA(1mL,0.1eq),在室温再搅拌 3h。用 EtOAc 稀释该混合物,用水 (3x) 洗涤。用 EtOAc(3x) 萃取水层,合并合并的有机萃取物,用盐水洗涤,干燥 (硫酸钠),过滤,真空浓缩。通过色谱法纯化粗产物 (330g SiO_2,0 — 5% MeOH(包含 10% 氢氧化铵)/DCM),得到产物,为黄色固体 (20.24g,81%)。MS(ES+)432.0.

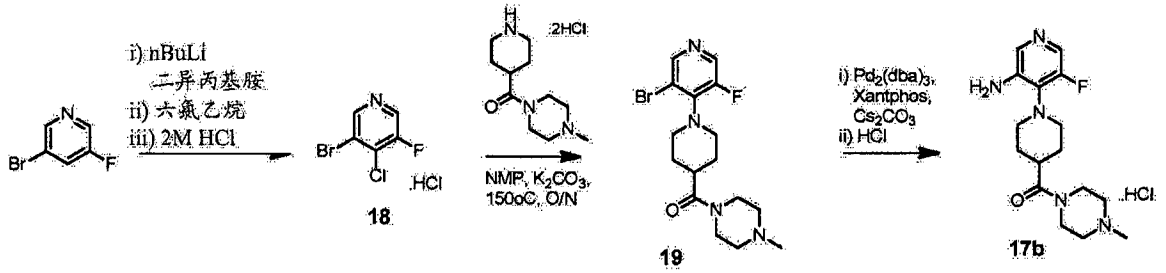
[1096] 步骤 2 :(1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 基)(4- 甲基哌嗪 -1- 基) 甲酮氢溴酸盐 17a

[1097] 将 [1-(2- 溴 -5- 氟 -3- 硝基 -4- 吡啶基)-4- 哌啶基]-(4- 甲基哌嗪 -1- 基) 甲酮 16(20.24g,47.04mmol) 溶于 / 混悬于 MeOH(389mL)/EtOAc(78mL),加入 $Pd(OH)_2$(1.651g,2.352mmol)。通过真空 / 氮气循环 (x5) 给得到的混合物脱气,通过真空 / 氢气循环 (x5) 交换气体。将该反应混合物在氢气气氛中 (气囊) 剧烈搅拌 6hrs。再加入 $Pd(OH)_2$(4.95g),将该反应混合物在氢气气氛中搅拌过夜。通过 C 盐过滤该混合物,用甲醇充分洗涤。真空浓缩滤液,得到橙色树胶状物。加入约 150mL 乙醇,使该混合物在 buchii 上选旋转 10mins,在此过程中黄色沉淀形成。将该混悬液超声处理 5mins,然后通过过滤采集固体,用少量乙醇洗涤,通过抽吸干燥 1h,得到产物,为淡黄色固体。通过真空浓缩滤液得到第二批粗产物。然后将残余物在少量乙醇中搅拌成淤浆,超声处理 5mins,然后通过过滤采集固体,通过抽吸干燥,得到第二批产物,为黄色固体。合并两批产物,得到产物,为黄色固体 (15.8g,79%)。MS(ES+)322.2.

[1098] 制备例 N-14：(1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)(4-甲基哌嗪-1-基)甲酮(盐酸盐)17b

[1099] 方案 6

[1100]



[1101] 步骤 1：3-溴-4-氯-5-氟吡啶盐酸盐 18

[1102] 向冷却至-78℃的二异丙基胺(6.899g,9.555mL,68.18mmol)在 THF(75mL)中的溶液中加入丁基锂(25mL 的 2.5M 己烷溶液,62.5mmol)。将该反应混合物温至-20℃,然后冷却回-78℃。滴加 3-溴-5-氟-吡啶(10g,56.82mmol)在 THF(25mL)中的溶液,保持温度低于-70℃(约 30mins)。将该反应混合物在-78℃搅拌 30min,然后滴加 1,1,1,2,2,2-六氯乙烷(14.8g,62.5mmol)在 THF(20mL)中的溶液,保持温度低于-70℃(在约 30mins 内)。将该混合物在-78℃搅拌 20 分钟,温至室温,冷却回 0℃,用水(100mL)猝灭。然后加入 EtOAc(400mL),分离有机层,用水(2x)、盐水(1x)洗涤,干燥($MgSO_4$),过滤,真空浓缩,得到棕色固体。将固体在戊烷(100mL)中研磨 10 分钟,然后过滤。真空浓缩滤液,得到产物,为棕色油状物,静置时变成结晶固体,11.85g,89%)。^1H NMR(DMSO-d6) δ 8.78(s,1H),8.76(s,1H)。

[1103] 向 3-溴-4-氯-5-氟-吡啶(7.56g,32.18mmol)在戊烷(100mL)中的溶液中加入氯化氢(2M 的乙醚溶液)(17.7mL 的 2M,35.4mmol)。即刻形成灰白色沉淀。将该混合物搅拌 5 分钟,然后通过过滤采集光标条,用戊烷洗涤,通过抽吸干燥,得到期望的产物,为灰白色固体(4.79g,60%)。^1H NMR(DMSO-d6) δ 8.77(s,1H),8.75(s,1H)。

[1104] 步骤 2：(1-(3-溴-5-氟吡啶-4-基)哌啶-4-基)(4-甲基哌嗪-1-基)甲酮 19

[1105] 将(4-甲基哌嗪-1-基)-(4-哌啶基)甲酮二盐酸盐(50.65g,178.2mmol),3-溴-4-氯-5-氟-吡啶盐酸盐 18(40g,162mmol)和碳酸二钾(94.04g,680.4mmol)在 NMP(400mL)中的混合物在 150℃加热过夜。将该混合物冷却至室温,然后过滤,以除去无机盐,真空浓缩滤液。将残余物溶于 EtOAc(800mL),用盐水(100mL x 4)洗涤,干燥($MgSO_4$),过滤,真空浓缩,得到棕色粘性油状物。通过硅胶柱纯化该残余物(约 800g 硅胶),使产物上 DCM 中的硅胶,然后用 3%甲醇(包含 10%氢氧化铵)/DCM 洗脱,得到期望的产物,为棕色油状物,静置时结晶(27.44g,44%)。MS(ES+)387.1.

[1106] 步骤 3：(1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)(4-甲基哌嗪-1-基)甲酮盐酸盐 17b

[1107] 在圆底烧瓶中在 N_2 气氛中将 $Pd_2(dba_3)$(3.818g,4.169mmol)和 Xantphos(4.824g,8.337mmol)加入到脱气的(3x 真空/N_2 循环)的二苯基甲亚胺(16.62g,15.39mL,91.71mmol)、[1-(3-溴-5-氟-4-吡啶基)-4-哌啶基]-(4-甲基哌嗪-1-基)甲酮 19(32.12g,83.37mmol)、氨基甲酸叔丁酯(3.649g,31.15mmol)和 Cs_2CO_3(81.49g,

250.1mmol) 在二噁烷 (550mL) 中的混合物中。通过 2x 真空 /N_2循环给该反应混合物充氮气，然后在 100℃在气氛中 N_2搅拌过夜。将该混合物冷却至室温，然后分配在 EtOAc(1L) 与水 (100mL) 之间。分离有机层，用水 (2x 100mL)、盐水 (1x 100mL) 洗涤，干燥 ($MgSO_4$)，过滤，真空浓缩，得到深橙色粘性油状物 (56.15g)。然后将该粗残余物溶于 THF(482mL) 和氯化氢 (300mL 的 2M，600mmol)，将该混合物在 60℃加热 30 分钟。真空除去 THF，用 EtOAc(2x) t 洗涤剩余的水溶液，然后用 2M NaOH 溶液 (约 310mL) 碱化至 pH ＝ 8，用 EtOAc(3x) 萃取。用盐水 (1x) 洗涤合并的有机萃取物，干燥 ($MgSO_4$)，过滤，真空浓缩，得到橙色固体 (25.44g)。将橙色固体溶于二噁烷 (300mL)，然后在 10mins 内缓慢地加入 4M HCl 的二噁烷溶液 (19.8mL，79.16mmol)。将该混合物搅拌 20 分钟，通过过滤采集形成的沉淀，用二噁烷 (约 100mL)、乙醚 (100mL) 洗涤，通过抽吸干燥，得到期望的产物，为白色固体 (25.13g，84％)。MS(ES+) 322.2.

[1108] 步骤 3a：(1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 基)(4- 甲基哌嗪 -1- 基) 甲酮 17

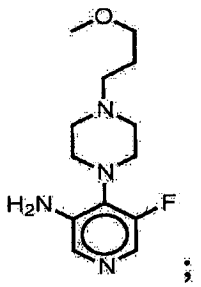
[1109] 在上述步骤 3 的可替代方法中，在 N_2气氛中将三 (二亚苄基丙酮) 二钯 (1.189g，1.298mmol) 和 xantphos(1.502g，2.596mmol) 加入到脱气的 (3x 真空 /N_2循环) [1-(3- 溴 -5- 氟 -4- 吡啶基)-4- 哌啶基]-(4- 甲基哌嗪 -1- 基) 甲酮 19(10g，25.96mmol) 和 Cs_2CO_3(16.92g，51.92mmol) 在二噁烷 (150mL) 中的混合物中。将该混合物在 100℃搅拌过夜。将该反应该体系冷却至环境温度，过滤出沉淀，用 EtOAc(50mL) 洗涤。使滤液分配在 EtOAc 与水之间。用水、盐水洗涤合并的有机层，干燥 ($MgSO_4$)，真空浓缩，得到 N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基] 氨基甲酸叔丁酯，为红色固体，将其不经进一步纯化用于下一步。MS(ES+) 422.2.

[1110] 向 N-[5- 氟 -4-[4-(4- 甲基哌嗪 -1- 羰基)-1- 哌啶基]-3- 吡啶基] 氨基甲酸叔丁酯 (3.34g，7.924mmol) 在二噁烷 (25mL) 中的混悬液中加入 HCl(4M 的二噁烷溶液)(8mL 的 4M)，将该混合物在 40℃加热过夜。将该混合物冷却至 RT，通过过滤采集固体，用二噁烷 (15mL)、然后用 EtOAc(2x 20ml) 洗涤，真空干燥，得到白色固体，使其分配在 EtOAc(70ml) 与 1M 碳酸钠 (50ml) 之间。干燥合并的有机萃取物，真空浓缩，得到 2.26g 灰白色固体，将其在 MeCN(5mL) 中搅拌成淤浆。通过过滤采集固体，用少量 MeCN(3 — 5mL) 洗涤，通过抽吸干燥，得到 (1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 基)(4- 甲基哌嗪 -1- 基) 甲酮，为白色固体。MS(ES+) 322.1.

[1111] 使用与制备例 N-13 或制备例 N-14 类似的方法制备了如下氨基吡啶中间体：

[1112] 5- 氟 -4-(4-(3- 甲氧基丙基) 哌嗪 -1- 基) 吡啶 -3- 胺：

[1113]



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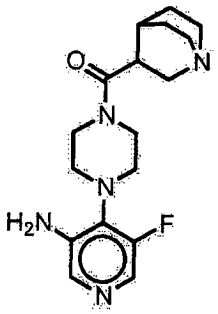
[1114] (4-(3-氨基-5-氟吡啶-4-基)哌嗪-1-基)(奎宁环-3-基)甲酮：

[1115]



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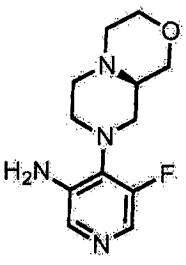
[1116] (R)-5-氟-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-胺：

[1117]



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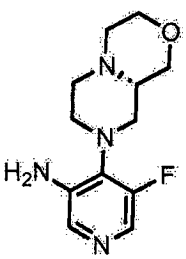
[1118] (S)-5-氟-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-胺：

[1119]



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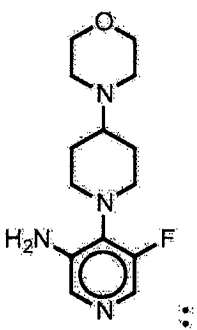
[1120] 5-氟-4-(4-吗啉代哌啶-1-基)吡啶-3-胺：

[1121]



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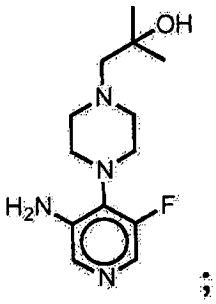
[1122] 1-(4-(3-氨基-5-氟吡啶-4-基)哌嗪-1-基)-2-甲基丙-2-醇：

[1123]



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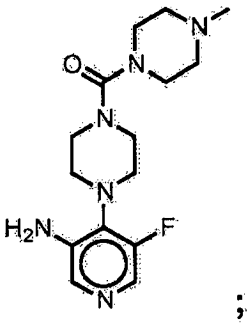
[1124] (4-(3-氨基-5-氟吡啶-4-基)哌嗪-1-基)(4-甲基哌嗪-1-基)甲酮：

[1125]



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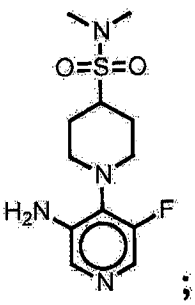
[1126] 1-(3-氨基-5-氟吡啶-4-基)-N,N-二甲基哌啶-4-磺酰胺：

[1127]



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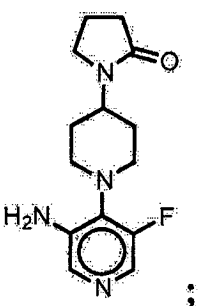
[1128] 1-(1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)吡咯烷-2-酮：

[1129]



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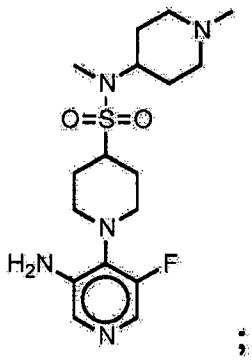
[1130] 1-(3-氨基-5-氟吡啶-4-基)-N-甲基-N-(1-甲基哌啶-4-基)哌啶-4-磺酰胺：

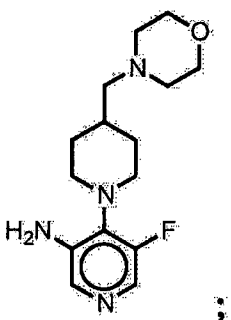
[1131]



;

[1132] 5- 氟 -4-(4-(吗啉代甲基) 哌啶 -1- 基) 吡啶 -3- 胺 :

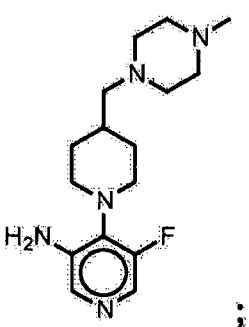
[1133]



;

[1134] 5- 氟 -4-(4-((4- 甲基哌嗪 -1- 基) 甲基) 哌啶 -1- 基) 吡啶 -3- 胺 :

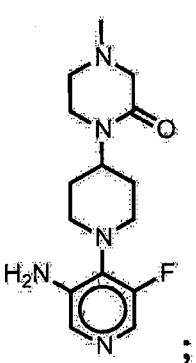
[1135]



;

[1136] 1-(1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 基)-4- 甲基哌嗪 -2- 酮 :

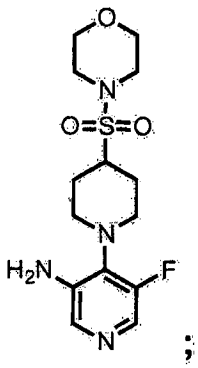
[1137]



;

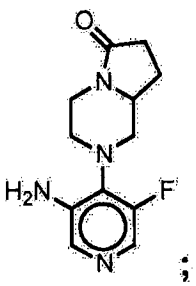
[1138] 5- 氟 -4-(4-(吗啉代磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺 :

[1139]



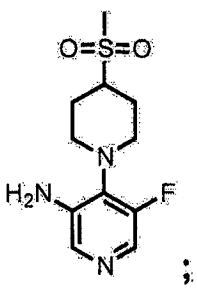
[1140] 2-(3-氨基-5-氟吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-6(2H)-酮：

[1141]



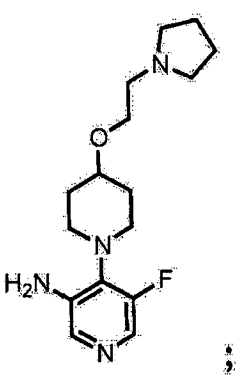
[1142] 5-氟-4-(4-(甲基磺酰基)哌啶-1-基)吡啶-3-胺：

[1143]



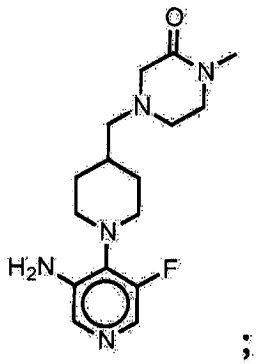
[1144] 5-氟-4-(4-(2-(吡咯烷-1-基)乙氧基)哌啶-1-基)吡啶-3-胺：

[1145]



[1146] 4-((1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)甲基)-1-甲基哌嗪-2-酮：

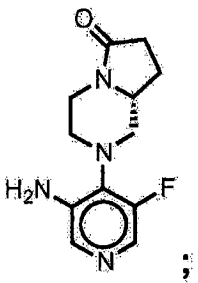
[1147]



;

[1148] (R)-2-(3-氨基-5-氟吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-6(2H)-酮:

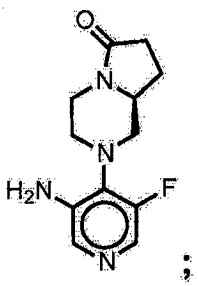
[1149]



;

[1150] (S)-2-(3-氨基-5-氟吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-6(2H)-酮:

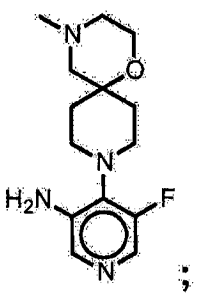
[1151]



;

[1152] 5-氟-4-(4-甲基-1-氧杂-4,9-二氮杂螺[5.5]十一烷-9-基)吡啶-3-胺:

[1153]



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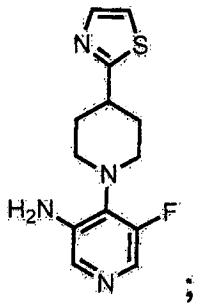
[1154] 5-氟-4-(4-(噻唑-2-基)哌啶-1-基)吡啶-3-胺:

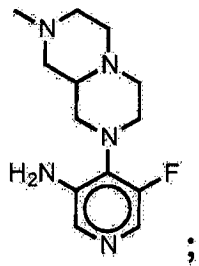
[1155]



;

[1156] 5- 氟 -4-(8- 甲基六氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -2(6H)- 基) 吡啶 -3- 胺 :

[1157]



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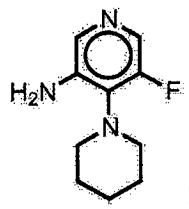
[1158] 5- 氟 -4-(哌啶 -1- 基) 吡啶 -3- 胺 :

[1159]



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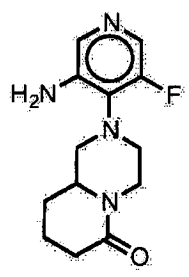
[1160] 2-(3- 氨基 -5- 氟吡啶 -4- 基) 六氢 -1H- 吡啶并 [1,2-a] 吡嗪 -6(2H)- 酮 :

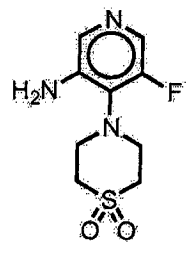
[1161]



;

[1162] 4-(3- 氨基 -5- 氟吡啶 -4- 基) 硫吗啉 1,1- 二氧化物 :

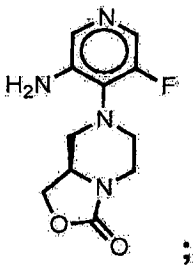
[1163]



;

[1164] (R)-7-(3-氨基-5-氟吡啶-4-基)四氢-1H-噁唑并[3,4-a]吡嗪-3(5H)-酮：

[1165]



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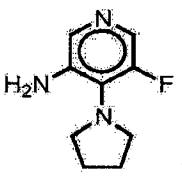
[1166] 5-氟-4-(吡咯烷-1-基)吡啶-3-胺：

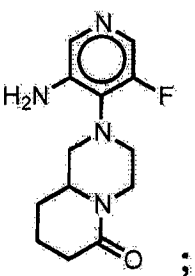
[1167]



；

[1168] 2-(3-氨基-5-氟吡啶-4-基)六氢-1H-吡啶并[1,2-a]吡嗪-6(2H)-酮：

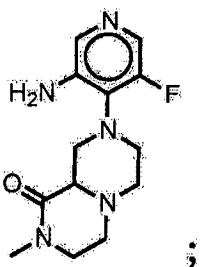
[1169]



；

[1170] 8-(3-氨基-5-氟吡啶-4-基)-2-甲基八氢-1H-吡嗪并[1,2-a]吡嗪-1-酮：

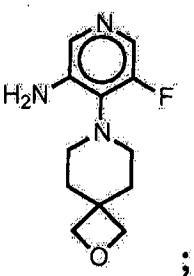
[1171]



；

[1172] 5-氟-4-(2-氧杂-7-氮杂螺[3.5]壬-7-基)吡啶-3-胺：

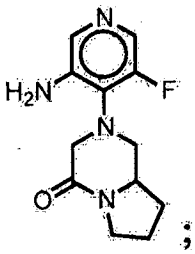
[1173]



；

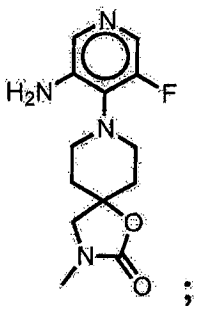
[1174] 2-(3-氨基-5-氟吡啶-4-基)六氢吡咯并[1,2-a]吡嗪-4(1H)-酮：

[1175]



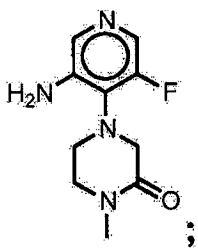
[1176] 8-(3-氨基-5-氟吡啶-4-基)-3-甲基-1-氧杂-3,8-二氮杂螺[4.5]癸-2-酮：

[1177]



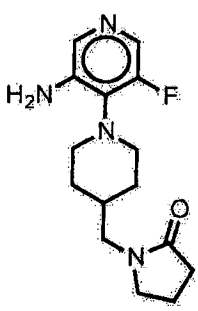
[1178] 4-(3-氨基-5-氟吡啶-4-基)-1-甲基哌嗪-2-酮：

[1179]



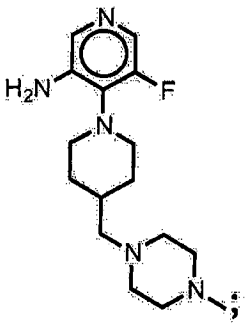
[1180] 1-((1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)甲基)吡咯烷-2-酮：

[1181]

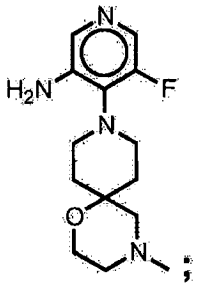


[1182] 5-氟-4-(4-((4-甲基哌嗪-1-基)甲基)哌啶-1-基)吡啶-3-胺：

[1183]

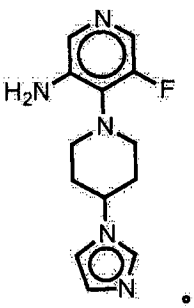


[1184] 5- 氟 -4-(4- 甲基 -1- 氧杂 -4,9- 二氮杂螺 [5.5] 十一烷 -9- 基) 吡啶 -3- 胺 :

[1185]  以及

[1186] 4-(4-(1H- 咪唑 -1- 基) 哌啶 -1- 基)-5- 氟吡啶 -3- 胺 :

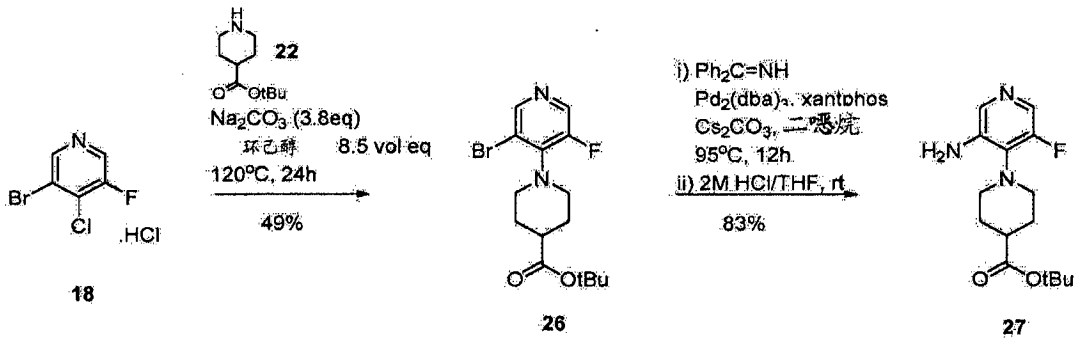
[1187]



[1188] 制备例 N-15 :1-(3- 氨基 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯

[1189] 方案 7a :

[1190]



[1191] 步骤 1 :1-(3- 溴 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯 26

[1192] 将安装了温度计、氮气管和高架搅拌器的 3L 梨形烧瓶在 40℃ (外部) 加热,然后加入环己醇 (750mL)、碳酸二钠 (129.8g,1.225mol)、3- 溴 -4- 氯 -5- 氟 - 吡啶 (盐酸 18)(137.5g,556.8mmol) 和用环己醇 (350mL) 冲洗的哌啶 -4- 甲酸叔丁酯 (123.8g,

668.2mmol)。将混合物加热至 120℃内部温度过夜 (18h)。从热板上取下反应混合物,冷却至室温。加入水 (687.5mL) 和 EtOAc(687.5mL),搅拌 10mins,然后转入分液漏斗。再加入 EtOAc(1.238L),混合,除去水相。再水 (687mL) 用洗涤有机相,除去水相,采集有机层。合并水相,用 EtOAc(687.5mL) 反萃取,除去水层,合并有机层与其它有机层。真空浓缩有机层 (水浴温度= 60℃,真空降至 2mBar),得到粘性棕色油状物。

[1193] 将油溶于 25% EtOAc/ 石油醚,然后通过短硅胶柱,用 25% EtOAc/ 石油醚洗脱至不再有产物出现。真空浓缩滤液,得到棕色油状物 127.1g。通过 ISCO companion(1.5Kg 硅胶,上 DCM,洗脱 0 — 20% EtOAc/ 石油醚) 再纯化产物,合并产物级分,真空浓缩,得到期望的产物,为淡黄色至乳膏状固体 (98g,49%收率)。^{1}H NMR(500MHz, DMSO-d6) δ 8.47(s, 1H),8.41(d,1H),3.39 - 3.36(m,2H),3.12(tt,2H),2.49 - 2.43(m,1H),1.91 - 1.87(m, 2H),1.71 - 1.64(m,2H) 和 1.43(s,9H)。MS(ES+)361.0.

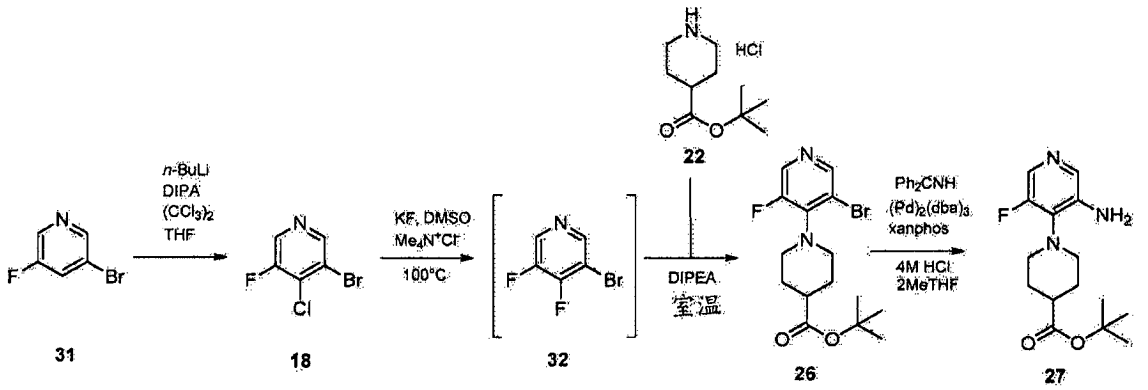
[1194] 步骤 2 :1-(3- 氨基 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯 27

[1195] 向 1-(3- 溴 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯 26(98g,272.8mmol)、二苯基甲亚胺 (59.34g,54.94mL,327.4mmol) 和 Cs2CO3(177.8g,545.6mmol) 在二噁烷 (1.274L) 中的溶液中加入 xantphos(15.78g,27.28mmol) 和 $Pd2(dba)_3$(12.49g,13.64mmol)。将该混合物在氮气气氛中在 95℃搅拌过夜。将该混合物冷却至室温,然后分配在 EtOAc(1000mL, 10vol eq.) 与水 (490mL,5vol eq.) 之间,混合,分离有机层。再用水 (1x 250mL)、盐水 (250mL) 洗涤有机层,干燥 ($MgSO_4$),过滤,真空浓缩。得到粗产物,为深红色粘性油状物 185.3g。

[1196] 将得到的产物油状物 (185.3g) 溶于 THF(882.0mL),加入 HCl(545.5mL 的 2M, 1.091mol)。将得到的混合物在室温搅拌 20mins。真空除去 THF,然后再加入 (HCl(2M) (588.0mL)。用 EtOAc(294.0mL) 将水层洗涤 2 次。在有机相和水相的萃取过程中形成大量黄色沉淀,通过过滤采集来自有机相和水相的固体,通过抽吸干燥。将混合的有机和水滤液加入到分液漏斗中,用 2M HCl(2x 200mL) 萃取。合并全部水相与烧结物上采集的固体 (产物),得到混悬液。使用 2M NaOH 将 pH 调整至 6,用 DCM(3x 600mL) 萃取。合并有机层,干燥 ($MgSO_4$),过滤,真空浓缩,得到淡橙色蜡状固体 112.2g。将该固体在 MeCN(200mL) 中搅拌成淤浆,搅拌 10mins,然后通过过滤采集,用少量 MeCN 洗涤,通过抽吸干燥,得到产物 27,为白色固体 (66.8g,83%收率)。^{1}H NMR(500MHz,DMSO-d6) δ 7.82(d,1H),7.63(d,1H),5.22(s, 2H),3.11-3.00(m,2H),2.91(tt,2H),2.36(tt,1H),1.88 - 1.83(m,2H),1.79-1.71(m,2H), 1.43(s,9H)。MS(ES+)297.1.

[1197] 方案 7b :1-(3- 氨基 -5- 氟 -4- 吡啶基) 哌啶 -4- 甲酸叔丁酯的可替代合成

[1198]



[1199] 步骤 1 :3- 溴 -4- 氯 -5- 氟吡啶盐酸盐 18

[1200] 将二异丙基胺 (101.2g,140.2mL,1.000mol) 在四氢呋喃 (1.148L) 中的溶液冷却至 -25℃ — -20℃。以维持反应温度低于 -20℃这样的速率加入丁基锂 (2.5M 的己烷溶液) (400mL 的 2.5M,1.000mol)(添加 20 分钟)。然后将该混合物在 1 小时内温至 4℃,再冷却至 -78℃。在 40 分钟内加入在四氢呋喃 (382.5mL) 中的 3- 溴 -5- 氟 - 吡啶 (153.0g,869.6mmol)。将该混合物搅拌 90 分钟,然后在 40 分钟内滴加 1,1,1,2,2,2- 六氯乙烷 (205.9g,869.6mmol) 在四氢呋喃 (350.0mL) 中的溶液。一旦添加完成,则将该混合物温至环境过夜。将该混合物冷却至 0℃,然后转入冷水 (2L),搅拌 20mins,然后加入 MTBE(2.5L),剧烈搅拌 30mins,然后转入分液漏斗,分离有机层。使水层返回反应容器,再用 MTBE(2.5L) 萃取,剧烈搅拌 10mins,然后转入分液漏斗,分离有机层。合并有机层,干燥 ($MgSO_4$),过滤,浓缩至得到棕色油状物。将该油状物溶于戊烷 (500ml) 和乙醚 (300ml)。在搅拌下缓慢地加入 HCl(2M 的乙醚溶液)(434.8mL 的 2M,869.6mmol)。在添加完成时,将该混合物搅拌 20mins,然后通过过滤采集固体,用乙醚系得,真空干燥 1h,得到产物 18,为黄褐色固体 (148.9g,69%) ;^1H NMR(500MHz, DMSO-d6) δ 8.77(2H, s) ;19F NMR(500MHz, DMSO-d6) δ -124.8 ;MS 210.8.

[1201] 步骤 2 :1-(3- 溴 -5- 氟吡啶 -4- 基) 哌啶 -4- 甲酸叔丁酯 26

[1202] 将 3- 溴 -4- 氯 -5- 氟 - 吡啶盐酸盐 18(62g,251.1mmol) 混悬于 DCM(600mL),搅拌。用冰浴冷却该混合物,缓慢地加入氢氧化钠 (276.2mL 的 1M,276.2mmol)。将得到的混合物搅拌 1 小时。使该混合物相分离。再加入 DCM/ 水以辅助相分离。在水相中保留一些焦油状的颗粒。用盐水洗涤有机相,干燥 ($MgSO_4$),过滤,浓缩。将残余物与庚烷一起研磨。通过 florsil 垫过滤庚烷溶液,用庚烷洗脱。将滤液浓缩至得到油状物,固化。得到 41g 游离碱。

[1203] 将充分搅拌的 3- 溴 -4- 氯 -5- 氟吡啶游离碱 (55g,0.26mol)、氟化钾 (31g,0.53mol) 和 Me_4NCl(5.8g,53mmol) 在 DMSO(400mL) 中的混合物加热至 130℃ 2 小时。将该反应混合物冷却至室温,加入哌啶 -4- 甲酸叔丁酯盐酸盐 22(66g,0.30mol) 和 DIPEA(65g,0.50mol)。将该反应混合物在室温搅拌过夜。真空蒸发溶剂。使残余物分配在 DCM/ 水之间。用水 (3x) 洗涤有机层,用 Na_2SO_4 干燥,用硅胶过滤,使用 DCM 作为洗脱剂。蒸发滤液,得到 1-(3- 溴 -5- 氟吡啶 -4- 基) 哌啶 -4- 甲酸叔丁酯 26(61g,65%),为淡黄色固体 ;1H NMR(500MHz, DMSO-d_6) δ 8.47(s,1H),8.41(d,1H),3.39 - 3.36(m,2H),3.12(tt,2H),2.49 - 2.43(m,1H),1.91 - 1.87(m,2H),1.71 - 1.64(m,2H) 和 1.43(s,9H) ;19F

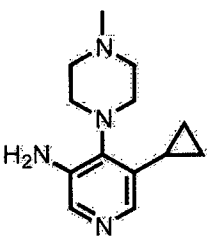
NMR(500MHz, DMSO-d6) δ -135.2 ;MS(ES+)361.0.

[1204] 步骤 3 :1-(3- 氨基 -5- 氟吡啶 -4- 基) 哌啶 -4- 甲酸叔丁基酯 27

[1205] 将 1-(3- 溴 -5- 氟吡啶 -4- 基) 哌啶 -4- 甲酸叔丁酯 26(800g,2.23mol) 溶于 1,4- 二噁烷 (7.5L)。一次加入二苯基甲亚胺 (484g,2.67mol),然后加入碳酸铯 (1.45Kg, 4.45mol)、xantphos(129g,223mmol) 和 $Pd_2(dba)_3$(102g,111mmol)。再加入 1,4- 二噁烷 (2.9L),将该混合物在氮气气氛中加热至 95℃,直到反应完成为止 (通过 HPLC 分析测定)。将该混合物冷却至 20℃,加入乙酸乙酯 (8L) 和水 (4L)。分离有机相,用水 (4L) 和盐水 (3.5L) 洗涤,用硫酸镁干燥,过滤。浓缩滤液,得到棕色油状物 (1.3Kg)。将该油状物溶于 2- 甲基四氢呋喃 (7.2L),在 20℃加入 2MHCl,将该混合物搅拌 30 分钟。分离水层,用 2M HCl(1.2L) 洗涤有机层。用 2M NaOH(5.4L, pH 8-9) 中和合并的水层。将产物萃取入 2- 甲基四氢呋喃 (14L,然后 2x5L)。用水 (1.6L) 洗涤合并的萃取物,浓缩有机溶液。将残余物在乙腈 (2L) 中搅拌成淤浆,过滤,干燥。得到产物 27,为白色固体 (568.7g, 86.5%) ;1H NMR(500MHz, DMSO-d_6) δ 7.82(d,1H),7.63(d,1H),5.22(s,2H),3.11-3.00(m, 2H),2.91(tt,2H),2.36(tt,1H),1.88 - 1.83(m,2H),1.79-1.71(m,2H),1.43(s,9H) ;19F NMR(500MHz, DMSO-d6) δ - 140.0 ;MS(ES+)297.1.

[1206] 制备例 N-16 :5- 环丙基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1207]



[1208] 步骤 1 :1-(3- 环丙基 -5- 硝基吡啶 -4- 基)-4- 甲基哌嗪

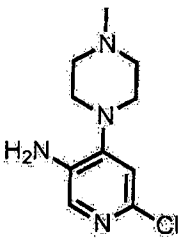
[1209] 给 1-(3- 溴 -5- 硝基 -4- 吡啶基)-4- 甲基 - 哌嗪 (由 1- 甲基哌嗪和 3- 溴 -4- 氯 -5- 硝基吡啶使用制备 N-1 步骤 1 的方法合成)(467.4mg,1.552mmol)、亚铁 ; 二氯 - 双 [环戊 -1,4- 二烯 -1- 基 (二苯基) 正膦鎓基 (phosphaniumyl)] 钯 (2-) ;二氯甲烷 (63.37mg,0.07760mmol)、碳酸钾 (429.0mg,3.104mmol) 和环丙基硼酸 (200.0mg, 2.328mmol) 在二噁烷 (5mL) 中的混合物脱气,充氮气 (x2)。将该反应体系在 100℃在密封试管中加热 18h。在室温通过 C 盐过滤该反应混合物,蒸发至干,得到 1-(3- 环丙基 -5- 硝基吡啶 -4- 基)-4- 甲基哌嗪,为深橙色固体,将其不经进一步纯化直接用于下一步反应 (288mg,66%)。MS(ES+)263.2

[1210] 步骤 2 :5- 环丙基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1211] 向 1-(3- 环丙基 -5- 硝基 -4- 吡啶基)-4- 甲基 - 哌嗪 (220.4mg,0.8403mmol) 在甲醇 (25mL) 中的混合物中加入批 Pd 碳 (10%,Degussa,6.387mg,0.006002mmol)。将该反应混合物在室温在氢气气囊中搅拌 7h。通过 C 盐垫过滤该反应体系,用 MeOH 洗涤,真空浓缩滤液,得到 5- 环丙基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺,为橙色残余物 (194mg,99%)。

[1212] 制备例 N-17 :6- 氯 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1213]



[1214] 步骤 1 :1-(2- 氯 -5- 硝基吡啶 -4- 基)-4- 甲基哌嗪

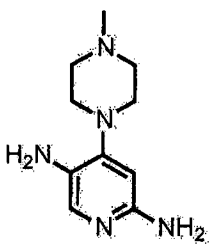
[1215] 在 0 ℃在氮气气氛中将在 THF(5mL) 中的 1- 甲基哌嗪 (298.5mg,330.6 μL, 2.980mmol) 加入到搅拌的 2,4- 二氯 -5- 硝基 - 吡啶 (500mg,2.591mmol) 和 DIPEA(401.8mg, 541.5 μL,3.109mmol) 在 THF(10mL) 中的溶液中。将该反应体系在环境温度搅拌 1 小时,然后真空除去溶剂。通过柱色谱法纯化残余物 (ISCO Companion,40g 柱,用 0 — 10% MeOH/DCM 溶液洗脱),得到 1-(2- 氯 -5- 硝基吡啶 -4- 基)-4- 甲基哌嗪,为黄色固体 (638mg,96% 收率)。MS(ES+) 257.1.

[1216] 步骤 2 :6- 氯 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺

[1217] 将 1-(2- 氯 -5- 硝基 -4- 吡啶基)-4- 甲基 - 哌嗪 (580mg,2.260mmol) 溶于 AcOH(20mL)/ 水 (2mL),加入 Fe(2.524g,45.20mmol)。将得到的混合物在 50℃搅拌 30 分钟。将该反应体系冷却至环境温度,然后上 50gSCX-2 柱 (用 MeOH 预洗涤)。用 DCM/MeOH 混合物洗涤柱,然后用 2M NH_3的 MeOH/DCM 混合物溶液洗脱产物。真空除去溶剂,得到 6- 氯 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -3- 胺,为紫色固体 (510mg,99% 收率)。MS(ES+) 227.1.

[1218] 制备例 N-18 :4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺

[1219]



[1220] 步骤 1 :4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺

[1221] 在 0 ℃在氮气气氛中将在 THF(5mL) 中的 1- 甲基哌嗪 (265.5mg,294.0 μL, 2.651mmol) 加入到搅拌的 4- 氯 -5- 硝基 - 吡啶 -2- 胺 (400mg,2.305mmol) 和 DIPEA(357.5mg,481.8 μL,2.766mmol) 在 THF(10mL) 中的混悬液中。将该反应体系在环境温度搅拌 90 小时,然后真空除去溶剂。从 DCM/MeOH 中研磨残余物,用 DCM/MeOH 溶液洗涤得到的沉淀。真空除去滤液,通过柱色谱法纯化残余物 (ISCO Companion,40g 柱,用 0 — 10% 2M NH_3的 MeOH/DCM 溶液洗脱),得到 4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺,为黄色固体 (355mg,65% 收率)。MS(ES+) 238.1.

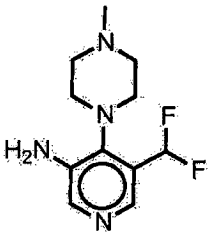
[1222] 步骤 2 :4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺

[1223] 将披 Pd C(10%,湿的,Degussa)(140mg,0.1316mmol) 加入到搅拌的 4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺 (355mg,1.496mmol) 在 EtOAc(5mL) 和 EtOH(50mL) 的混合物中的溶液中。将该反应体系放入氢气气氛中,在环境温度搅拌 16 小时。通过经 C 盐垫过滤除去催化剂,真空浓缩滤液,得到 4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺,为棕色固

体 (291mg,94%收率)。MS(ES+)208.1.

[1224] 制备例 N-19 :5-(二氟甲基)-4-(4-甲基哌嗪-1-基)吡啶-3-胺

[1225]



[1226] 步骤 1 :5-溴-4-(4-甲基哌嗪-1-基)吡啶-3-胺

[1227] 在 RT 将在 DCM(62.50mL) 中的 1-甲基哌嗪 (2.109g,21.06mmol) 加入到搅拌的 3-溴-4-氯-5-硝基-吡啶 (5000mg,21.06mmol) 和 DIPEA(3.266g,4.402mL,25.27mmol) 在 DCM(62.50mL) 中的溶液中。将该反应体系在环境温度搅拌 2H,然后真空浓缩。使残余物分配在饱和 $NaHCO_3$水溶液与 DCM 之间。干燥合并的有机萃取物,真空浓缩。将橙色固体混悬于乙酸 (60.00mL),然后加入铁 (7.059g,126.4mmol)。将该混合物在 50℃温热,搅拌 15min。将该混合物冷却至 RT,将 DCM :EtOAc(4 :1)(400mL) 加入到该反应体系中。使用预湿润的 C 盐柱 (25g) 过滤得到的棕色混悬液,再用 DCM :MeOH(4 :1)(200mL) 洗涤。真空浓缩合并的滤液,得到红色 / 棕色树胶状物,通过硅胶色谱法纯化 (Rf companion,80g 柱),用 100-0 — 20 :80 梯度的 DCM-DCM :MeOH :NE3(90 :10 :1) 洗脱。采集包含澄清产物的级分,真空浓缩,得到 5-溴-4-(4-甲基哌嗪-1-基)吡啶-3-胺,为粘性澄清淡黄色油状物,静置时固化。MS(ES+)273.1.

[1228] 步骤 2 :1-(3-溴-5-(2,5-二甲基-1H-吡咯-1-基)吡啶-4-基)-4-甲基哌嗪

[1229] 将在乙酸 (20mL) 中的 5-溴-4-(4-甲基哌嗪-1-基)吡啶-3-胺 (3000mg,11.06mmol)、己-2,5-二酮 (6.312g,6.487mL,55.30mmol) 在 70℃加热过夜。真空浓缩该反应混合物,使残余物分配在 EtOAc 与饱和 $NaHCO_3$水溶液之间。用盐水洗涤合并的有机萃取物,干燥 ($MgSO_4$),真空浓缩,得到油状物,通过硅胶过滤纯化,得到 1-(3-溴-5-(2,5-二甲基-1H-吡咯-1-基)吡啶-4-基)-4-甲基哌嗪,为灰白色固体。MS(ES+)351.1.

[1230] 步骤 3 :5-(2,5-二甲基-1H-吡咯-1-基)-4-(4-甲基哌嗪-1-基)烟醛

[1231] 将 1-[3-溴-5-(2,5-二甲基吡咯-1-基)-4-吡啶基]-4-甲基-哌嗪 (1250mg,3.579mmol) 在 THF(35.79mL) 中的溶液冷却至 -78 ℃,滴加 t-BuLi(2.105mL 的 1.7M,3.579mmol)。将该混合物在 -78 ℃搅拌 30mins,然后滴加 DMF(261.6mg,277.1μL,3.579mmol)。将该混合物在 -78℃搅拌 2h。用 MeOH(5mL) 使反应停止,温热至室温。用饱和氯化铵水溶液 (50mL) 洗涤该反应体系,用 EtOAc(100mL 和 50mL) 萃取。干燥合并的有机层 ($MgSO_4$),蒸发至得到橙色油状物。通过柱色谱法纯化 (EtOAc — EtOAc :MeOH 20%),得到 5-(2,5-二甲基-1H-吡咯-1-基)-4-(4-甲基哌嗪-1-基)烟醛,为淡黄色结晶固体。MS(ES+)299.2.

[1232] 步骤 4 :1-(3-(二氟甲基)-5-(2,5-二甲基-1H-吡咯-1-基)吡啶-4-基)-4-甲基哌嗪

[1233] 在 RT 向 5-(2,5-二甲基吡咯 1-1-基)-4-(4-甲基哌嗪-1-基)吡啶-3-甲醛 (100mg,0.3351mmol) 在二氯甲烷 (335.1μL) 中的溶液中加入 2-甲氧基-N-(2-甲氧基乙

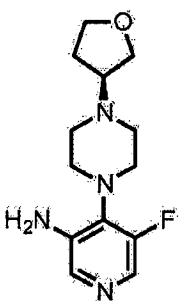
基)-N-(三氟-{4}-硫烷基)乙胺(370.8mg,1.676mmol),将该混合物回流加热18h。在室温用水(2mL)使反应停止,用二氯甲烷(2x 5mL)萃取,得到1-(3-(二氟甲基)-5-(2,5-二甲基-1H-吡咯-1-基)吡啶-4-基)-4-甲基哌嗪,为黄色油状物。MS(ES+)321.2.

[1234] 步骤5:5-(二氟甲基)-4-(4-甲基哌嗪-1-基)吡啶-3-胺

[1235] 将1-[3-(二氟甲基)-5-(2,5-二甲基吡咯-1-基)-4-吡啶基]-4-甲基-哌嗪(80mg,0.2497mmol)和NH_2OH(165.0mg,4.994mmol)在三乙胺(101.1mg,139.3μL,0.9988mmol)、乙醇(1mL)和H_2O(0.25mL)的混合物中的溶液回流加热20h。冷却至RT后,通过直接上SCX-2柱使反应停止,用MeOH、然后用NH_3/MeOH洗脱。真空浓缩碱性级分,得到5-(二氟甲基)-4-(4-甲基哌嗪-1-基)吡啶-3-胺,将其不经进一步纯化用于下一步。MS(ES+)243.1.

[1236] 制备例N-20:(S)-5-氟-4-(4-(四氢呋喃-3-基)哌嗪-1-基)吡啶-3-胺

[1237]



[1238] 步骤1:(S)-1-(3-氯-5-氟吡啶-4-基)-4-(四氢呋喃-3-基)哌嗪

[1239] 在0℃将MsCl(393.3mg,265.7μL,3.433mmol)加入到(3R)-四氢呋喃-3-醇(275mg,3.121mmol)和Et_3N(379.0mg,522.0μL,3.745mmol)在DCM(5mL)中的溶液中,将得到的溶液在RT搅拌过夜。用水(5mL)和DCM(5mL)稀释该反应混合物,分离各层。再用DCM(2x5mL)萃取水层,用饱和碳酸氢钠水溶液(1x 5mL)洗涤合并的有机萃取物,用$MgSO_4$干燥,真空浓缩。将残余物溶于n-BuOH(5mL),加入1-(3-氯-5-氟-4-吡啶基)哌嗪(1.010g,4.682mmol),将该反应混合物在118℃加热过夜。将该反应混合物冷却至RT,真空浓缩。通过硅胶柱色谱法纯化残余物(24g柱,0-100% EtOAc/石油醚)。合并产物级分,真空浓缩,得到(S)-1-(3-氯-5-氟吡啶-4-基)-4-(四氢呋喃-3-基)哌嗪,为灰白色固体。MS(ES+)288.1.

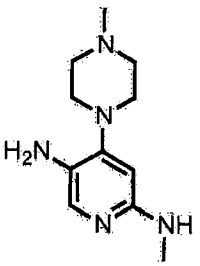
[1240] 步骤2:(S)-5-氟-4-(4-(四氢呋喃-3-基)哌嗪-1-基)吡啶-3-胺

[1241] 将BrettPhos预催化剂(pre-catalyst)(4.183mg,0.005250mmol)和BrettPhos(2.818mg,0.005250mmol)加入到氨基甲酸叔丁酯(153.7mg,1.312mmol)、叔丁醇钠物(128.7mg,1.339mmol)和1-(3-氯-5-氟-4-吡啶基)-4-[(3S)-四氢呋喃-3-基]哌嗪(75mg,0.2625mmol)在甲苯(1.500mL)中的溶液中,密封得到的混合物(反应体系在微波试管中),在100℃放入预热的干燥合成(drysyn)块,加热6h。再加入BrettPhos预催化剂(4.183mg,0.005250mmol)和BrettPhos(2.818mg,0.005250mmol),再密封该反应混合物,在100℃加热过夜。将该反应混合物冷却至RT,通过添加饱和NH_4Cl水溶液猝灭,然后通过C盐垫过滤,用乙酸乙酯洗涤。用乙酸乙酯(2x 5mL)萃取滤液,用$MgSO_4$干燥合并的有机萃取物,真空浓缩,得到淡黄色油状物(102mg)。将残余物溶于DCM(2mL),

加入 TFA(299.3mg,202.2μL,2.625mmol),将得到的溶于在 rt 搅拌 2h。真空浓缩该混合物,使其通过 SCX 柱,用 2M 氨的甲醇溶液洗脱产物。真空浓缩滤液,通过硅胶柱色谱法纯化,用 0-20% MeOH/DCM 洗脱 4g 柱。合并产物级分,真空浓缩,得到产物,为无色油状物。MS(ES+)267.2.

[1242] 制备例 N-21 :N2- 甲基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺

[1243]



[1244] 步骤 1 :1-(2- 氯 -5- 硝基吡啶 -4- 基)-4- 甲基哌嗪

[1245] 在 0℃在氮气气氛中将在 THF(1.5mL) 中的 1- 甲基哌嗪 (119.3mg,132.6μL,1.191mmol) 加入到搅拌的 2,4- 二氯 -5- 硝基 - 吡啶 (200mg,1.036mmol) 和 DIPEA(160.6mg,216.4μL,1.243mmol) 在 THF(3.000mL) 中的溶液中。将该反应体系在环境温度搅拌过夜。使该反应混合物分配在乙酸乙酯与 $NaHCO_3$(饱和水溶液) 之间。用盐水洗涤合并的有机层,用 $MgSO_4$ 干燥,减压浓缩,得到 1-(2- 氯 -5- 硝基 -4- 吡啶基)-4- 甲基 - 哌嗪。(100%) MS(ES+)257.1.

[1246] 步骤 2 :N- 甲基 -4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺

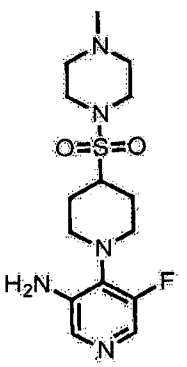
[1247] 将 1-(2- 氯 -5- 硝基 -4- 吡啶基)-4- 甲基 - 哌嗪 (265.9mg,1.036mmol) 和 2M 在 THF 中的甲胺 (2.590mL 的 2M,5.180mmol) 在密封试管中在 60℃加热过夜。通过硅胶色谱法纯化该混合物 (Companion 12g),用 0.5-15% MeOH :DCM 洗脱,得到 N- 甲基 -4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺 (243mg,93%)。MS(ES+)252.1.

[1248] 步骤 3 :N2- 甲基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺

[1249] 将 N- 甲基 -4-(4- 甲基哌嗪 -1- 基)-5- 硝基 - 吡啶 -2- 胺 (243mg,0.9670mmol) 溶于甲醇 (10mL),加入披 Pd C 湿的 Degussa(50mg,0.4698mmol)。将该反应体系抽真空,充 3 次氢气,保持在 RT 搅拌过夜。过滤出催化剂,减压除去溶剂,得到 N2- 甲基 -4-(4- 甲基哌嗪 -1- 基) 吡啶 -2,5- 二胺 (173mg,81%)。MS(ES+)222.1.

[1250] 制备例 N-22 :5- 氟 -4-(4-((4- 甲基哌嗪 -1- 基) 磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺

[1251]



[1252] 步骤 1 :1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 醇

[1253] 向 3- 氯 -5- 氟 -4- 碘 - 吡啶 (1g,3.885mmol) 在 NMP(1mL) 中的溶液中加入 DIPEA(753.1mg,1.015mL,5.828mmol) 和哌啶 -4- 醇 (589.4mg,5.828mmol),将该混合物加热至 120℃ 4 小时。用乙酸乙酯 (30ml) 稀释该混合物,用水 (20ml) 和盐水洗涤 2 次。用 $MgSO_4$ 干燥有机层,真空浓缩,得到黄色固体,通过柱色谱法纯化,使用 DCM 且然后使用 2% MeOH/DCM 作为洗脱剂,得到 1-(3- 氯 -5- 氟 -4- 吡啶基) 哌啶 -4- 醇。MS(ES+)231.0.

[1254] 步骤 2 :S- 乙硫代酸 (1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 基) 酯

[1255] 在 -20℃将 (NE)-N- 异丙氧基羰基亚氨基氨基甲酸异丙酯 (723.1mg,3.576mmol) 滴加到 1-(3- 氯 -5- 氟 -4- 吡啶基) 哌啶 -4- 醇 (750mg,3.251mmol) 和三苯膦 (937.9mg,828.5μL,3.576mmol) 在 THF 中的溶液中。搅拌 15mins 后,加入乙硫代 S- 酸 (272.2mg,255.6μL,3.576mmol),将该混合物温至室温,再搅拌 30 分钟。然后用乙酸乙酯 (30ml) 稀释该混合物,用水 (20ml) 和盐水洗涤 2 次。用 $MgSO_4$ 干燥有机层,真空浓缩,得到黄色固体,通过柱色谱法纯化,用 5/95 乙醚 / 石油醚洗脱,以洗脱副产物,然后用 10/90 乙醚 / 石油醚洗脱,合并相关级分,真空浓缩,得到 S- 乙硫代酸 (1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 基) 酯,为绿色固体。MS(ES+)289.0.

[1256] 步骤 3 :1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 磺酰氯

[1257] 向 HCl(1.038mL 的 2M,2.077mmol) 和 MeCN(8mL) 的混合物中加入 NCS(693.4mg,5.193mmol),将该混合物冷却至 10℃,搅拌至大部分 NCS(693.4mg,5.193mmol) 溶解。滴加 S- 乙硫代酸 [1-(3- 氯 -5- 氟 -4- 吡啶基)-4- 哌啶基] 酯 (500mg,1.731mmol) 在 MeCN(8mL) 中的溶液。将该溶液在 10℃搅拌 30 分钟,用乙醚稀释,用稀盐水洗涤。用 $MgSO_4$ 干燥有机层,真空浓缩,得到 1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 磺酰,为黄色固体。MS(ES+)313.0.

[1258] 步骤 4 :1-((1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 基) 磺酰基)-4- 甲基哌嗪

[1259] 向 1-(3- 氯 -5- 氟 -4- 吡啶基) 哌啶 -4- 磺酰氯 (400mg,1.277mmol) 在 DCM(5mL) 中的溶液中加入 TEA(129.2mg,178.0μL,1.277mmol),然后加入 1- 甲基哌嗪 (255.8mg,2.554mmol)。将该混合物在室温搅拌 1h。用乙酸乙酯 (30ml) 稀释该混合物,用水 (20ml) 和盐水洗涤 2 次。用 $MgSO_4$ 干燥有机层,真空浓缩,得到黄色固体。通过柱色谱法纯化产物,用 5/95 甲醇 /DCM 洗脱。合并相关级分,真空浓缩得到 1-((1-(3- 氯 -5- 氟吡啶 -4- 基) 哌啶 -4- 基) 磺酰基)-4- 甲基哌嗪,为绿色固体。MS(ES+)377.1.

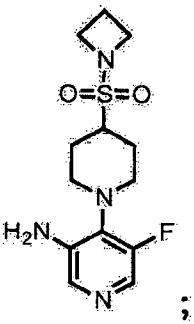
[1260] 步骤 5 :5- 氟 -4-(4-((4- 甲基哌嗪 -1- 基) 磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺

[1261] 用真空 / 氮气循环 (x5) 给氨基甲酸叔丁酯 (211.3mg,1.804mmol)、叔丁醇钠 (173.4mg,1.804mmol)、BrettPhos 预催化剂 (143.7mg,0.1804mmol) 和 BrettPhos(96.83mg,0.1804mmol) 脱气。加入 1-[[1-(3- 氯 -5- 氟 -4- 吡啶基)-4- 哌啶基] 磺酰基]-4- 甲基 - 哌嗪 (340mg,0.9022mmol) 在干甲苯 (9.884mL) 中的溶液,将得到的混合物加热至 80℃。在 80℃ 5 分钟后,将该反应体系冷却至 RT,分配在乙酸乙酯与水之间。用 $MgSO_4$ 干燥合并的有机层,真空浓缩,得到黄色固体。通过柱色谱法纯化黄色固体,使用 1% MeOH/DCM 洗脱副产物,然后 5-10% MeOH/DCM 洗脱产物。合并相关级分,真空浓缩,得到黄色固体。将其溶于 DCM(10mL),然后添加 TFA(1.029g,695.3μL,9.022mmol)。将该混合物在室温搅拌 2 小时。真空浓缩该混合物,得到 5- 氟 -4-(4-((4- 甲基哌嗪 -1- 基) 磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺,为淡橙色固体。MS(ES+)358.1.

[1262] 根据与方法 N-22 中所述类似的方法制备了如下胺类：

[1263] 4-(4-(氮杂环丁烷 -1- 基磺酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 胺：

[1264]



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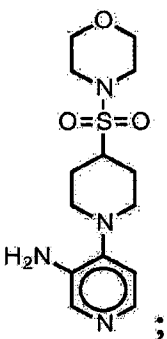
[1265] 4-(4-(吗啉代磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺：

[1266]



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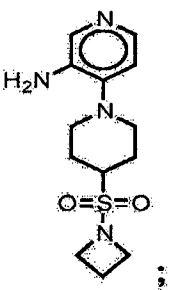
[1267] 4-(4-(氮杂环丁烷 -1- 基磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺：

[1268]



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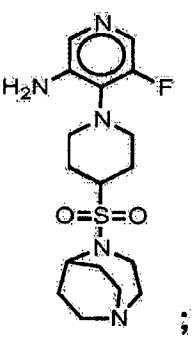
[1269] 4-(4-(1,4- 二氮杂双环 [3.2.2] 壬 -4- 基磺酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 胺：

[1270]



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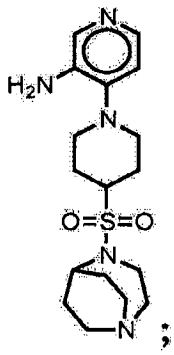
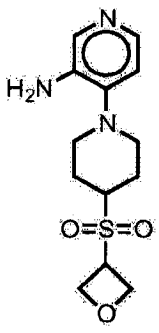
[1271] 4-(4-(1,4-二氮杂双环[3.2.2]壬-4-基磺酰基)哌啶-1-基)吡啶-3-胺：

[1272]

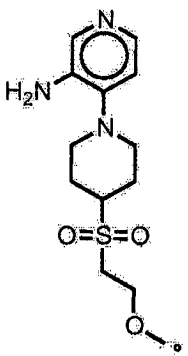


[1273] 4-(4-(氧杂环丁烷-3-基磺酰基)哌啶-1-基)吡啶-3-胺：

[1274]  以及

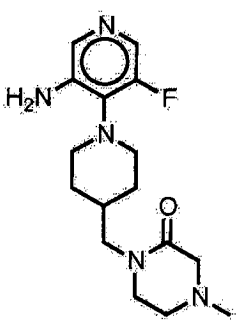
[1275] 4-(4-((2-甲氧基乙基)磺酰基)哌啶-1-基)吡啶-3-胺：

[1276]



[1277] 制备例N-23：1-((1-(3-氨基-5-氟吡啶-4-基)哌啶-4-基)甲基)-4-甲基哌嗪-2-酮

[1278]



[1279] 步骤 1 :4-(((甲基磺酰基)氧基)甲基)哌啶 -1- 甲酸叔丁酯

[1280] 在 0℃将甲磺酰氯 (186.3mg,125.9μL,1.626mmol) 滴加到搅拌的 4-(羟基甲基)哌啶 -1- 甲酸叔丁酯 (350mg,1.626mmol) 和 DIPEA(222.8mg,300.3μL,1.724mmol) 在 DCM(5mL) 中的溶液中。将该反应混合物在 16 小时内温至环境温度,然后用水处理。分离各相,用 DCM(x 3) 萃取水相。干燥 ($MgSO_4$) 合并的有机萃取物,过滤,真空浓缩,得到小标题化合物,为白色固体 (505mg, >100% 收率),直接使用,推定 100% 收率和纯度。MS(ES+-t-Bu)238.0.

[1281] 步骤 2 :4-((4- 甲基 -2- 氧代哌嗪 -1- 基)甲基)哌啶 -1- 甲酸叔丁酯

[1282] 将 60% 氢化钠的分散液 (84.55mg,2.114mmol) 加入到搅拌的 4- 甲基哌嗪 -2- 酮 (241.3mg,2.114mmol) 在 DMF(10mL) 中的溶液中,将该反应体系在环境温度搅拌 30 分钟。滴加在 DMF(5mL) 中的 4-(甲基磺酰基氧基甲基)哌啶 -1- 甲酸叔丁酯 (477mg,1.626mmol),将该反应体系在环境温度再搅拌 92 小时,然后在 50℃再搅拌 20 小时。将该反应体系冷却至环境温度,通过添加水使反应停止,用 EtOAc 萃取该混合物 (x3)。用盐水 (x 3) 洗涤合并的有机萃取物,干燥 ($MgSO_4$),过滤,真空浓缩。通过柱色谱法纯化残余物 (ISCO Companion, 40g 柱,用 0 — 10% MeOH/DCM 洗脱,载入 DCM),得到 4-((4- 甲基 -2- 氧代哌嗪 -1- 基)甲基)哌啶 -1- 甲酸叔丁酯产物,为无色油状物 (99mg,20% 收率)。MS(ES+)312.2.

[1283] 步骤 3 :4- 甲基 -1-(哌啶 -4- 基甲基)哌嗪 -2- 酮

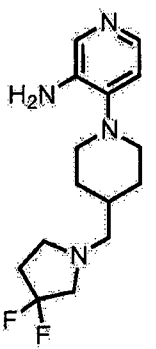
[1284] 将 TFA(1mL,12.98mmol) 加入到搅拌的 4-[(4- 甲基 -2- 氧代 - 哌嗪 -1- 基)甲基]哌啶 -1- 甲酸叔丁酯 (98mg,0.3147mmol) 在 DCM(2mL) 中的溶液中,将该反应体系在环境温度搅拌 16 小时。真空除去溶剂,将残余物与 DCM(x 2) 和乙醚 (x 2) 一起共沸。使残余物通过 5g SCX-2 柱,用 MeOH/DCM 混合物洗涤。通过用 2M NH_3的 MeOH/DCM 混合物的溶液洗涤柱洗脱产物。真空除去溶剂,得到 4- 甲基 -1-(哌啶 -4- 基甲基)哌嗪 -2- 酮,为无色油状物 (65mg,98% 收率)。MS(ES+)212.0.

[1285] 步骤 4 :4-(((甲基磺酰基)氧基)甲基)哌啶 -1- 甲酸叔丁酯

[1286] 遵循制备例 N-13。MS(ES+)322.1.

[1287] 制备例 N-24 :4-(4-((3,3- 二氟吡咯烷 -1- 基)甲基)哌啶 -1- 基)吡啶 -3- 胺

[1288]



[1289] 步骤 1 :4-((3,3- 二氟吡咯烷 -1- 基)甲基)哌啶 -1- 甲酸叔丁酯

[1290] 将 3,3- 二氟吡咯烷酮 (盐酸 (1))(965mg,6.722mmol),4- 甲酰基哌啶 -1- 甲酸叔丁酯 (1.720g,8.066mmol)、DIPEA(955.6mg,1.288mL,7.394mmol) 和碎 4A MS(965mg,) 在 DCE(30mL) 中的混合物在环境温度搅拌 3 小时。加入 $NaBH(OAc)_3$(钠离子 (1))(2.848g,

13.44mmol)，将该反应体系在环境温度再搅拌 16 小时。通过 C 盐过滤该混合物（用 DCM 洗涤），真空浓缩滤液。通过柱色谱法纯化残余物（ISCO Companion，80g 柱，用 0 － 10％ MeOH/DCM 洗脱，载入 DCM），得到 4-((3,3- 二氟吡咯烷 -1- 基）甲基）哌啶 -1- 甲酸叔丁酯，为无色油状物，直接脱保护，推定 100％收率和纯度。MS(ES+)305.1.

[1291] 步骤 2：4-((3,3- 二氟吡咯烷 -1- 基）甲基）哌啶

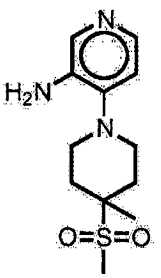
[1292] 将 TFA(766.5mg,517.9μL,6.722mmol) 加入到搅拌的 4-[(3,3- 二氟吡咯烷 -1- 基）甲基］哌啶 -1- 甲酸叔丁酯 (2.046g,6.722mmol) 在 DCM(15mL) 中的溶液中，将该反应体系在环境温度搅拌 66 小时。真空除去溶剂，将残余物与 DCM(x 2) 和乙醚 (x 2) 一起共沸。使残余物通过 50g SCX-2 柱，用 MeOH/DCM 混合物洗涤。通过用 2M NH_3的 MeOH/DCM 混合物的溶液洗涤柱洗脱产物。真空除去溶剂，得到 4-((3,3- 二氟吡咯烷 -1- 基）甲基）哌啶，为灰白色固体 (1.15g，2 步内 84％收率）。MS(ES+)205.1.

[1293] 步骤 3：4-(4-((3,3- 二氟吡咯烷 -1- 基）甲基）哌啶 -1- 基）吡啶 -3- 胺

[1294] 遵循制备例 N-1。MS(ES+)297.2.

[1295] 制备例 N-25：4-(4- 甲基 -4-（甲基磺酰基）哌啶 -1- 基）吡啶 -3- 胺

[1296]



[1297] 步骤 1：1- 硫杂 -6- 氮杂螺 [2.5] 辛烷 -6- 甲酸叔丁酯

[1298] 向 1- 氧杂 -8- 氮杂螺 [2.5] 辛烷 -8- 甲酸叔丁酯 (1g,4.689mmol) 和硫脲 (356.9mg,4.689mmol) 的混合物中加入水，将该混合物在室温搅拌 72h。使该反应混合物分配在 DCM 与水之间，用盐水洗涤有机萃取物，干燥 ($MgSO_4$)，浓缩，得到 1- 硫杂 -6- 氮杂螺 [2.5] 辛烷 -6- 甲酸酯，为淡黄色油状物，静置时固化 (910mg，84％）。MS(ES+-t-Bu)173.9.

[1299] 步骤 2：4- 巯基 -4- 甲基哌啶 -1- 甲酸叔丁酯

[1300] 向 1- 硫杂 -6- 氮杂螺 [2.5] 辛烷 -6- 甲酸叔丁酯 (430mg,1.875mmol) 在 THF(5mL) 中的溶液中加入 $LiAlH_4$（锂离子 (1)）(0.9375mL 的 2M,1.875mmol)，将该溶液在室温搅拌 1h。通过谨慎地滴加水 (2ml) 使反应停止，搅拌 10mins，然后使该反应混合物分配在水与 EtOAc 之间。用盐水洗涤有机萃取物，干燥 ($MgSO_4$)，浓缩，得到 4- 甲基 -4- 硫烷基 - 哌啶 -1- 甲酸叔丁酯，为无色油状物 (380mg，87％）。MS(ES-)231.0.

[1301] 步骤 3：4- 甲基 -4-（甲硫基）哌啶 -1- 甲酸叔丁酯

[1302] 向冷却至 -78℃的 4- 甲基 -4- 硫烷基 - 哌啶 -1- 甲酸叔丁酯 (380mg,1.642mmol) 在 THF(5mL) 中的溶液中加入 LiHMDS(1.724mL 的 1M,1.724mmol)，将该溶液搅拌 10mins，然后加入 MeI(256.3mg,0.1124mL,1.806mmol)，将该溶液在约 1h 内温至 0℃。然后谨慎地通过添加饱和氯化铵使反应停止，萃取入 EtOAc。再用 EtOAc 萃取水层，用盐水洗涤合并的有机层，干燥 ($MgSO_4$)，浓缩，得到黄色油状物 (390mg，96％）。

[1303] 步骤 4：4- 甲基 -4-（甲基磺酰基）哌啶 -1- 甲酸叔丁酯

[1304] 将 4- 甲基 -4- 甲基硫烷基 - 哌啶 -1- 甲酸叔丁酯 (380mg,1.549mmol) 在 DCM(15mL) 中的溶液冷却至 0℃,在约 10mins 内逐步加入 3- 氯过氧苯甲酸 (867.8mg, 3.872mmol)。将该溶液搅拌 30mins,然后温至室温,再搅拌 1h。用饱和碳酸氢钠 (4ml) 和饱和硫代硫酸钠 (4ml) 使反应停止,剧烈搅拌 5mins。除去 DCM 层,在用 DCM 萃取水层。用饱和碳酸钠和盐水洗涤合并的有机层,干燥 ($MgSO_4$),浓缩,得到 4- 甲基 -4-(甲基磺酰基) 哌啶 -1- 甲酸叔丁酯,为粘性油状物,静置时固化 (450mg,100%)。

[1305] 步骤 5 :4- 甲基 -4-(甲基磺酰基) 哌啶

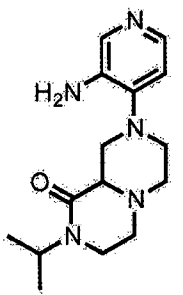
[1306] 向 4- 甲基 -4- 甲基磺酰基 - 哌啶 -1- 甲酸叔丁酯 (430mg,1.550mmol) 在 DCM(10mL) 中的溶液中加入 TFA(3mL,38.94mmol),将该溶液在室温搅拌 1h。浓缩该反应体系,与 DCM 一起共沸 2 次,得到 4- 甲基 -4-(甲基磺酰基) 哌啶,为粘性油状物,将其不经进一步纯化用于下一步。MS(ES+)178.0.

[1307] 步骤 6 :4-(4- 甲基 -4-(甲基磺酰基) 哌啶 -1- 基) 吡啶 -3- 胺

[1308] 遵循制备例 N-1。MS(ES+)270.1.

[1309] 制备例 N-26 :8-(3- 氨基吡啶 -4- 基)-2- 异丙基八氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -1- 酮

[1310]



[1311] 步骤 1 :2- 异丙基 -8-(3- 硝基吡啶 -4- 基) 八氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -1- 酮

[1312] 在 N_2 气氛中将 NaH(15.87mg,0.3967mmol)、然后将 2- 碘丙烷 (73.56mg,43.19μL, 0.4327mmol) 加入到 2-(3- 硝基 -4- 吡啶基)-3,4,6,7,8,9a- 六氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -9- 酮 (100mg,0.3606mmol)(根据与制备例 N-1 步骤 1 类似的方法制备) 在 THF(5mL) 中的溶液中。将该反应混合物回流搅拌 24h,然后使其分配在 EtOAc 与饱和碳酸氢钠水溶液之间。用盐水洗涤合并的有机萃取物,用 $MgSO_4$ 干燥,真空浓缩,产生油状物,将其不经进一步纯化用于下一步。MS(ES+)320.1.

[1313] 步骤 2 :8-(3- 氨基吡啶 -4- 基)-2- 异丙基八氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -1- 酮

[1314] 遵循制备例 N-1 的步骤 2。MS(ES+)290.2

[1315] 制备例 N-27 :(S)-5-(3- 氨基吡啶 -4- 基) 六氢 -2H- 异噻唑并 [2,3-a] 吡嗪 1,1- 二氧化物

[1316] 步骤 1 :(S)-4-(甲基磺酰基)-3-((((甲基磺酰基) 氧基) 甲基) 哌嗪 -1- 甲酸叔丁酯

[1317] 在 0℃ 在氮气气氛中向 (3S)-3-(羟基甲基) 哌嗪 -1- 甲酸叔丁酯 (2.5g, 11.56mmol) 在 DCM(16.25mL) 中的溶液中加入 TEA(1.872g,2.579mL,18.50mmol),然后滴加 MsCl(2.913g,1.968mL,25.43mmol)。将该反应体系温至环境温度,在此搅拌 18 小时。使

该混悬液分配在 DCM(2x50mL) 与水 (50mL) 之间，用盐水 (50mL) 洗涤合并的有机层，干燥 (Na_2SO_4)，真空浓缩，得到淡蜜黄色油状物 (4.9g)。通过 ISCO Companion(ELSD) 柱色谱法纯化残余物，用 DCM(A) ：甲醇 (B) (0-10％ (B)，80g，16.0 CV，60mL/min) 洗脱，得到产物混合物 (2.3g)。再通过 ISCO Companion(ELSD) 柱色谱法纯化油状残余物，用 DCM(A) ：乙酸乙酯 (B) (0-50％ (B)，40g，25.0 CV，40mL/min) 洗脱，得到 (S)-4-(甲基磺酰基)-3-(((甲基磺酰基) 氧基) 甲基) 哌嗪 -1- 甲酸叔丁酯，为无色油状物 (1.58g，37％)。MS(ES+)317.0.

[1318] 步骤 2 ：(S)- 四氢 -2H- 异噻唑并 [2,3-a] 吡嗪 -5(3H)- 甲酸叔丁酯 1,1- 二氧化物

[1319] 在 -78℃向 (3S)-4- 甲基磺酰基 -3-(甲基磺酰基氧基甲基) 哌嗪 -1- 甲酸叔丁酯 (500mg，1.342mmol) 在无水 THF(10mL) 中的溶液中滴加 LiHMDS(1M 的 THF 溶液) (1.476mL 的 1.0M，1.476mmol)。搅拌该反应混合物，允许缓慢地在 90mins 内达到环境温度，在此搅拌 18 小时。再将该反应体系冷却至 -78℃，向其中滴加 LiHMDS(1M 的 THF 溶液) (1.476mL 的 1.0M，1.476mmol)。搅拌该反应混合物，允许缓慢地在 90mins 内达到环境温度，在此再搅拌 2 小时。用水 (5mL) 使反应停止，分配在水与乙酸乙酯 (3x50mL) 之间。干燥合并的有机层 (Na_2SO_4)，真空浓缩，得到橙色油状物 (490mg)。通过柱 ISCO Companion(ELSD) 色谱法纯化残余物，用石油醚 (A) ：乙酸乙酯 (B) (0-40％ (B)，12g，21.0min，30mL/min) 洗脱，得到 (S)- 四氢 -2H- 异噻唑并 [2,3-a] 吡嗪 -5(3H)- 甲酸叔丁酯 1,1- 二氧化物，为灰白色乳膏状固体 (361mg，97％)。MS(ES+-t-Bu)221.0

[1320] 步骤 3 ：(S)- 六氢 -2H- 异噻唑并 [2,3-a] 吡嗪 1,1- 二氧化物

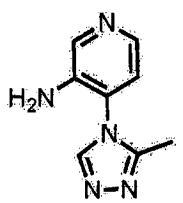
[1321] 在 0℃向 (3aS)-1,1- 二氧代 -2,3,3a,4,6,7- 六氢异噻唑并 [2,3-a] 吡嗪 -5- 甲酸叔丁酯 (360mg，1.303mmol) 在 DCM(5mL) 中的溶液中滴加 TFA(1.25mL，16.22mmol)，搅拌该反应体系，在 45mins 内缓慢地温至环境温。真空浓缩该反应混合物，使残余物吸附在预润湿的 (甲醇 /DCM(1 ：1)，10mL)SCX-2 柱 (10g) 上，用 DCM/ 甲醇 (1 ：1，50mL) 冲洗，然后用 2M 氨的甲醇溶液 (50mL) 洗脱碱性组分。蒸发碱性洗脱液至干，得到 (S)- 六氢 -2H- 异噻唑并 [2,3-a] 吡嗪 1,1- 二氧化物，为无色油状物 (192mg，84％)。

[1322] 步骤 4 ：(S)-5-(3- 氨基吡啶 -4- 基) 六氢 -2H- 异噻唑并 [2,3-a] 吡嗪 1,1- 二氧化物

[1323] 遵循制备例 N-1。MS(ES+)269.1

[1324] 制备例 N-28 ：4-(3- 甲基 -4H-1,2,4- 三唑 -4- 基) 吡啶 -3- 胺

[1325]



[1326] 步骤 1 ：3- 溴 -4- 异硫氰酸根合吡啶

[1327] 将 3- 溴吡啶 -4- 胺 (5g，28.90mmol) 混悬于干甲苯 (100mL) 用冰浴冷却。在 25mins 内滴加硫光气 (6.646g，4.407mL，57.80mmol) 在干甲苯 (100mL) 中的溶液中。将得到的橙色 / 红色混悬液回流搅拌过夜。将红色混悬液冷却至 RT，减压浓缩，得到深棕色 / 红色固体。使该物质分配在饱和 $NaHCO_3$ 与 DCM 之间。再用 DCM(3x 50mL) 萃取水层，用 Na_2SO_4 干燥合并

的有机层，过滤，减压浓缩，得到深红色固体 / 树胶状物。将该物质混悬于 MeOH/DCM，减压吸附在硅胶上，通过柱色谱法纯化 (75％ EtOAc 的己烷溶液，～ 300mL 硅胶)，得到 3- 溴 -4- 异硫氰酸根合吡啶，为红色油状物，静置时固化 (3.513g，57％收率)。MS(ES+)216.9.

[1328] 步骤 2 ：2- 乙酰基 -N-(3- 溴吡啶 -4- 基) 肼硫代甲酰胺 (carbothioamide)

[1329] 将 3- 溴 -4- 异硫氰酸根合 - 吡啶 (1g，4.650mmol) 和乙酰肼 (344.5mg，4.650mmol) 溶于干 1，4- 二噁烷 (10mL)，在 80℃搅拌 0.75hrs。将橙色混悬液冷却至 RT。用乙醚稀释粘性混悬液，通过过滤采集固体，用乙醚 (3x 5mL) 洗涤，得到 2- 乙酰基 -N-(3- 溴吡啶 -4- 基) 肼硫代甲酰铵，为橙红色 - 粉红色固体 (1.2187g，91％收率)。MS(ES-)288.9.

[1330] 步骤 3 ：4-(3- 溴吡啶 -4- 基)-5- 甲基 -4H-1，2，4- 三唑 -3- 硫醇

[1331] 将 2- 乙酰基 -N-(3- 溴吡啶 -4- 基) 肼硫代甲酰胺 (200mg，0.6917mmol) 溶于碳酸氢钠 (4mL，)，在 50℃搅拌 2hrs，在 100℃搅拌 5hrs。然后将该反应混合物在 RT 静置 48h，然后谨慎地用稀 HCl 中和，用 10％ MeOH 的 DCM 溶液分配。再用 10％ MeOH 的 DCM 溶液 (3x 10mL) 萃取水层，用 Na_2SO_4 干燥合并的有机层，过滤，减压浓缩，得到 4-(3- 溴吡啶 -4- 基)-5- 甲基 -4H-1，2，4- 三唑 -3- 硫醇，为橙色固体 (152.6mg)。MS(ES+)272.9.

[1332] 步骤 4 ：3- 溴 -4-(3- 甲基 -4H-1，2，4- 三唑 -4- 基) 吡啶

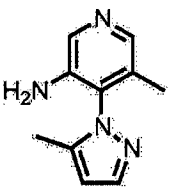
[1333] 将 4-(3- 溴 -4- 吡啶基)-5- 甲基 -1，2，4- 三唑 -3- 硫醇 (145mg，0.5348mmol) 混悬于干 DCM(4mL)，用冰浴冷却。缓慢地滴加过氧化氢 (133.5μL 的 30％ w/v，1.177mmol) 在 AcOH(1.5mL) 中的溶液，将得到的混合物在 RT 搅拌 2hrs。用冰浴冷却该反应混合物，通过缓慢添加 2M NaOH 猝灭，用 DCM 分配。再用 DCM(3x 10mL) 萃取水层，用 Na_2SO_4 干燥合并的有机层，过滤，减压浓缩，得到黄色树胶状物 / 固体 (112.5mg)。将该物质再溶于 MeOH/DCM，减压吸附在硅胶上，通过柱色谱法纯化 (7.5％ MeOH 的 DCM 溶液，～ 75mL 硅胶)，得到 3- 溴 -4-(3- 甲基 -4H-1，2，4- 三唑 -4- 基) 吡啶，为乳膏状固体 (82.3mg，64％收率)。MS(ES+)240.9.

[1334] 步骤 5 ：4-(3- 甲基 -4H-1，2，4- 三唑 -4- 基) 吡啶 -3- 胺

[1335] 使用与制备例 N-14 步骤 3a 类似的方法。

[1336] 制备例 N-29 ：5- 甲基 -4-(5- 甲基 -1H- 吡唑 -1- 基) 吡啶 -3- 胺

[1337]



[1338] 步骤 1 ：3- 溴 -4- 肼基 -5- 硝基吡啶

[1339] 将 3- 溴 -4- 氯 -5- 硝基 - 吡啶 (500mg，2.106mmol)、水合肼 (158.1mg，153.6μL，3.159mmol) 在乙醇 (5.000mL) 中的溶液在 RT 搅拌 1h。过滤淡黄色沉淀，用甲醇洗涤，真空干燥，得到 3- 溴 -4- 肼基 -5- 硝基吡啶 (390mg，79.5％)。MS(ES-)232.8.

[1340] 步骤 2 ：3- 溴 -4-(5- 甲基 -1H- 吡唑 -1- 基)-5- 硝基吡啶

[1341] 将 2-(2- 甲基 -1，3- 二氧戊环 -2- 基) 乙醛 (320mg，2.459mmol) 和 (3- 溴 -5- 硝基 -4- 吡啶基) 肼 (286.4mg，1.229mmol) 在乙醇 (2.864mL) 中回流加热过夜。真空浓缩该反应混合物，使残余物分配在 DCM 与饱和碳酸氢钠水溶液之间。用 $MgSO_4$ 干燥合并的有机

萃取物，真空浓缩，得到 3- 溴 -4-(5- 甲基 -1H- 吡唑 -1- 基)-5- 硝基吡啶，为黄色油状物 (200mg，85％)。MS(ES+)284.9.

[1342] 步骤 3 :3- 甲基 -4-(5- 甲基 -1H- 吡唑 -1- 基)-5- 硝基吡啶

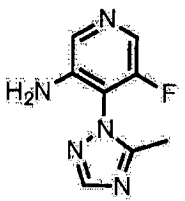
[1343] 在氮气气氛中向烘干的烧瓶中加入 3- 溴 -4-(5- 甲基吡唑 -1- 基)-5- 硝基 - 吡 啶 (200mg，0.6005mmol)、Pd_2dba_3(8.249mg，0.009008mmol) 和 X-Phos(8.590mg，0.01802mmol)。加入无水 THF(1.700mL)，然后加入 1,4- 二氮杂双环 [2.2.2] 辛烷 ；三甲基 alumane(153mg，0.6005mmol)。将该反应体系回流加热 2 小时，然后冷却至环境温度，然后通过添加水猝灭。用 EtOAc(x 3) 萃取该混合物，用盐水洗涤合并的有机萃取物，干燥 ($MgSO_4$)，真空浓缩，得到 3- 甲基 -4-(5- 甲基 -1H- 吡唑 -1- 基)-5- 硝基吡啶和 4-(5- 甲基 -1H- 吡唑 -1- 基)-3- 硝基吡啶的 3/1 混合物，不经进一步纯化用于下一步 (140mg 产物，分离为混合物)。MS(ES+)219.0.

[1344] 步骤 4 :5- 甲基 -4-(5- 甲基 -1H- 吡唑 -1- 基) 吡啶 -3- 胺

[1345] 根据制备例 N-1 步骤 2 进行还原。MS(ES+)189.0.

[1346] 制备例 N-30 :5- 氟 -4-(5- 甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶 -3- 胺

[1347]



[1348] 步骤 1 :3- 溴 -5- 氟 -4- 肼基吡啶

[1349] 将在环己醇中的 3- 溴 -4- 氯 -5- 氟 - 吡啶 (500mg，2.376mmol)、肼 (761.4mg，745.7μL，23.76mmol)、Na_2CO_3(503.7mg，4.752mmol) 在 100C 加热过夜。用 C 盐过滤该反应混合物，上 SCX 柱，用 DCM/MeOH 混合物洗涤，用 2M NH_3的 MeOH 溶液洗脱。真空浓缩滤液，将 3- 溴 -5- 氟 -4- 肼基吡啶和 3- 溴 -4- 氯 -5- 肼基吡啶的 3/1 混合物不经进一步纯化用于下一步。MS(ES+)205.9.

[1350] 步骤 2 :3- 溴 -5- 氟 -4-(5- 甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶

[1351] 可在二噁烷中的乙酰胺 (136.7mg，2.315mmol)、1,1- 二甲氧基 -N,N- 二甲基 - 甲胺 (382.0mg，425.9μL，3.206mmol) 在 45-50℃在 150mm Hg 真空中加热 2h。真空浓缩该反应混合物。向残余物中加入 (3- 溴 -5- 氟 -4- 吡啶基) 肼 (367mg，1.781mmol) 和二噁烷 - 乙酸 (1/1)，将该混合物在 130℃加热 1h，然后在 160℃加热 2h。在 RT，使残余物上 SCX 柱，用 MeOH/DCM 混合物洗脱。真空浓缩滤液，得到纯 3- 溴 -5- 氟 -4-(5- 甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶，为深色油状物。MS(ES+)257.0.

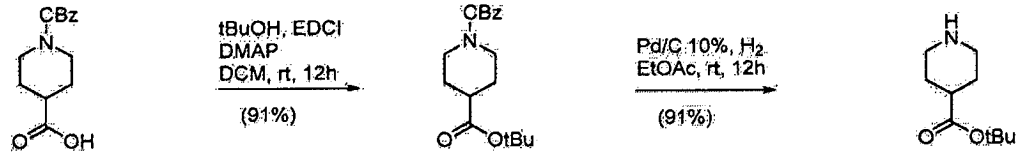
[1352] 步骤 3 :5- 氟 -4-(5- 甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶 -3- 胺

[1353] 根据与制备例 N-14 步骤 3 类似的方法进行氨基化反应。MS(ES+)194.0.

[1354] 制备例 N-31 :哌啶 -4- 甲酸叔丁酯

[1355] 方案 8

[1356]



20 21 22

[1357] 步骤 1 :哌啶 -1, 4- 二甲酸 01- 苄基 04- 叔丁酯 21

[1358] 在 5L 梨形烧瓶中加入在 DCM(500.0mL) 中的 1- 苄氧基羰基哌啶 -4- 甲酸 20(200g, 759.6mmol), 然后再加入 DCM(2.000L)、叔丁醇 (140.8g, 181.7mL, 1.899mol) 和 DMAP(46.40g, 379.8mmol)。用冰 / 盐 / 水浴冷却该混合物 (内部 -3.4℃)。在 15mins 内逐步加入 3-(乙基亚氨基亚甲基氨基)-N, N- 二甲基 - 丙 -1- 胺 (盐酸 (1)) (145.6g, 759.6mmol), 用 DCM(500.0mL) 冲洗加液漏斗。在冰浴上将混合物搅拌约 2h。然后除去冰浴 (内部 3℃), 温至室温过夜。用 5% 柠檬酸 (2x 500mL)、然后用饱和 $NaHCO_3$(500mL)、水 (500mL) 洗涤混合物, 用 $MgSO_4$ 干燥有机层, 然后过滤, 真空浓缩, 得到产物 21, 为粘性淡黄色油状物, 静置时变成白色固体 (246.1g, 101%)。^1H NMR(500MHz, DMSO-d6) δ 7.40 - 7.31(m, 5H), 5.08(s, 2H), 3.90(dt, 2H), 2.93(br s, 2H), 2.43(tt, 1H), 1.80 - 1.76(m, 2H) 和 1.45 - 1.37(m, 11H)。

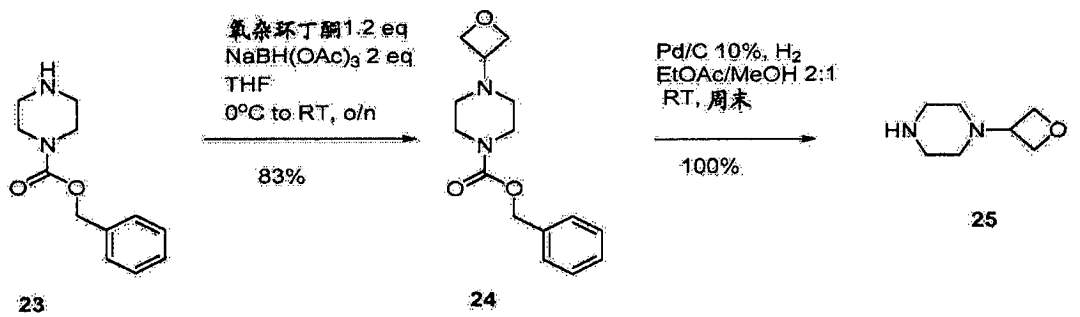
[1359] 步骤 2 :哌啶 -4- 甲酸叔丁酯 22

[1360] 在氮气气氛中向 3L florentine 中加入披 Pd C 湿 Degussa(10% Pd, 50% WATER) (8.120g, 76.30mmol), 然后加入 EtOAc(1.706L)。通过 N_2/ 真空循环 (3x) 给该混合物脱气, 然后加入哌啶 -1, 4- 二甲酸 01- 苄基 04- 叔丁酯 21(243.7g, 763.0mmol) 在 EtOAc(243.7mL) 中的溶液。将混合物在氢气气氛中搅拌过夜。充满氢气, 将混合物再搅拌 3.5h。加入甲醇 (60mL) 以辅助沉淀溶解, 然后通过 C 盐过滤, 用甲醇充分洗涤。真空浓缩滤液。得到棕色油状物与白色固体的带有适度混悬液 138.6g。通过过滤除去固体, 用少量 EtOAc 洗涤。真空浓缩滤液, 得到期望的产物, 为浅棕色油状物 (129g, 91%)。^1H NMR(500MHz, DMSO-d6) δ 2.88(dt, 2H), 2.44(td, 2H), 2.23(tt, 1H), 1.69 - 1.64(m, 2H) 和 1.41 - 1.33(m, 11H)。

[1361] 制备例 N-32 :1-(氧杂环丁烷 -3- 基) 哌嗪

[1362] 方案 9

[1363]



23 24 25

[1364] 步骤 1 :4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 甲酸苄酯 24

[1365] 将哌嗪 -1- 甲酸苄酯 23(27.3mL, 142.2mmol) 溶于干 THF(313.1mL), 加入氧杂环丁烷 -3- 酮 (12.29g, 10.93mL, 170.6mmol)。用冰浴冷却得到的溶液。在 30mins 内逐步加入 $NaBH(OAc)_3$(59.99g, 284.4mmol)。具体约四分之一。从冰浴中取出混合物, 温至室温, 然后

在 30mins 内逐步持续添加 $NaBH(OAc)_3$。在添加完成时，观察到 22℃缓慢地放热至 32℃，由此随后用冰浴冷却该混合物，直到达到内部为 22℃。除去冰浴，该反应混合物的内部温度稳定在 22℃。将该混合物在室温搅拌过夜。

[1366] 通过添加 2M 碳酸钠溶液（约 150mL）(pH = 8) 使得到的白色混悬液猝灭，减压浓缩以除去 THF。然后用 EtOAc(3x 250mL) 萃取产物。合并有机层，用 $MgSO_4$ 干燥，过滤，减压浓缩，得到产物 24，为白色固体 (32.7g 83％收率）。^1H NMR(500MHz, DMSO-d6) δ 7.39 - 7.30(m,5H), 5.07(s,2H), 4.52(t,2H), 4.42(t,2H), 3.43 - 3.39(m,5H) 和 2.22(t,4H)。MS(ES+) 276.8.

[1367] 步骤 2：1-（氧杂环丁烷 -3- 基）哌嗪 25

[1368] 在氮气气氛中在 1L florentine 中加入 $Pd(OH)_2$(1.661g,2.366mmol)。加入 MeOH(130.8mL) 和 EtOAc(261.6mL)，通过真空 / 氮气循环 (3x) 给该混合物脱气。然后加入 4-（氧杂环丁烷 -3- 基）哌嗪 -1- 甲酸苄酯 24(32.7g,118.3mmol)，将该混合物在氢气气氛中搅拌一个周末。通过 C 盐垫过滤混合物，用 EtOAc、然后用甲醇充分洗涤。真空浓缩滤液，得到产物 25，为橙色油状物 (8.1g，定量收率）。^1H NMR(500MHz, DMSO-d6) δ 4.51(t,2H), 4.41(t,2H), 3.36 - 3.30（掩蔽的信号，1H), 2.69(t,4H) 和 2.14(br s,4H)。

[1369] 使用与实施例 1 或实施例 3a-3e 类似的方法成功地制备了如下化合物：

[1370] 2- 氨基 -6- 氟 -N-(4-(4- 异丙基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-4）；

[1371] 2- 氨基 -N-(5- 环丙基 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-5）；

[1372] 2- 氨基 -N-(5- 氯 -4-(8- 甲基六氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -2(6H)- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-6）；

[1373] N-(4-(1H- 咪唑 -1- 基）吡啶 -3- 基）-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-7）；

[1374] 2- 氨基 -6- 氟 -N-(4-(4-(2-（甲基氨基）乙基）-1H- 吡唑 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-8）；

[1375] 2- 氨基 -N-(4-(4-(2-（二甲基氨基）乙基）-1H- 吡唑 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-9）；

[1376] (R)-2- 氨基 -6- 氟 -N-(4-(4-（四氢呋喃 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-10）；

[1377] 2- 氨基 -6- 氟 -N-(4-(4-（四氢 -2H- 吡喃 -4- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-11）；

[1378] (S)-2- 氨基 -6- 氟 -N-(4-(4-（四氢呋喃 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-12）；

[1379] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-（氧杂环丁烷 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-13）；

[1380] 2- 氨基 -6- 氯 -N-(5- 氟 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-14）；

[1381] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a]

嘧啶 -3- 甲酰胺（化合物 I-N-15）；

[1382] 2-氨基-6-氟-N-(5-甲基-4-(4-(氧杂环丁烷-3-基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-16）；

[1383] 2-氨基-N-(4-(4-乙基哌嗪-1-基）吡啶-3-基）-6-氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-17）；

[1384] N-(4-(1,4-二氮杂双环 [3.2.2] 壬-4-基）吡啶-3-基）-2-氨基-6-氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-18）；

[1385] (R,S)-2-氨基-6-氟-N-(4-(4-(四氢呋喃-3-基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-19）；

[1386] 2-氨基-6-氟-N-(4-(4-(2,2,2-三氟乙基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-20）；

[1387] (S)-2-氨基-6-氟-N-(4-(六氢吡咯并 [1,2-a] 吡嗪-2(1H)-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-21）；

[1388] 2-氨基-6-氟-N-(4-(4-(2-甲氧基乙基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-22）；

[1389] (R)-2-氨基-6-氟-N-(4-(2-甲基-4-(氧杂环丁烷-3-基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-23）；

[1390] (S)-2-氨基-6-氟-N-(4-(2-甲基-4-(氧杂环丁烷-3-基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-24）；

[1391] 2-氨基-6-氯-N-(4-(4-(3-甲基氧杂环丁烷-3-基）哌嗪-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-25）；

[1392] N-(4-(1H-吡唑-1-基）吡啶-3-基）-2-氨基-6-氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-26）；

[1393] 2-氨基-6-氟-N-(4-(4-(三氟甲基）-1H-咪唑-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-27）；

[1394] 2-氨基-6-氟-N-(4-(2-甲基-1H-咪唑-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-28）；

[1395] N-(4-(1H-咪唑-1-基）吡啶-3-基）-2-氨基-6-氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-29）；

[1396] 2-氨基-6-氟-N-(4-(2-甲基-4-(三氟甲基）-1H-咪唑-1-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-30）；

[1397] 2-氨基-6-氟-N-(4-(5-(氧杂环丁烷-3-基）-2,5-二氮杂双环 [4.1.0] 庚-2-基）吡啶-3-基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-31）；

[1398] 2-氨基-N-(5-环丙基-4-(4-(氧杂环丁烷-3-基）哌嗪-1-基）吡啶-3-基）-6-氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-32）；

[1399] 2-氨基-N-(4-(4-环丙基哌嗪-1-基）吡啶-3-基）-6-氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-33）；

[1400] 2-氨基-N-(4-(4-(叔丁基）哌嗪-1-基）吡啶-3-基）-6-氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-34）；

[1401] 2-氨基-6-氯-N-(4-((3S,4S)-4-(二甲基氨基)-3-羟基哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-35);

[1402] 2-氨基-6-氯-N-(4-(4-((二甲基氨基)甲基)-4-羟基哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-36);

[1403] 2-氨基-6-氯-N-(4-(4-(二甲基氨基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-37);

[1404] 2-氨基-6-氯-N-(4-(4-异丙基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-39);

[1405] 2-氨基-6-氯-N-(4-(3-(二甲基氨基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-40);

[1406] 2-氨基-6-氯-N-(5-氯-4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-41);

[1407] 2-氨基-6-氯-N-(4-(3-羟基-8-氮杂双环[3.2.1]辛-8-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-42);

[1408] 2-氨基-6-氯-N-(4-(4-甲基-1,4-二氮杂庚环-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-43);

[1409] 2-氨基-6-氯-N-(4-(5,6-二氢咪唑并[1,2-a]吡嗪-7(8H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-44);

[1410] 2-氨基-6-氯-N-(4-(4-((二甲基氨基)甲基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-45);

[1411] 2-氨基-6-氯-N-(4-(4-((二甲基氨基)甲基)-4-甲氧基哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-46);

[1412] 2-氨基-6-氯-N-(4-(3-(甲氧基甲基)-4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-47);

[1413] 2-氨基-6-氯-N-(4-(4-环丁基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-48);

[1414] 2-氨基-6-氯-N-(4-(4-(2-(二甲基氨基)乙基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-49);

[1415] 2-氨基-N-(6-氨基-4-(4-甲基哌嗪-1-基)吡啶-3-基)-6-氯吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-50);

[1416] 2-氨基-6-氯-N-(4-(4-乙基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-51);

[1417] 2-氨基-6-氯-N-(6-氯-4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-52);

[1418] 2-氨基-6-氯-N-(4-(3,3,4-三甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-53);

[1419] 2-氨基-6-氯-N-(4-(3,4-二甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-54);

[1420] 2-氨基-N-(4-(3-氨基哌啶-1-基)吡啶-3-基)-6-氯吡唑并[1,5-a]嘧

啶 -3- 甲酰胺（化合物 I-N-55）；

[1421] N-(4-(1,4- 二氮杂双环 [3.2.2] 壬 -4- 基）吡啶 -3- 基）-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-56）；

[1422] 2- 氨基 -6- 氯 -N-(5- 甲基 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-57）；

[1423] 2- 氨基 -6- 氯 -N-(4-(4-（氧杂环丁烷 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-58）；

[1424] 2- 氨基 -6- 氯 -N-(4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-59）；

[1425] 2- 氨基 -6- 氯 -N-(4-(4-(2- 甲氧基乙基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-60）；

[1426] 2- 氨基 -6- 氯 -N-(4-(8- 甲基六氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -2(6H)- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-61）；

[1427] 2- 氨基 -6- 氟 -N-(4-(4-(3- 甲基氧杂环丁烷 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-62）；

[1428] 2- 氨基 -6- 氯 -N-(4-(3-（羟基甲基）-4- 甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-63）；

[1429] 2- 氨基 -6- 氯 -N-(4-(4- 环丙基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-64）；

[1430] (R)-2- 氨基 -6- 氯 -N-(4-（六氢吡咯并 [1,2-a] 吡嗪 -2(1H)- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-65）；

[1431] 2- 氨基 -6- 氯 -N-(4-(4- 羟基 -4- 甲基哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-66）；

[1432] 2- 氨基 -6- 氯 -N-(4-(4-(2,2,2- 三氟乙基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-67）；

[1433] 2- 氨基 -6- 氯 -N-(4-(1- 氧化硫代吗啉代）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-68）；

[1434] 2- 氨基 -6- 氯 -N-(4-(4-(2- 羟基丙 -2- 基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-69）；

[1435] 2- 氨基 -6- 氯 -N-(4-(3-（三氟甲基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-70）；

[1436] (S)-2- 氨基 -6- 氯 -N-(4-（六氢吡咯并 [1,2-a] 吡嗪 -2(1H)- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-71）；

[1437] 2- 氨基 -6- 氯 -N-(4-(2,4- 二甲基哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-72）；

[1438] 2- 氨基 -6- 氯 -N-(4-(4- 甲氧基哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-73）；

[1439] 甲基 -1-(3-(2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰氨基）吡啶 -4- 基）哌啶 -4- 甲酸酯（化合物 I-N-74）；

[1440] 2-氨基-6-氯-N-(4-(5,6-二氢咪唑并[1,5-a]吡嗪-7(8H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-75);

[1441] 2-氨基-6-(2-氰基丙-2-基)-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-76);

[1442] 2-氨基-6-(氰基甲基)-N-(4-(吡咯烷-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-77);

[1443] 2-氨基-6-(1-氰基乙基)-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-78);

[1444] 2-氨基-N-(4-(氮杂庚环-1-基)吡啶-3-基)-6-(氰基甲基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-79);

[1445] 2-氨基-6-(氰基甲基)-N-(5-氟-4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-80);

[1446] 2-氨基-6-(氰基甲基)-N-(4-吗啉代吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-81);

[1447] 2-氨基-6-(氰基甲基)-N-(4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-82);

[1448] 2-氨基-6-(氰基甲基)-N-(4-(4-羟基哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-83);

[1449] 2-氨基-6-(氰基甲基)-N-(4-(哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-84);

[1450] 2-氨基-N-(5-氯-4-(4-甲基哌嗪-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-85);

[1451] 2-氨基-N-(5-(二氟甲基)-4-(4-甲基哌嗪-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-111)

[1452] 2-氨基-6-氟-N-(4-(5-(氧杂环丁烷-3-基)-2,5-二氮杂双环[4.1.0]庚-2-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-112);

[1453] 2-氨基-6-氟-N-(5-氟-4-(8-甲基六氢-1H-吡嗪并[1,2-a]吡嗪-2(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-114);

[1454] (S)-2-氨基-6-氟-N-(4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-115);

[1455] (R)-2-氨基-6-氟-N-(4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-116);

[1456] 2-氨基-6-氯-N-(5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-117);

[1457] (S)-2-氨基-6-氟-N-(5-氟-4-(4-(四氢呋喃-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-125);

[1458] 2-氨基-6-氟-N-(5-氟-4-(4-(2-甲氧基乙基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-127);

[1459] 2-氨基-6-氟-N-(5-氟-4-(4-(奎宁环-3-羰基)哌嗪-1-基)吡啶-3-基)

吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-130);

[1460] 2-氨基-6-氟-N-(4-(1-甲基-9-氧杂-1,4-二氮杂螺[5.5]十一烷-4-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-133);

[1461] (R)-2-氨基-6-氟-N-(5-氟-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-135);

[1462] 2-氨基-6-氟-N-(4-(4-氧代六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-136);

[1463] (S)-2-氨基-6-氟-N-(5-氟-4-(六氢吡嗪并[2,1-c][1,4]噁嗪-8(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-137);

[1464] 2-氨基-6-(2-氰基丙-2-基)-N-(5-氟-4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-138);

[1465] 2-氨基-6-氟-N-(5-氟-4-(4-(2-羟基-2-甲基丙基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-139);

[1466] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基哌嗪-1-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-140);

[1467] 2-氨基-6-氟-N-(4-吗啉代吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-141);

[1468] 2-氨基-6-(2-氰基丙-2-基)-N-(4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-142);

[1469] 2-氨基-6-(1-氰基乙基)-N-(4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-143);

[1470] 2-氨基-6-(1-氰基乙基)-N-(4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-144);

[1471] 2-氨基-6-(2-氰基丙-2-基)-N-(5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-145);

[1472] 2-氨基-N-(4-(4-(N,N-二甲基氨磺酰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-146);

[1473] 2-氨基-6-氟-N-(5-氟-4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-147);

[1474] 2-氨基-6-氟-N-(5-氟-4-(4-(N-甲基-N-(1-甲基哌啶-4-基)氨磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-148);

[1475] 2-氨基-6-氟-N-(5-氟-4-(4-(吗啉代甲基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-149);

[1476] 2-氨基-6-氟-N-(5-氟-4-(4-((4-甲基哌嗪-1-基)甲基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-150);

[1477] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基-2-氧代哌嗪-1-基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-151);

[1478] 2-氨基-6-氟-N-(4-(哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-152);

[1479] 2-氨基-6-氟-N-(5-氟-4-(4-(吗啉代磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-155);

[1480] 2-氨基-6-氟-N-(4-(3-甲基-1H-1,2,4-三唑-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-161);

[1481] 2-氨基-6-氟-N-(4-(5-甲基-1H-1,2,4-三唑-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-162);

[1482] 2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-163);

[1483] 2-氨基-6-氟-N-(5-氟-4-(4-(甲基磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-165);

[1484] 2-氨基-6-氟-N-(5-氟-4-(4-((4-甲基哌嗪-1-基)磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-166);

[1485] 2-氨基-6-氟-N-(5-氟-4-(4-(2-(吡咯烷-1-基)乙氧基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-167);

[1486] 2-氨基-N-(4-(4-(氮杂环丁烷-1-基磺酰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-169);

[1487] 2-氨基-6-氟-N-(4-(4-(吗啉代磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-170);

[1488] 2-氨基-6-氟-N-(5-氟-4-(4-((4-甲基-3-氧代哌嗪-1-基)甲基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-171);

[1489] 2-氨基-6-(1-氰基环丙基)-N-(5-氟-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-180);

[1490] (R)-2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-182);

[1491] 2-氨基-6-氟-N-(4-(4-甲基-1-氧杂-4,9-二氮杂螺[5.5]十一烷-9-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-183);

[1492] 2-氨基-6-氟-N-(5-氟-4-(4-(噻唑-2-基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-184);

[1493] (R)-2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-186);

[1494] 2-氨基-6-氟-N-(5-氟-4-(4-(2-(吡咯烷-1-基)乙酰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-187);

[1495] 2-氨基-6-氟-N-(5-氟-4-(4-吗啉代哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-189);

[1496] 2-氨基-6-氟-N-(4-(4-(甲基磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-190);

[1497] 2-氨基-6-氟-N-(5-氟-4-(3-(4-甲基哌嗪-1-羰基)吡咯烷-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-191);

[1498] 2-氨基-6-(1-氰基环丙基)-N-(5-氟-4-(4-((4-甲基哌嗪-1-基)甲基)哌

啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-192) ;

[1499] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((4- 甲基 -2- 氧代哌嗪 -1- 基) 甲基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-193) ;

[1500] N-(4-(4-(1,4- 二氮杂双环 [3.2.2] 壬 -4- 基磺酰基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-196) ;

[1501] 2- 氨基 -N-(4-(4-((3,3- 二氟吡咯烷 -1- 基) 甲基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-197) ;

[1502] 2- 氨基 -6- 氟 -N-(4-(4-(氧杂环丁烷 -3- 基磺酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-200) ;

[1503] 2- 氨基 -N-(4-(2- 环丙基 -1H- 咪唑 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-202) ;

[1504] 2- 氨基 -6- 氟 -N-(4-(4-((2- 甲氧基乙基) 磺酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-208) ;

[1505] 2- 氨基 -6- 氟 -N-(4-(4- 甲基 -3- 氧代哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-209) ;

[1506] 2- 氨基 -N-(4-(1,1- 二氧化硫代吗啉代) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-210) ;

[1507] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4- 甲基 -3- 氧代哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-212) ;

[1508] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((2- 氧代吡咯烷 -1- 基) 甲基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-213) ;

[1509] 2- 氨基 -6- 氟 -N-(4-(4-((甲基磺酰基) 甲基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-215) ;

[1510] 2- 氨基 -6- 氟 -N-(4-(3- 甲基 -2- 氧代 -1- 氧杂 -3,8- 二氮杂螺 [4.5] 癸 -8- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-216) ;

[1511] (S)-2- 氨基 -6- 氟 -N-(4-(6- 氧代六氢吡咯并 [1,2-a] 吡嗪 -2(1H)- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-217) ;

[1512] 2- 氨基 -N-(4-(3,5- 二甲基 -1H-1,2,4- 三唑 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-218) ;

[1513] 2- 氨基 -6- 氟 -N-(4-(2-(三氟甲基)-1H- 咪唑 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-219) ;

[1514] 2- 氨基 -N-(4-(2,2- 二甲基吡咯烷 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-220) ;

[1515] 2- 氨基 -6- 氟 -N-(4-(3-(甲基磺酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-221) ;

[1516] 2- 氨基 -6- 氟 -N-(4-(4- 氧代六氢吡咯并 [1,2-a] 吡嗪 -2(1H)- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-222) ;

[1517] 2- 氨基 -6- 氟 -N-(4-(5- 甲基 -1H- 吡唑 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-223) ;

[1518] 2-氨基-6-氟-N-(4-((3aR,7aR)-2-甲基-3-氧代六氢-1H-吡咯并[3,4-c]吡啶-5(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-224);

[1519] 2-氨基-6-氟-N-(4-(3-甲基-1H-吡唑-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-225);

[1520] N-(4-(2-氧杂-7-氮杂螺[3.5]壬-7-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-226);

[1521] 2-氨基-6-氟-N-(5-氟-4-(3-甲基-2-氧代-1-氧杂-3,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-229);

[1522] 2-氨基-6-氟-N-(4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-230);

[1523] 2-氨基-6-氟-N-(4-(2-甲基-3-氧代-2,9-二氮杂螺[5.5]十一烷-9-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-231);

[1524] 2-氨基-6-氟-N-(5-氟-4-(4-氧代六氢吡咯并[1,2-a]吡嗪-2(1H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-232);

[1525] 2-氨基-6-氟-N-(4-(8-甲基-9-氧代六氢-1H-吡嗪并[1,2-a]吡嗪-2(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-233);

[1526] 4-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)吡啶-4-基)-N,N-二甲基吗啉-2-甲酰胺(化合物I-N-234);

[1527] 2-氨基-6-氟-N-(4-(1-甲基-2-氧代-1,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-235);

[1528] 2-氨基-6-氟-N-(4-(2-甲基-3-氧代-2,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-236);

[1529] 2-氨基-6-氟-N-(4-(3-氧代四氢-1H-噁唑并[3,4-a]吡嗪-7(3H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-238);

[1530] 2-氨基-6-氟-N-(5-氟-4-(2-氧杂-7-氮杂螺[3.5]壬-7-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-239);

[1531] 2-氨基-6-氟-N-(5-氟-4-(8-甲基-9-氧代六氢-1H-吡嗪并[1,2-a]吡嗪-2(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-240);

[1532] N-(4-(4-(1,2,4-噁二唑-3-基)哌啶-1-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-241);

[1533] 2-氨基-6-氟-N-(5-氟-4-(5-甲基-1H-1,2,4-三唑-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-242);

[1534] 2-氨基-6-氟-N-(4-(4-甲基-4-(甲基磺酰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-243);

[1535] 2-氨基-6-氟-N-(4-(6-氧代六氢-1H-吡啶并[1,2-a]吡嗪-2(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-244);

[1536] 2-氨基-6-氟-N-(4-(8-异丙基-9-氧代六氢-1H-吡嗪并[1,2-a]吡嗪-2(6H)-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-245);

[1537] 2-氨基-6-氟-N-(5-氟-4-(吡咯烷-1-基)吡啶-3-基)吡唑并[1,5-a]嘧

啶 -3- 甲酰胺（化合物 I-N-246）；

[1538] (S)-2- 氨基 -N-(4-(1,1- 二氧化四氢 -2H- 异噻唑并 [2,3-a] 吡嗪 -5(3H)- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-247）；

[1539] (S)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(3- 氧代四氢 -1H- 噁唑并 [3,4-a] 吡嗪 -7(3H)- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-248）；

[1540] 2- 氨基 -N-(4-(1,1- 二氧化硫代吗啉代）-5- 氟吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-250）；

[1541] 2- 氨基 -N-(4-(2,2- 二甲基 -1,1- 二氧化硫代吗啉代）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-252）；

[1542] N-(4-(2- 氧杂 -6- 氮杂螺 [3.5] 壬 -6- 基）吡啶 -3- 基）-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-253）；

[1543] 2- 氨基 -6- 氟 -N-(4-(4-(5- 甲基 -1,3,4- 噁二唑 -2- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-256）；

[1544] (R)-2- 氨基 -6- 氟 -N-(4-(6- 氧代六氢吡咯并 [1,2-a] 吡嗪 -2(1H)- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-258）；

[1545] 2- 氨基 -6- 氟 -N-(1- 甲基 -1H- 吡咯并 [3,2-c] 吡啶 -7- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-259）；

[1546] 2- 氨基 -6- 氟 -N-(4-(4-(4- 甲基 -1,2,5- 噁二唑 -3- 基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-260）；

[1547] 2- 氨基 -6- 氟 -N-(4-(3- 甲基 -4H-1,2,4- 三唑 -4- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-263）；

[1548] 2- 氨基 -N-(4-（氮杂庚环 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-264）；

[1549] 2- 氨基 -6- 氟 -N-(4-(4-(5- 甲基 -1,3,4- 噁二唑 -2- 基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-265）；

[1550] 2- 氨基 -6- 氟 -N-(4-(4- 甲氧基哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-266）；

[1551] 2- 氨基 -N-(4-(4-((二甲基氨基）甲基）哌啶 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-267）；

[1552] N-(4-(4-(1,3,4- 噁二唑 -2- 基）哌啶 -1- 基）吡啶 -3- 基）-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-268）；

[1553] 2- 氨基 -N-(4-(4,5- 二甲基 -1H- 咪唑 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-269）；

[1554] 2- 氨基 -6- 氟 -N-(5- 氟 -4-（哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-270）；

[1555] 2- 氨基 -N-(4-(4-（氮杂环丁烷 -1- 基磺酰基）哌啶 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-271）；

[1556] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4- 甲基 -1- 氧杂 -4,9- 二氮杂螺 [5.5] 十一

烷-9-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-272）；

[1557] N-(4-(4-(1,4-二氮杂双环[3.2.2]壬-4-基磺酰基）哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-273）；

[1558] 2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢-1H-吡啶并[1,2-a]吡嗪-2(6H)-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-277）；

[1559] (S)-2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢-1H-吡啶并[1,2-a]吡嗪-2(6H)-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-279）；

[1560] (R)-2-氨基-6-氟-N-(5-氟-4-(6-氧代六氢-1H-吡啶并[1,2-a]吡嗪-2(6H)-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-280）；

[1561] 2-氨基-N-(5-氯-4-(吡咯烷-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-281）；

[1562] 2-氨基-6-氟-N-(4-(4-(甲氧基甲基）哌啶-1-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-282）；

[1563] 2-氨基-6-氟-N-(4-(5-甲基-1H-咪唑-1-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-283）；

[1564] 2-氨基-N-(5-氯-4-(3-羟基吡咯烷-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-284）；

[1565] (R)-2-氨基-N-(5-氯-4-(3-氰基吡咯烷-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-285）；

[1566] 2-氨基-N-(5-氯-4-(5-甲基六氢吡咯并[3,4-c]吡咯-2(1H)-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-286）；

[1567] 2-氨基-N-(5-氯-4-(3-(甲基磺酰基）吡咯烷-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-287）；

[1568] N-(4-(4-(1H-咪唑-1-基）哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-288)

[1569] 2-氨基-6-氟-N-(5-氟-4-(3-(4-甲基哌嗪-1-羰基）哌啶-1-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-289）；

[1570] 2-氨基-N-(4-(3-(二甲基氨基甲酰基）哌啶-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-N-290）；

[1571] 2-氨基-6-氟-N-(5'-甲氧基-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-82）；

[1572] 2-氨基-6-氟-N-(4-(1-(2-甲氧基乙基)-1H-咪唑-5-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-83）；

[1573] 2-氨基-N-(4-环丙基-5-甲氧基吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-84）；

[1574] 2-氨基-6-氟-N-(4-(4-(4-甲基哌嗪-1-羰基）哌啶-1-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-G-1）；

[1575] 2-氨基-N-(4-(4-(二甲基氨基甲酰基）哌啶-1-基）吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-G-2）；

[1576] 2-氨基-N-(5-氯-4-(4-(4-甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-3);

[1577] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-4);

[1578] 2-氨基-6-氯-N-(5-氟-4-(4-(4-甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-5);

[1579] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基-1,4-二azepane-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-6);

[1580] N-(4-(4-(1,4-二氮杂双环[3.2.2]壬烷-4-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-7);

[1581] 2-氨基-N-(4-(4-(4-环丙基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-13);

[1582] 2-氨基-6-氟-N-(5-氟-4-(4-(3,3,4-三甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-15);

[1583] 2-氨基-N-(4-(4-氰基-4-(4-甲基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-25);

[1584] 2-氨基-6-氟-N-(5-氟-4-(4-甲基-4-(4-甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-54);

[1585] 2-氨基-6-氟-N-(5-氟-4-(4-(5-甲基-2,5-二氮杂双环[4.1.0]庚烷-2-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-65);且

[1586] N-(4-(4-(1,4-二氮杂双环[3.2.2]壬烷-4-羰基)哌啶-1-基)-5-氯吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-66)。

[1587] 根据与实施例2中描述的程序中所述的方法类似的方法制备了下面的化合物:

[1588] 2-氨基-N-(4-(4-氨基哌啶-1-基)吡啶-3-基)-6-氯吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-86);

[1589] 2-氨基-6-氯-N-(4-(4-(甲基氨基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-87);

[1590] 2-氨基-6-氯-N-(4-(哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-88);

[1591] 2-氨基-6-(氰基甲基)-N-(4-(哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-89);

[1592] 2-氨基-N-(4-(2-(氨基甲基)吗啉代)吡啶-3-基)-6-(氰基甲基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-90);

[1593] 2-氨基-N-(4-(4-(氨基甲基)哌啶-1-基)吡啶-3-基)-6-氯吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-91);

[1594] 2-氨基-6-氟-N-(5-氟-4-(哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-118);

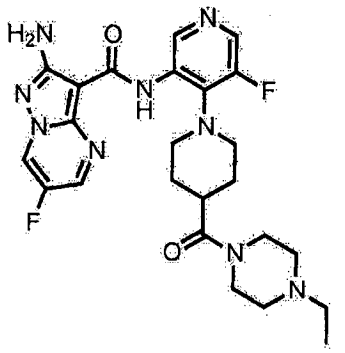
[1595] 2-氨基-N-(5-氯-4-(哌嗪-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-126);

[1596] 2-氨基-6-氟-N-(6-(甲基氨基)-4-(4-甲基哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-129);且

[1597] N-(4-(2,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-255)。

[1598] 实施例4:2-氨基-N-(4-(4-(4-乙基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-9)

[1599]



[1600] 步骤1:1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸(化合物I-N-92)

[1601] 将根据与实施例1中所述的方法类似的方法制备的1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)吡啶-4-基)哌啶-4-甲酸叔丁酯溶于DCM(5mL)。添加TFA(1mL,12.98mmol)并在RT搅拌混合物5hr。浓缩反应混合物以得到1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-甲酸,为米色固体,未经进一步纯化,将其用于下一步骤中。MS(ES+)418.1.

[1602] 步骤2:2-氨基-N-(4-(4-(4-乙基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺

[1603] 在室温搅拌1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)吡啶-4-基)哌啶-4-甲酸(三氟乙酸(2))(30mg,)、(苯并三唑-1-基氧基-二甲基氨基-亚甲基)-二甲基-铵(四氟化硼离子(1))(46.17mg,0.1438mmol)和TEA(33.07mg,45.55μL,0.3268mmol)在DMF中的混合物5分钟,接着添加1-乙基哌嗪(13.68mg,0.1198mmol)。在室温搅拌混合物1小时。将混合物过滤并通过fractionlynx直接纯化,得到2-氨基-N-(4-(4-(4-乙基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺。收率38% MS(ES+)514.0.

[1604] 使用与实施例4类似的方法成功地制备了下面的化合物:

[1605] 2-氨基-N-(4-(4-(氮杂环丁烷-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-8);

[1606] 2-氨基-6-氟-N-(5-氟-4-(4-(八氢吡咯并[1,2-a]吡嗪-2-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-10);

[1607] (R)-2-氨基-N-(4-(4-(3-(二甲基氨基)吡咯烷-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-11);

[1608] N-(4-(4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-羰基)哌啶-1-基)-5-氟吡

啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-14) ;

[1609] 2- 氨基 -N-(4-(4-((3-(二甲基氨基) 丙基)(甲基) 氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-16) ;

[1610] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(5- 甲基八氢吡咯并 [3,4-c] 吡咯 -2- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-18) ;

[1611] 2- 氨基 -N-(4-(4-(叔丁基氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-19) ;

[1612] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((1- 甲基哌啶 -4- 基) 氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-20) ;

[1613] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3- 甲氧基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-21) ;

[1614] 2- 氨基 -N-(4-(4-(3-(二甲基氨基) 氮杂环丁烷 -1- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-22) ;

[1615] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((1- 甲基氮杂环丁烷 -3- 基) 氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-23) ;

[1616] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((1- 甲基吡咯烷 -3- 基) 氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-24) ;

[1617] 2- 氨基 -N-(4-(4-((3-(二甲基氨基) 丙基) 氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-26) ;

[1618] 2- 氨基 -N-(4-(4-(二甲基氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-29) ;

[1619] 2- 氨基 -N-(4-(4-((2-(二甲基氨基) 乙基) 氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-30) ;

[1620] 2- 氨基 -N-(4-(4-((2-(二甲基氨基) 乙基)(甲基) 氨基甲酰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-31) ;

[1621] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-32) ;

[1622] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(甲基氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-33) ;

[1623] 2- 氨基 -N-(4-(4-(4- 环丁基哌嗪 -1- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-35) ;

[1624] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(吗啉 -4- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-36) ;

[1625] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(氧杂环丁烷 -3- 基氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-37) ;

[1626] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基 -4,7- 二氮杂螺 [2.5] 辛烷 -7- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-38) ;

[1627] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((2- 甲氧基乙基)(甲基) 氨基甲酰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-40) ;

[1628] 2-氨基-6-氟-N-(5-氟-4-(4-(3-羟基氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-41);

[1629] 2-氨基-N-(4-(4-((2-(氮杂环丁烷-1-基)乙基)氨基甲酰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-42);

[1630] 2-氨基-6-氟-N-(5-氟-4-(4-(3-(吡咯烷-1-基)氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-43);

[1631] N-(4-(4-(1,4-二氮杂双环[3.2.1]辛烷-4-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-46);

[1632] (S)-2-氨基-N-(4-(4-(3,4-二甲基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-47);

[1633] N-(4-(4-([1,3'-二氮杂环丁烷]-1'-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-49);

[1634] (R)-2-氨基-N-(4-(4-(3,4-二甲基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-50);

[1635] 2-氨基-6-氟-N-(5-氟-4-(4-(8-甲基-3,8-二氮杂双环[3.2.1]辛烷-3-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-52);

[1636] 2-氨基-6-氟-N-(5-氟-4-(4-(5-甲基-2,5-二氮杂双环[2.2.1]庚烷-2-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-53);

[1637] 2-氨基-6-氟-N-(5-甲基-4-(4-(4-甲基哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-55);

[1638] 2-氨基-6-氟-N-(5-氟-4-(4-(3-(哌啶-1-基)氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-57);

[1639] (S)-N-(4-(4-([1,3'-二吡咯烷]-1'-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-58);

[1640] 2-氨基-6-氟-N-(5-氟-4-(4-(4-(吡咯烷-1-基)哌啶-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-59);

[1641] N-(4-(4-([1,4'-二哌啶]-1'-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-60);

[1642] 2-氨基-6-氟-N-(5-氟-4-(4-(3-羟基-3-甲基氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-63);

[1643] 2-氨基-6-氟-N-(5-氟-4-(4-(3-(哌啶-1-基)吡咯烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-64);

[1644] 2-氨基-6-氟-N-(5-氟-4-(4-(3-氟氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-67);

[1645] 2-氨基-N-(4-(4-(4-(氮杂环丁烷-1-基)哌啶-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-68);

[1646] N-(4-(4-(1,4-二氮杂双环[3.2.1]辛烷-4-羰基)哌啶-1-基)-5-氯吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-69);

[1647] N-(4-(4-((5S)-1,4-二氮杂双环[3.2.1]辛烷-4-羰基)哌啶-1-基)-5-氟吡

啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-70) ;

[1648] N-(4-(4-((5R)-1,4- 二氮杂双环 [3.2.1] 辛烷 -4- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-71) ;

[1649] N-(4-(4-(2- 氧杂 -6- 氮杂螺 [3.3] 庚烷 -6- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-72) ;

[1650] 2- 氨基 -N-(4-(4-(3,3- 二氟氮杂环丁烷 -1- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-73) ;

[1651] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3- 氟氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-74) ;

[1652] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3- 甲氧基 -3- 甲基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-75) ;

[1653] 2- 氨基 -N-(4-(4-(3- 氰基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-76) ;

[1654] 2- 氨基 -N-(4-(4-(氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-77) ;

[1655] 2- 氨基 -6- 氟 -N-(4-(4-(3- 甲氧基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-78) ;

[1656] 2- 氨基 -6- 氟 -N-(4-(4-(3- 甲氧基 -3- 甲基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-79) ;

[1657] 2- 氨基 -N-(4-(4-(3,3- 二氟氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-80) ;

[1658] 2- 氨基 -N-(4-(4-(3- 氰基氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-81) ;

[1659] 2- 氨基 -6- 氟 -N-(4-(4-(3- 氟氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-82) ;

[1660] 2- 氨基 -6- 氟 -N-(4-(4-(吡咯烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-83) ;

[1661] N-(4-(4-(2- 氧杂 -6- 氮杂螺 [3.4] 辛烷 -6- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-84) ;

[1662] 2- 氨基 -6- 氟 -N-(4-(4-(吗啉 -4- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-85) ;

[1663] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3-(甲基磺酰基) 氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-86) ;

[1664] N-(4-(4-(1,4- 二氮杂双环 [3.2.2] 壬烷 -4- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-87) ;

[1665] N-(4-(4-(2- 氧杂 -6- 氮杂螺 [3.3] 庚烷 -6- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-88) ;

[1666] 2- 氨基 -6- 氟 -N-(4-(4-(3-(甲基磺酰基) 氮杂环丁烷 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-89) ;

[1667] N-(4-(4-(1-氧杂-6-氮杂螺[3.3]庚烷-6-羰基)哌啶-1-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-90);

[1668] 2-氨基-N-(4-(4-(3-乙氧基氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-91);

[1669] 2-氨基-6-氟-N-(5-氟-4-(4-(4-(3-甲基氧杂环丁烷-3-基)哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-92);

[1670] (R)-2-氨基-6-氟-N-(4-(4-(3-甲氧基吡咯烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-93);

[1671] (S)-2-氨基-6-氟-N-(4-(4-(3-甲氧基吡咯烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-94);

[1672] 4-(1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-羰基)-1-甲基哌嗪1-氧化物(化合物I-G-95);

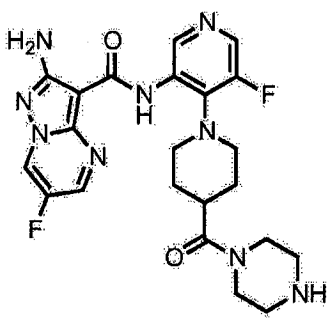
[1673] 2-氨基-6-氟-N-(5-氟-4-(4-(4-(1-甲基氮杂环丁烷-3-基)哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-96);

[1674] 2-氨基-6-氟-N-(5-氟-4-(4-(3-(甲氧基甲基)氮杂环丁烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-98);且

[1675] (S)-2-氨基-6-氟-N-(5-氟-4-(4-(3-甲氧基吡咯烷-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-99)。

[1676] 实施例5:2-氨基-6-氟-N-(5-氟-4-(4-(哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-12)

[1677]



[1678] 将使用与实施例4类似的方法制备的4-(1-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌啶-4-羰基)哌嗪-1-甲酸叔丁酯溶于DCM(5mL)/TFA(1mL,12.98mmol)的混合物中,并在RT搅拌90分钟,然后真空浓缩。通过fractionlynx纯化残余物。冻干清洁的级分,得到2-氨基-6-氟-N-(5-氟-4-(4-(哌嗪-1-羰基)哌啶-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。MS(ES+)486.2.

[1679] 使用与实施例5类似的方法成功地制备了下面的化合物:

[1680] 2-氨基-N-(4-(4-(3,3-二甲基哌嗪-1-羰基)哌啶-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-27);

[1681] N-(4-(4-(4,7-二氮杂螺[2.5]辛烷-7-羰基)哌啶-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-G-28);

[1682] 2-氨基-6-氟-N-(5-氟-4-(4-(3-(甲基氨基)氮杂环丁烷-1-羰基)哌

啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-34) ;

[1683] N-(4-(4-(3,8- 二氮杂双环 [3.2.1] 辛烷 -3- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-44) ;

[1684] (R)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-45) ;

[1685] 2- 氨基 -N-(5- 氯 -4-(4-(哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-48) ;

[1686] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(八氢吡咯并 [3,4-c] 吡咯 -2- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-51) ;

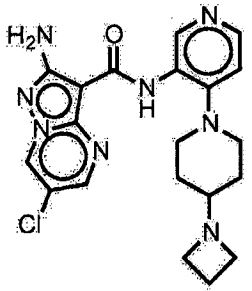
[1687] 2- 氨基 -6- 氟 -N-(5- 甲基 -4-(4-(哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-56) ;

[1688] (S)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(3- 甲基哌嗪 -1- 羰基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-61) ;且

[1689] N-(4-(4-(2,5- 二氮杂双环 [4.1.0] 庚烷 -2- 羰基) 哌啶 -1- 基)-5- 氟吡啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-G-62)。

[1690] 实施例 6 :2- 氨基 -N-(4-(4-(氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-93)

[1691]



[1692] 步骤 1 :2- 氨基 -6- 氯 -N-(4-(4- 氧代哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺

[1693] 向 2- 氨基 -6- 氯 -N-[4-(1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸 -8- 基)-3- 吡啶基] 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (根据与实施例 1 类似的方法制备)(420mg,0.9771mmol) 在四氢呋喃 (10mL) 中的溶液中加入 HCl(4.886mL,2M,9.771mmol)。在室温将得到的混合物搅拌过夜。将得到的反应混合物用水 (100mL) 稀释,用 2.5N 氢氧化钠水溶液使其变成碱性并用二氯甲烷 (100mL) 萃取三次。将合并的有机层用无水硫酸钠干燥,过滤并减压浓缩,得到 2- 氨基 -6- 氯 -N-(4-(4- 氧代哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺,为淡黄色固体,未经进一步纯化使用它。MS(ES+)386.1.

[1694] 步骤 2 :2- 氨基 -N-(4-(4-(氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺

[1695] 用 Dean-Stark 装置将 2- 氨基 -6- 氯 -N-[4-(4- 氧代 -1- 哌啶基)-3- 吡啶基] 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (50mg,0.1296mmol)、氮杂环丁烷 (盐酸 (1))(12.12mg,0.1296mmol) 和甲酸铵 (8.172mg,0.1296mmol) 在甲苯中的溶液中回流加热 1h。将反应

冷却至室温并蒸发。将得到的黄色固体溶于 DMSO 并通过 fractionlynx 纯化，得到 2- 氨基 -N-(4-(4-(氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基)-6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺，为白色固体。(27mg，31％)。MS(ES+)427.2.

[1696] 使用与实施例 6 类似的方法成功地制备了下面的化合物：

[1697] 2- 氨基 -6- 氯 -N-(4-(4-(3-(二甲基氨基) 氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-94)；

[1698] 2- 氨基 -6- 氯 -N-(4-(4-(3- 甲氧基吡咯烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-95)；

[1699] N-(4-(4-(2- 氧杂 -6- 氮杂螺 [3.3] 庚 -6- 基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-96)；

[1700] 2- 氨基 -6- 氯 -N-(4-(4-(4- 甲基哌嗪 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-97)；

[1701] (R)-2- 氨基 -6- 氯 -N-(4-(4-(3- 氟吡咯烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-98)；

[1702] N-(4-(4-(2- 氧杂 -6- 氮杂螺 [3.4] 辛烷 -6- 基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-99)；

[1703] 2- 氨基 -6- 氯 -N-(4-(4-(1- 氧化硫代吗啉代) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-100)；

[1704] 2- 氨基 -6- 氯 -N-(4-(4-(5,6- 二氢咪唑并 [1,5-a] 吡嗪 -7(8H)- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-101)；

[1705] 2- 氨基 -6- 氯 -N-(4-(4-(5,6- 二氢咪唑并 [1,2-a] 吡嗪 -7(8H)- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-102)；

[1706] (S)-2- 氨基 -6- 氯 -N-(4-(4-(3- 氟吡咯烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-103)；

[1707] 2- 氨基 -6- 氯 -N-(4-(4- 吗啉代哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-104)；

[1708] 2- 氨基 -6- 氯 -N-(4-(4-(吡咯烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-105)；

[1709] 2- 氨基 -6- 氯 -N-(4-(4-(3-(二甲基氨基) 吡咯烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-106)；

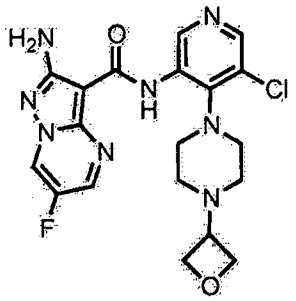
[1710] 2- 氨基 -6- 氯 -N-(4-(4-(3- 甲氧基氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-107)；

[1711] 2- 氨基 -6- 氯 -N-(4-(4-(3,3- 二氟氮杂环丁烷 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-108)；且

[1712] N-(4-(4-(6- 氧杂 -1- 氮杂螺 [3.3] 庚 -1- 基) 哌啶 -1- 基) 吡啶 -3- 基)-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-109)。

[1713] 实施例 7：2- 氨基 -N-(5- 氯 -4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-110)

[1714]



[1715] 向 2- 氨基 -N-(5- 氯 -4-(哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (51mg,0.13mmol)(根据与实施例 2 类似的方法合成) 在 THF(4mL) 中的溶液中加入氧杂环丁烷 -3- 酮 (14.31mg,11.63μL,0.1986mmol) 和三乙酰氧基硼氢化物 (钠离子 (1))(56.12mg,0.2648mmol),并在室温搅拌混合物 4h。将反应混合物分配在 $NaHCO_3$ 饱和水溶液和乙酸乙酯之间。将有机萃取物用盐水洗涤,用 $MgSO_4$ 干燥并减压浓缩。通过 fractionlynx 纯化残余物,得到 2- 氨基 -N-(5- 氯 -4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺。MS(ES+)447.2.

[1716] 根据与实施例 7 类似的方法合成了下面的化合物 :

[1717] 2- 氨基 -N-(5- 氯 -4-(8-(氧杂环丁烷 -3- 基) 六氢 -1H- 吡嗪并 [1,2-a] 吡嗪 -2(6H)- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-38) ;

[1718] (R)-2- 氨基 -N-(5- 环丙基 -4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-119) ;

[1719] (S)-2- 氨基 -N-(5- 环丙基 -4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-120) ;

[1720] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(四氢 -2H- 吡喃 -4- 基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-121) ;

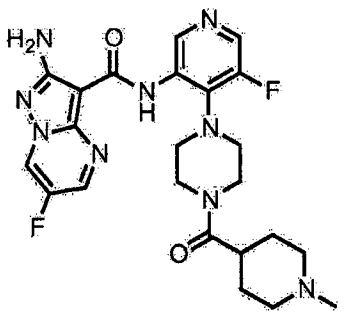
[1721] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-122) ;

[1722] 2- 氨基 -6- 氟 -N-(5- 甲基 -4-(4-(四氢 -2H- 吡喃 -4- 基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-123) ;且

[1723] 2- 氨基 -N-(5- 氯 -4-(4-(四氢呋喃 -3- 基) 哌嗪 -1- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-124)。

[1724] 实施例 8 :2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基哌啶 -4- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-128)

[1725]



[1726] 将 NMP(0.5mL) 中的 2- 氨基 -6- 氟 -N-(5- 氟 -4- 哌嗪 -1- 基 -3- 吡啶基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (79mg,0.2110mmol)(根据与实施例 2 类似的方法合成)、1- 甲基哌啶 -4- 甲酸 (盐酸 (1))(37.90mg,0.2110mmol)、TBTU(74.52mg,0.2321mmol)、Et_3N(46.97mg,64.70μL,0.4642mmol) 装入微波瓶,将所述管密封并在 100℃搅拌过夜。将混合物冷却至 RT 并装入 MeOH 预洗涤的 SCX 柱,用 MeOH 冲洗并用甲醇氨释放。减压下浓缩氨萃取物,得到 110mg 棕色油 / 胶状物,通过 Fraction Lynx 反相柱色谱法纯化它。将清洁的级分合并并冻干,得到 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基哌啶 -4- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺。MS(ES+)500.2.

[1727] 根据与实施例 8 类似的方法合成了下面的化合物 :

[1728] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(奎宁环 -4- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-134) ;

[1729] 2- 氨基 -N-(4-(4-(2-(二甲基氨基) 乙酰基) 哌嗪 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-153) ;

[1730] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基吡咯烷 -3- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-156) ;

[1731] (S)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基吡咯烷 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-157) ;

[1732] 2- 氨基 -N-(4-(4-(2-(氮杂环丁烷 -1- 基) 乙酰基) 哌嗪 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-160) ;

[1733] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基哌啶 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-173) ;

[1734] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(4- 甲基吗啉 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-174) ;

[1735] (R)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 甲基吡咯烷 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-181) ;

[1736] 2- 氨基 -N-(4-(4-(1- 乙基吡咯烷 -2- 羰基) 哌嗪 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-185) ;

[1737] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(2-(吡咯烷 -1- 基) 乙酰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-187) ;

[1738] (S)-2- 氨基 -6- 氟 -N-(4-(4-(1- 甲基吡咯烷 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-198) ;

[1739] (R)-2- 氨基 -6- 氟 -N-(4-(4-(1- 甲基吡咯烷 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3-

[1740] yl) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-199) ;

[1741] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(八氢吲嗪 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-203) ;

[1742] 2- 氨基 -N-(4-(4-(1- 乙基哌啶 -2- 羰基) 哌嗪 -1- 基)-5- 氟吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-204) ;

[1743] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(1- 异丙基吡咯烷 -2- 羰基) 哌嗪 -1- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-N-205) ;

[1744] 2-氨基-6-氟-N-(5-氟-4-(4-(1-异丙基吡咯烷-3-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-206);

[1745] 2-氨基-N-(4-(4-(1-乙基吡咯烷-3-羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-207);

[1746] 2-氨基-6-氟-N-(5-氟-4-(4-(1-(氧杂环丁烷-3-基)哌啶-4-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-211);

[1747] 2-氨基-6-氟-N-(5-氟-4-(4-(1-甲基哌啶-2-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-214);

[1748] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基吗啉-3-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-227);

[1749] 2-氨基-6-氟-N-(4-(4-(氧杂环丁烷-3-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-254);

[1750] N-(4-(2-乙酰基-2,7-二氮杂螺[3.5]壬-7-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-251);

[1751] N-(4-(4-乙酰基哌嗪-1-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-254);

[1752] N-(4-(2-乙酰基-2,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-257);

[1753] 甲基-4-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌嗪-1-甲酸酯(化合物I-N-261);

[1754] N-(4-(1-乙酰基-1,8-二氮杂螺[4.5]癸-8-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-262);

[1755] N-(4-(1-乙酰基哌啶-4-基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-69);

[1756] 2-氨基-N-(4-(1-(环丙烷羰基)哌啶-4-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-70);

[1757] 2-氨基-N-(4-(1-(1-氰基环丙烷羰基)哌啶-4-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-71);

[1758] 2-氨基-6-氟-N-(5-氟-4-(4-(四氢呋喃-3-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-274);

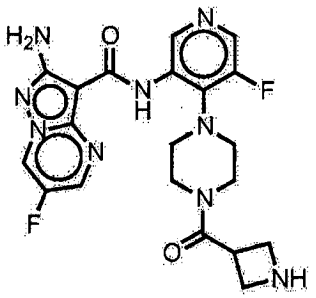
[1759] N-(4-(4-乙酰基哌嗪-1-基)-5-氟吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-275);

[1760] 2-氨基-N-(4-(4-(环丙烷羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-276);且

[1761] 2-氨基-6-氟-N-(5-氟-4-(4-(氧杂环丁烷-3-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-278)。

[1762] 实施例9:2-氨基-N-(4-(4-(氮杂环丁烷-3-羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-168)

[1763]



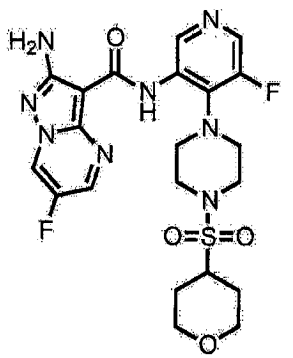
[1764] 将3-(4-(3-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-5-氟吡啶-4-基)哌嗪-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(73mg,0.1309mmol)(使用与实施例8类似的方法制备)溶于DCM(219.0μL)。添加TFA(298.5mg,201.7μL,2.618mmol)并在RT搅拌混合物2小时。真空浓缩反应混合物并通过fractionlynx纯化残余物,得到2-氨基-N-(4-(4-(氮杂环丁烷-3-羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺,为膏状固体。MS(ES+)458.1.

[1765] 根据与实施例9类似的方法合成了下面的化合物:

[1766] 2-氨基-6-氟-N-(5-氟-4-(4-(吗啉-2-羰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-172)。

[1767] 实施例10:2-氨基-6-氟-N-(5-氟-4-(4-((四氢-2H-吡喃-4-基)磺酰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-158)

[1768]



[1769] 将四氢吡喃-4-磺酰氯(16.28mg,0.08815mmol)加入2-氨基-6-氟-N-(5-氟-4-哌嗪-1-基-3-吡啶基)吡唑并[1,5-a]嘧啶-3-甲酰胺(30mg,0.08014mmol)(根据与实施例2类似的方法合成)和Et_3N(12.16mg,16.75μL,0.1202mmol)在DMF(0.2mL)中的混悬液中。通过fractionlynx HPLC纯化粗制混合物。将清洁的含水级分合并并冻干,得到2-氨基-6-氟-N-(5-氟-4-(4-((四氢-2H-吡喃-4-基)磺酰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。MS(ES+)523.1.

[1770] 根据与实施例10中描述的程序中所述方法类似的方法合成了下面的化合物:

[1771] 2-氨基-N-(4-(4-(环丙基磺酰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-159);

[1772] 2-氨基-6-氟-N-(5-氟-4-(4-((1-甲基哌啶-4-基)磺酰基)哌嗪-1-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-175);

[1773] 2-氨基-N-(4-(4-(环丙基磺酰基)哌嗪-1-基)吡啶-3-基)-6-氟吡唑并

[1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-176）；

[1774] 2- 氨基 -6- 氟 -N-(4-(4-((四氢 -2H- 吡喃 -4- 基）磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-177）；

[1775] 2- 氨基 -6- 氟 -N-(4-(4-(甲基磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-178）；

[1776] 2- 氨基 -6- 氟 -N-(4-(4-((四氢呋喃 -3- 基）磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-179）；

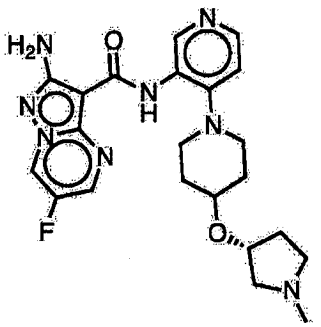
[1777] 2- 氨基 -6- 氟 -N-(4-(4-((1- 甲基哌啶 -4- 基）磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-188）；

[1778] 2- 氨基 -6- 氟 -N-(4-(4-(氧杂环丁烷 -3- 基磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-195）；且

[1779] 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-(氧杂环丁烷 -3- 基磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-202）。

[1780] 实施例 11 ：2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((四氢 -2H- 吡喃 -4- 基）磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-131）

[1781]



[1782] 将 (R)-2- 氨基 -6- 氟 -N-(4-(4-(吡咯烷 -3- 基氧基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（根据与实施例 2 类似的方法合成）溶解在 DCE(5.0mL) 和 AcOH(0.050mL) 中。添加甲醛 (37％水溶液，47.46mg，0.5848mmol) 并在 RT 搅拌混合物 30 分钟。分次添加三乙酰氧基硼氢化物 (boranuide)(钠离子 (1))(186mg，0.8772mmol)。在 RT 搅拌混合物 1 小时并通过添加水和甲醇将其淬灭。减压浓缩混合物并通过 fractionlynx 纯化残余物，得到 2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((四氢 -2H- 吡喃 -4- 基）磺酰基）哌嗪 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺。MS(ES+)455.2.

[1783] 根据与实施例 11 类似的方法合成了下面的化合物：

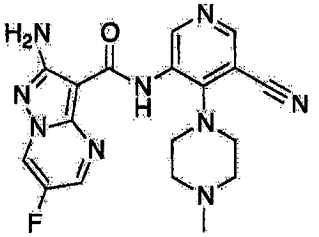
[1784] (R)-2- 氨基 -6- 氟 -N-(5- 氟 -4-(4-((1- 甲基吡咯烷 -3- 基）氧基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-132）；

[1785] 2- 氨基 -6- 氟 -N-(4-(4-((1- 甲基哌啶 -4- 基）氧基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-154）；且

[1786] 2- 氨基 -6- 氟 -N-(4-(4-((1- 甲基氮杂环丁烷 -3- 基）氧基）哌啶 -1- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-164）。

[1787] 实施例 12 ：2- 氨基 -N-(5- 氰基 -4-(4- 甲基哌嗪 -1- 基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-N-113）

[1788]



[1789] 将根据与实施例1类似的方法合成的2-氨基-N-[5-溴-4-(4-甲基哌嗪-1-基)-3-吡啶基]-6-氟-吡唑并[1,5-a]嘧啶-3-甲酰胺(80.4mg,0.1790mmol)、$Pd_2(dba)_3$(6.557mg,0.007160mmol)、氰化锌(18.92mg,10.23μL,0.1611mmol)和xantphos(8.286mg,0.01432mmol)的混合物置入密封的微波管中、抽真空并用氮气冲洗。添加溶剂DMF(1.6mL)并使氮气通过反应鼓泡(用针作为出口和入口)5分钟。在120℃加热反应1小时。LCMS显示反应接近完全,因此将其冷却至室温并装上SCX-2筒,用MeOH然后用NH_3/MeOH洗脱。将碱性级分蒸发并通过fractionlynx纯化和冻干,得到2-氨基-N-(5-氰基-4-(4-甲基哌嗪-1-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺,为白色固体。MS(ES+)396.2.

[1790] 实施例13:2-氨基-N-(4-(4-(氮杂环丁烷-3-羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-194);

[1791] 在RT将2-氨基-N-[4-[4-(氮杂环丁烷-3-羰基)哌嗪-1-基]-5-氟-3-吡啶基]-6-氟-吡唑并[1,5-a]嘧啶-3-甲酰胺(三氟乙酸(2))(20mg,0.02918mmol),(根据实施例9合成)和甲醛(3.552μL of 37% w/v,0.04377mmol)在DMF(1mL)中的溶液搅拌1小时。添加三乙酰氧基硼氢化物(钠离子(1))(9.277mg,0.04377mmol)并在RT搅拌反应混合物2小时,然后通过添加甲醇将其淬灭。通过fractionlynx HPLC纯化粗制混合物。将含水级分合并并冻干,得到2-氨基-N-(4-(4-(氮杂环丁烷-3-羰基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(3mg,21%)。MS(ES+)472.1.

[1792] 实施例14:2-氨基-N-(4-(4-(2-(氮杂环丁烷-1-基)-2-氧代乙基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-N-228)

[1793] 将1-(氮杂环丁烷-1-基)-2-氯乙酮(12.03mg,0.09003mmol)加入2-氨基-6-氟-N-(5-氟-4-哌嗪-1-基-3-吡啶基)吡唑并[1,5-a]嘧啶-3-甲酰胺(三氟乙酸(3))(50mg,0.06002mmol)(根据与实施例2类似的方法合成)和Et_3N(30.37mg,41.83μL,0.3001mmol)在DMF(2mL)中的溶液。在RT搅拌溶液18小时。

[1794] 通过fractionlynx HPLC纯化粗制混合物。将含水级分合并并冻干,得到2-氨基-N-(4-(4-(2-(氮杂环丁烷-1-基)-2-氧代乙基)哌嗪-1-基)-5-氟吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(30mg,71%)。MS(ES+)472.1.

[1795] 化合物分析数据

[1796]

化合物编号	LCMS ES+	LCMS (Rt分)	HNMR
I-N-1	413.3	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.46 (dd, J = 4.8, 2.5 Hz, 1H), 9.42 (s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.19 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.58 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.1 Hz, 2H), 3.60 (p, J = 6.3 Hz, 1H), 2.98 (t, J = 4.7 Hz, 4H), 2.50 (t, J = 3.5 Hz, 4H)。
I-N-2	392.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 9.47 (s, 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.20 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 5.3 Hz), 6.77 (s, 3H), 4.14 (s, 2H), 3.14 (dt, J = 12.9, 3.5 Hz, 2H), 2.77 (dd, J = 9.8, 5.2 Hz, 1H), 2.72 (td, J = 11.8, 11.4, 2.8 Hz, 2H), 1.91 - 1.82 (m, 2H), 1.67 - 1.55 (m, 2H)。
I-N-3	371.2	1.82*	^{1}H NMR (500 MHz, 甲醇-d4) δ 2.43 (3H、s), 2.75-2.75 (4H、m), 3.1-3.13 (4H、m), 7.22-7.23 (1H, d), 8.21-8.22 (1H, d), 8.72-8.73 (1H, d), 9.02-9.04 (1H, dd), 9.42 91H, s)。
I-N-4	399.2	2.16*	----------
I-N-5	411.3	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.54 (s, 1H), 9.27 (s, 1H), 8.96 (s, 1H), 8.17 (s, 1H), 6.80 (br, 2H), 3.23 (m, 4H), 2.93 (s, 3H), 2.52 (br, 4H), 2.13 (m, 1H), 1.09 (m, 2H), 0.92 (m, 2H)。
I-N-6	460.2	0.67	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.64 (s, 2H), 9.00 (s, 1H), 8.23 (s, 1H), 3.82 (td, J = 11.5, 2.9 Hz, 1H), 3.53 - 3.43 (m, 1H), 3.04 - 2.88 (m, 5H), 2.90 - 2.74 (m, 3H), 2.64 - 2.54 (m, 1H), 2.42 - 2.36 (m, 1H), 2.35 (s, 3H), 2.02 - 1.92 (m, 1H)。

[1797]

I-N-7	339.2	0.51	^{1}H NMR (500 MHz, 甲醇-d4)δ 9.62 (d, J = 0.6 Hz, 1H), 9.35 (t, J = 1.4 Hz, 1H), 9.03 (dd, J = 4.4, 2.5 Hz, 1H), 8.62 (d, J = 5.3 Hz, 1H), 8.47 (dd, J = 2.6, 0.5 Hz, 1H), 7.98 (dd, J = 1.9, 1.5 Hz, 1H), 7.86 (dd, J = 1.9, 1.3 Hz, 1H), 7.74 (dd, J = 5.2, 0.6 Hz, 1H)。
I-N-8	396.3	0.55	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.04 (d, J = 0.8 Hz, 1H), 8.89 (dd, J = 4.4, 2.6 Hz, 1H), 8.63 (d, J = 2.5 Hz, 1H), 8.48 (dd, J = 6.1, 0.8 Hz, 1H), 8.45 (d, J = 0.9 Hz, 1H), 8.06 (d, J = 0.7 Hz, 1H), 8.02 (d, J = 6.3 Hz, 1H), 3.35 (dd, J = 8.3, 7.0 Hz, 2H), 3.05 (dd, J = 8.0, 7.2 Hz, 2H), 2.78 (s, 3H)。
I-N-9	410.3	0.67	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.06 (d, J = 0.9 Hz, 1H), 8.93 - 8.87 (m, 1H), 8.64 (dd, J = 2.6, 0.7 Hz, 1H), 8.49 (dd, J = 6.2, 0.8 Hz, 1H), 8.46 (d, J = 0.9 Hz, 1H), 8.07 (s, 1H), 8.02 (d, J = 6.2 Hz, 1H), 3.51 - 3.44 (m, 2H), 3.15 - 3.08 (m, 2H), 2.99 (s, 6H)。
I-N-10	427.3	0.59	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.42 (s, 1H), 9.06 - 8.98 (m, 1H), 8.77 - 8.70 (m, 1H), 8.22 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 5.53 (s, 2H), 4.00 (td, J = 8.6, 4.1 Hz, 1H), 3.94 (dd, J = 8.8, 6.8 Hz, 1H), 3.83 (td, J = 8.5, 7.2 Hz, 1H), 3.73 (dd, J = 8.8, 6.5 Hz, 1H), 3.22 - 3.15 (m, 1H), 3.15 - 3.06 (m, 4H), 2.90 - 2.80 (m, 2H), 2.78 - 2.69 (m, 2H), 2.24 - 2.15 (m, 1H), 1.97 - 1.85 (m, 1H)。
I-N-11			^{1}H NMR (500 MHz, 甲醇-d4) δ 9.39 (d, J = 0.5 Hz, 1H), 9.05 (dd, J = 4.4, 2.6 Hz, 1H), 8.74 - 8.68 (m, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.23 (dd, J = 5.5, 0.5 Hz, 1H), 4.10 - 4.00 (m, 2H), 3.53 - 3.43 (m, 2H), 3.18 - 3.09 (m, 4H), 2.93 - 2.83 (m, 4H), 2.60 (tt, J = 11.3, 3.8 Hz, 1H), 1.93 (dm, 2H), 1.60 (qd, J = 12.2, 4.5 Hz, 2H)。

[1798]

I-N-12	427.3	0.59	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.42 (s, 1H), 9.06 - 8.98 (m, 1H), 8.77 - 8.70 (m, 1H), 8.22 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 5.53 (s, 2H), 4.00 (td, J = 8.6, 4.1 Hz, 1H), 3.94 (dd, J = 8.8, 6.8 Hz, 1H), 3.83 (td, J = 8.5, 7.2 Hz, 1H), 3.73 (dd, J = 8.8, 6.5 Hz, 1H), 3.22 - 3.15 (m, 1H), 3.15 - 3.06 (m, 4H), 2.90 - 2.80 (m, 2H), 2.78 - 2.69 (m, 2H), 2.24 - 2.15 (m, 1H), 1.97 - 1.85 (m, 1H)。
I-N-13	431.0	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.49 (q, J = 2.3 Hz, 2H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H),6.79 (s, 2H), 4.60 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.63 (p, J = 6.3 Hz, 1H), 3.13 (m, 4H), 2.50 (m, 4H)。
I-N-14	405.1	0.7	^{1}H NMR (500 MHz, DMSO-d6) δ 2.97 (3H、s), 3.21 (2H, m), 3.41 (4H、m), 3.60 (掩蔽的信号), 6.86 (2H, br s), 8.32 (1H, d), 8.83 (1H, m), 9.47 (2H, m) 和 10.00 (2H, m) ppm.
I-N-15	389.0	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.49 (s, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.8 Hz, 1H), 6.80 (s, 2H), 3.10 (t, J = 4.6 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.33 (s, 3H)。
I-N-16	427.2	1.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.1 (s, 1H), 9.47 (s, 1H), 9.36 (s, 1H), 8.80, (s, 1H), 8.05 (s, 1H), 6.78 (br, 2H), 4.59 (m, 2H), 4.45 (m, 2H), 3.57 (m, 1H), 3.12 (br, 4H) 2.52 (br, 4H), 2.40 (s, 3H)。
I-N-17	385.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ1.26-1.28 (3H、m), 3.20-3.40 (4H、masked)、3.60-3.80 (6H、m)、6.80 (2H, s), 7.49-7.51 (1H, d), 8.44-8.45 (1H, d), 9.01-9.02 (1H, dd), 9.42 (1H, s), 9.54-9.55 (1H, dd), 9.65 (1H, s), 9.90-10.05 (1H, br s)。
I-N-18	397.0	1.74*	----------

[1799]

I-N-19			^{1}H NMR (500 MHz, 甲醇-d4) δ 9.43 (d, J = 1.1 Hz, 1H), 9.14 (dd, J = 4.3, 2.5 Hz, 1H), 8.84 (dd, J = 2.6, 0.6 Hz, 1H), 8.43 (dd, J = 6.6, 1.1 Hz, 1H), 7.61 (d, J = 6.7 Hz, 1H), 4.23 (dd, J = 11.0, 3.4 Hz, 1H), 4.11 (td, J = 8.7, 4.3 Hz, 1H), 4.04 (d, J = 6.2 Hz, 1H), 3.92 (dd, J = 10.8, 6.1 Hz, 1H), 3.87 - 3.70 (m, 5H), 3.57 - 3.43 (m, 4H), 2.52 - 2.39 (m, 1H), 2.24 (ddd, J = 10.5, 6.2, 2.9 Hz, 1H)。
I-N-20	439.2	2.52*	----------
I-N-21	397.2	2.04*	----------
I-N-22	415.4	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 2.61 (2H, t), 2.68 (4H, m), 2.95 (4H, m), 3.26 (3H, s), 3.48 (2H, t), 6.77 (2H, br s), 7.17 (1H, m), 8.22 (1H, d), 8.81 (1H, m), 9.42 (1H, s), 9.48 (1H, dd)和 9.79 (1H, s) ppm.
I-N-23	427.3	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.65 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.61 (dt, J = 17.9, 6.5 Hz, 2H), 4.52 (t, J = 6.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 3.61 (p, J = 6.3 Hz, 1H), 2.95 (d, J = 11.1 Hz, 1H), 2.86 - 2.73 (m, 2H), 2.71 - 2.59 (m, 1H), 2.41 - 2.27 (m, 1H), 2.12 - 2.02 (m, 1H), 0.83 (d, J = 6.2 Hz, 3H)。1H多重峰隐蔽在水峰下。
I-N-24	427.3	0.64	^{1}H NMR (500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.65 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 6.76 (s, 2H), 4.61 (dt, J = 17.9, 6.5 Hz, 2H), 4.52 (t, J = 6.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 3.61 (p, J = 6.3 Hz, 1H), 2.95 (d, J = 11.2 Hz, 1H), 2.88 - 2.73 (m, 2H), 2.71 - 2.58 (m, 1H), 2.41 - 2.26 (m, 1H), 2.06 (t, J = 9.8 Hz, 1H), 0.82 (d, J = 6.1 Hz, 3H)。1H多重峰隐蔽在水峰下。

[1800]

I-N-25	443.0	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.21 (d, J = 1.1 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.82 (s, 2H), 4.69 (d, J = 6.8 Hz, 2H), 4.31 (d, J = 6.9 Hz, 2H), 3.59 (s, 4H), 3.01 (s, 4H), 1.54 (s, 3H)。
I-N-26	339.1	0.61	^{1}H NMR (500 MHz, 丙酮-d6) δ 11.17 (s, 2H), 9.80 (t, J = 0.5 Hz, 1H), 8.99 (dd, J = 4.6, 2.6 Hz, 1H), 8.70 (d, J = 2.6 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.30 (dd, J = 2.5, 0.6 Hz, 1H), 8.05 (dd, J = 1.9, 0.6 Hz, 1H), 7.57 (dd, J = 5.3, 0.5 Hz, 1H), 6.65 (dd, J = 2.5, 1.8 Hz, 1H), 6.37 (s, 1H)。
I-N-27	407.1	0.69	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.79 (s, 1H), 9.02 (dd, J = 4.4, 2.5 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 1.2, 0.7 Hz, 1H), 8.10 (t, J = 1.3 Hz, 1H), 7.61 (d, J = 5.2 Hz, 1H)。
I-N-28	353.2	0.55	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.66 (d, J = 0.6 Hz, 1H), 9.08 (dd, J = 4.4, 2.5 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.49 (dd, J = 2.5, 0.5 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 5.2, 0.6 Hz, 1H), 2.62 (s, 3H)。
I-N-29	355.1	0.56	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.63 (d, J = 0.6 Hz, 1H), 9.14 (s, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.77 (t, J = 1.6 Hz, 1H), 7.71 (dd, J = 5.3, 0.6 Hz, 1H)。
I-N-30	421.2	0.72	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.01 - 9.94 (m, 1H), 9.65 (s, 1H), 9.03 (dd, J = 4.4, 2.5 Hz, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.27 (ddd, J = 2.6, 1.2, 0.5 Hz, 1H), 7.89 (q, J = 1.4 Hz, 1H), 7.59 (dt, J = 5.1, 0.6 Hz, 1H), 2.32 (s, 3H)。

[1801]

I-N-31	425.3	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 9.18 (s, 1H), 8.80 (dd, J = 2.5, 0.5 Hz, 1H), 8.50 (s, 1H), 8.13 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 5.7 Hz, 1H), 6.65 (s, 2H), 4.60 - 4.50 (m, 4H), 3.70 (p, J = 6.4 Hz, 1H), 3.42 - 3.27 (m, 1H), 3.17 (ddd, J = 12.6, 10.4, 2.7 Hz, 1H), 2.76 (ddd, J = 8.1, 6.6, 4.2 Hz, 1H), 2.66 (ddd, J = 11.0, 4.1, 2.5 Hz, 1H), 2.59 - 2.51 (m, 1H), 2.31 - 2.16 (m, 1H), 0.61 (td, J = 5.6, 4.2 Hz, 1H), 0.37 (td, J = 6.8, 5.8 Hz, 1H)。
I-N-32	453.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.31 (s, 1H), 8.81 (d, J = 2.5 Hz, 1H), 7.97 (d, J = 0.6 Hz, 1H), 6.77 (s, 2H), 4.59 (t, J = 6.5 Hz, 2H), 4.45 (t, J = 6.1 Hz, 2H), 3.66 - 3.51 (m, 1H), 3.31 - 3.18 (m, 4H), 2.51 (p, J = 1.9 Hz, 4H), 2.13 (tt, J = 8.4, 5.4 Hz, 1H), 1.11 - 1.01 (m, 2H), 0.90 - 0.78 (m, 2H)。
I-N-33	397.2	2.25*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.55 (d, *J* = 4.0 Hz, 1H), 9.38 (s, 1H), 9.02 (s, 1H), 8.45 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 4.0 Hz, 1H), 6.80 (br, 2H), 2.90 (br, 8H), 0.87 (m, 2H), 0.80 (m, 2H)。
I-N-34	429.3	0.8	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.37 (s, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.16 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 2.93 (t, J = 4.6 Hz, 4H), 2.72 (t, J = 4.7 Hz, 4H), 1.07 (s, 9H)。

[1802]

I-N-35	431.2	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.29 (s, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.15 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 4.52 - 4.42 (m, 1H), 3.77 (t, J = 4.7 Hz, 1H), 3.31 - 3.22 (m, 1H), 3.18 (d, J = 11.0 Hz, 1H), 2.76 - 2.60 (m, 1H), 2.59 - 2.53 (m, 1H), 2.48 - 2.40 (m, 1H), 2.32 (s, 6H), 1.81 - 1.57 (m, 2H)。
I-N-36	445.2	0.7	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.53 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.22 (dd, J = 5.3, 0.6 Hz, 1H), 6.81 (s, 2H), 4.24 (s, 1H), 3.02 (td, J = 11.5, 10.3, 3.9 Hz, 2H), 2.87 (dd, J = 11.3, 4.2 Hz, 2H), 2.33 (s, 6H), 2.31 (s, 2H), 2.07 (td, J = 12.5, 4.2 Hz, 2H), 1.50 (d, J = 12.8 Hz, 2H)。
I-N-37	415.2	0.7	----------
I-N-38	502.2	1.97*	^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.73 (s, 1H), 8.74 (s, 1H), 8.51 (dd, J = 3.8, 2.5 Hz, 1H), 8.25 (s, 1H), 5.92 (s, 2H), 4.66 (dt, J = 19.3, 6.5 Hz, 2H), 4.57 (s, 1H), 3.87 (s, 1H), 3.62 - 3.39 (m, 2H), 2.92 (s, 2H), 2.79 (s, 2H), 2.65 - 2.44 (m, 2H), 2.28 (s, 1H), 1.89 (s, 1H), 1.67 (s, 2H)。
I-N-39	415.2	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.37 (s, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.95 (t, J = 4.7 Hz, 4H), 2.76 (s, 2H), 2.72 - 2.63 (m, 3H), 1.04 (d, J = 6.5 Hz, 6H)。

[1803]

I-N-40	415.2	0.72	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.34 (s, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.34 - 3.19 (m, 1H), 3.09 (d, J = 11.5 Hz, 1H), 2.69 - 2.47 (m, 3H), 2.09 (d, J = 5.2 Hz, 6H), 1.99 (d, J = 12.3 Hz, 1H), 1.90 - 1.70 (m, 2H), 1.28 (dd, J = 11.2, 6.4 Hz, 1H)。
I-N-41	421.1	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 2.32 (3H, s), 2.60 (4H, m), 3.25 (4H, m), 6.85 (2H, br s), 8.26 (1H, s), 8.59 (1H, m), 9.44 (1H, m), 9.53 (1H, s)和 10.28 (1H, br s) ppm.
I-N-42	414.1	0.65	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.05 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 1.3 Hz, 1H), 8.09 (dd, J = 7.3, 1.4 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 4.92 (d, J = 2.4 Hz, 2H), 4.05 - 4.01 (m, 1H), 2.45 - 2.37 (m, 2H), 2.22 - 2.14 (m, 2H), 2.10 - 2.03 (m, 2H), 1.89 - 1.82 (m, 2H)。
I-N-43	401.1	0.63	^{1}H NMR (500 MHz, 甲醇-d4) δ 8.89 (d, J = 2.2 Hz, 1H), 8.62 (s, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 5.8 Hz, 1H), 6.96 (d, J = 5.8 Hz, 1H), 3.45 - 3.39 (m, 2H), 3.39 - 3.31 (m, 2H), 2.72 - 2.67 (m, 2H), 2.66 - 2.60 (m, 2H), 2.26 (s, 3H), 1.93 - 1.85 (m, 2H)。
I-N-44	410.1	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.54 (s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.33 - 7.21 (m, 2H), 6.93 (d, J = 1.3 Hz, 1H), 6.78 (s, 2H), 4.24 - 4.10 (m, 4H), 3.62 - 3.50 (m, 2H)。
I-N-45	429.2	2.29*	----------

[1804]

I-N-46	459.2	0.8	^{1}H NMR (500 MHz, DMSO-d6) δ 10.02 (s, 1H), 9.50 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 3.16 (s, 3H), 2.94 - 2.83 (m, 4H), 2.40 (s, 2H), 2.31 (s, 6H), 2.06 - 1.95 (m, 2H), 1.84 - 1.73 (m, 2H)。
I-N-47	431.2	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.38 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.4, 0.5 Hz, 1H), 6.82 (s, 2H), 3.50 (dd, J = 9.9, 4.1 Hz, 1H), 3.28 - 3.23 (m, 1H), 3.18 (dd, J = 11.0, 2.3 Hz, 1H), 3.12 (s, 3H), 3.07 - 3.00 (m, 1H), 2.89 - 2.77 (m, 2H), 2.61 - 2.53 (m, 1H), 2.50 - 2.45 (m, 2H), 2.31 (s, 3H)。
I-N-48	427.2	0.79	^{1}H NMR (500 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.94 (t, J = 4.8 Hz, 4H), 2.91 - 2.82 (m, 1H), 2.50 - 2.46 (m, 4H), 1.99 (ddtd, J = 11.2, 8.7, 4.5, 2.6 Hz, 2H), 1.88 - 1.74 (m, 2H), 1.66 (tdd, J = 10.9, 6.0, 2.1 Hz, 2H)。
I-N-49	444.2	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.74 (s, 1H), 9.46 - 9.36 (m, 2H), 8.63 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.94 (t, J = 4.7 Hz, 4H), 2.69 - 2.62 (m, 4H), 2.53 (d, J = 6.9 Hz, 2H), 2.38 (dd, J = 7.8, 5.8 Hz, 2H), 2.17 (s, 6H)。
I-N-50	402.1	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 9.39 (d, J = 2.2 Hz, 1H), 9.28 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 6.75 (s, 2H), 6.20 (s, 1H), 5.66 (s, 2H), 2.92 - 2.84 (m, 4H), 2.50 (s, 4H), 2.24 (s, 3H)。

[1805]

I-N-51	401.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.62 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 2.97 (t, J = 4.8 Hz, 4H), 2.64 (d, J = 9.5 Hz, 4H), 2.50 - 2.43 (m, 2H), 1.05 (t, J = 7.1 Hz, 3H)。
I-N-52	421.0	0.75	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.53 (s, 1H), 9.47 (d, J = 2.2 Hz, 1H), 9.25 (s, 1H), 8.92 (d, J = 2.2 Hz, 1H), 7.34 (s, 1H), 6.84 (s, 2H), 3.65 - 3.48 (m, 4H), 3.32 - 3.21 (m, 2H), 3.15 - 3.04 (m, 2H), 2.97 (s, 3H)。
I-N-53	415.2	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.52 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.31 (s, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.12 (dd, J = 5.4, 0.5 Hz, 1H), 6.84 (s, 2H), 2.88 - 2.81 (m, 2H), 2.77 (s, 2H), 2.61 (t, J = 5.0 Hz, 2H), 2.19 (s, 3H), 1.14 (s, 6H)。
I-N-54	401.2	0.39	^{1}H NMR (500 MHz, DMSO-d6) δ 9.74 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.11 - 2.99 (m, 2H), 2.90 - 2.75 (m, 2H), 2.60 - 2.52 (m, 1H), 2.49 - 2.42 (m, 1H), 2.43 - 2.34 (m, 1H), 2.27 (s, 3H), 0.99 (d, J = 6.2 Hz, 3H)。
I-N-55	387.1	1.92*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.27 (d, J = 0.9 Hz, 1H), 9.00 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.25 (dd, J = 6.3, 0.9 Hz, 1H), 7.39 (d, J = 6.3 Hz, 1H), 3.74 (d, J = 11.8 Hz, 1H), 3.59 - 3.50 (m, 1H), 3.46 (d, J = 12.5 Hz, 1H), 3.38 - 3.22 (m, 2H), 3.13 - 3.02 (m, 1H), 2.95 (dd, J = 11.9, 9.7 Hz, 1H), 2.20 - 2.06 (m, 2H), 1.95 - 1.80 (m, 3H), 1.57 (dtd, J = 12.9, 10.5, 5.0 Hz, 2H)。

[1806]

I-N-56	413.1	0.65	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.10 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 1.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 6.9, 1.2 Hz, 1H), 7.50 (d, J = 6.9 Hz, 1H), 4.59 (ddd, J = 5.8, 3.8, 1.9 Hz, 1H), 4.14 - 4.04 (m, 2H), 3.74 - 3.67 (m, 2H), 3.67 - 3.57 (m, 2H), 3.50 (ddd, J = 14.3, 11.3, 6.4 Hz, 2H), 2.51 - 2.41 (m, 2H), 2.35 - 2.24 (m, 2H)。
I-N-57	401.2	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 2.30 (3H, s), 2.38 (3H, s), 2.57 (4H, m), 3.09 (4H, m), 6.83 (2H, br s), 8.05 (1H, s), 8.60 (1H, m), 9.34 (1H, s), 9.43 (1H, s)和 10.12 (1H, br s) ppm
I-N-58	429.1	0.62	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.40 (d, J = 0.5 Hz, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.25 (dd, J = 5.5, 0.5 Hz, 1H), 4.76 (t, J = 6.7 Hz, 2H), 4.65 (dd, J = 6.5, 5.9 Hz, 2H), 3.72 - 3.63 (m, 1H), 3.15 (t, J = 4.9 Hz, 5H), 2.65 (t, J = 4.8 Hz, 5H)。
I-N-59	387.0	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H),7.18 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 2.96 (t, J = 4.8 Hz, 4H), 2.56 (t, J = 4.5 Hz, 4H), 2.28 (s, 3H)。
I-N-60	431.2	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.44 - 9.39 (m, 2H), 8.63 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.81 (s, 2H), 3.49 (t, J = 5.6 Hz, 2H), 3.26 (s, 3H), 2.95 (t, J = 4.7 Hz, 4H), 2.68 (d, J = 4.2 Hz, 4H), 2.61 (t, J = 5.6 Hz, 2H)。
I-N-61	442.3	0.59	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.39 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.40 (dd, J = 6.7, 1.2 Hz, 1H), 7.60 (d, J = 6.7 Hz, 1H), 3.92 (d, J = 12.7 Hz, 2H), 3.79 (d, J = 12.1 Hz, 2H), 3.60 (d, J = 12.3 Hz, 2H), 3.10 - 2.97 (m, 2H), 2.95 (s, 3H), 2.86 - 2.58 (m, 5H)。

[1807]

I-N-62	427.0	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.21 (d, J = 0.9 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.54 (d, J = 6.5 Hz, 1H), 6.78 (s, 2H), 4.68 (d, J = 7.0 Hz, 2H), 4.30 (d, J = 6.8 Hz, 2H), 3.58 (s, 4H), 2.98 (s, 4H), 1.54 (s, 3H)。
I-N-63	417.1	0.47	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.40 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 4.43 (t, J = 5.5 Hz, 1H), 3.63 (ddd, J = 11.0, 5.6, 3.9 Hz, 1H), 3.28 - 3.20 (m, 1H), 3.08 - 2.97 (m, 1H), 2.93 - 2.75 (m, 2H), 2.54 (ddd, J = 11.1, 3.6, 1.8 Hz, 2H), 2.37 (H, J = 1.7 Hz, 1H), 2.31 (s, 3H)。
I-N-64	413.2	0.77	^{1}H NMR (500 MHz, DMSO-d6) δ 9 .77 (s, 1H), 9.41 (d, J = 2.2 Hz, 1H), 9.39 (s, 1H), 8.67 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 5.4 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 6.80 (s, 2H), 2.90 (t, J = 4.9 Hz, 4H), 2.77 (d, J = 5.3 Hz, 4H), 1.80 (pd, J = 6.6, 4.2, 3.4 Hz, 1H), 0.45 (dq, J = 6.6, 4.3, 3.8 Hz, 2H), 0.36 - 0.29 (m, 2H)。
I-N-65	413.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.46 - 9.39 (m, 2H), 8.58 (d, J = 2.3 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.4 Hz, 1H), 6.82 (s, 2H), 3.26 - 3.20 (m, 1H), 3.14 (d, J = 11.5 Hz, 1H), 3.05 - 2.96 (m, 2H), 2.78 (td, J = 11.4, 3.1 Hz, 1H), 2.63 (t, J = 10.3 Hz, 1H), 2.48 - 2.43 (m, 1H), 2.33 (d, J = 7.7 Hz, 1H), 2.20 (q, J = 7.9 Hz, 1H), 1.79 - 1.66 (m, 3H), 1.35 (tt, J = 14.8, 7.2 Hz, 1H)。

[1808]

I-N-66	402.1	0.67	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.42 (d, J = 0.5 Hz, 1H), 9.04 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 7.27 (dd, J = 5.5, 0.5 Hz, 1H), 3.24 - 3.14 (m, 2H), 3.06 (dd, J = 11.1, 5.6 Hz, 2H), 1.94 (ddd, J = 13.6, 9.8, 4.0 Hz, 2H), 1.85 (d, J = 13.2 Hz, 2H), 1.37 (s, 3H)。
I-N-67	455.1	0.84	^{1}H NMR (500 MHz, DMSO-d6) δ 2.89 (4H, m), 2.97 (4H, m), 3.37 掩蔽的信号, 6.82 (2H, br s), 7.20 (1H, m), 8.22 (1H, m), 8.70 (1H, m), 9.43 (2H, m) 和 9.75 (1H, s) ppm.
I-N-68	406.2	0.53	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.45 (d, J = 1.1 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.41 (dd, J = 6.6, 1.1 Hz, 1H), 7.68 (d, J = 6.6 Hz, 1H), 4.02 (ddd, J = 13.6, 11.1, 2.0 Hz, 2H), 3.83 - 3.75 (m, 2H), 3.33 - 3.28 (m, 2H), 3.16 - 3.08 (m, 2H)。
I-N-69	430.2	0.75	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.23 (d, J = 1.3 Hz, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.30 (dd, J = 6.8, 1.3 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 4.00 (dt, J = 13.0, 2.8 Hz, 2H), 3.15 - 3.03 (m, 2H), 2.00 - 1.90 (m, 2H), 1.74 (qd, J = 12.6, 3.8 Hz, 2H), 1.66 - 1.60 (m, 1H), 1.25 (s, 6H)。
I-N-70	441.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.50 - 9.40 (m, 2H), 8.77 (d, J = 2.2 Hz, 1H), 8.25 (d, J = 5.3 Hz, 1H), 7.25 (dd, J = 5.3, 0.5 Hz, 1H), 6.82 (s, 2H), 3.84 - 3.65 (m, 1H), 3.22 (d, J = 11.0 Hz, 1H), 3.12 - 2.90 (m, 3H), 2.81 (dd, J = 10.9, 10.1 Hz, 1H), 2.76 - 2.59 (m, 1H)。

[1809]

I-N-71	413.1	0.72	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.44 - 9.38 (m, 2H), 8.58 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.20 (dd, J = 5.4, 0.5 Hz, 1H), 6.82 (s, 2H), 3.31 - 3.20 (m, 2H), 3.14 (dd, J = 10.8, 2.9 Hz, 1H), 3.07 - 2.96 (m, 2H), 2.78 (td, J = 11.4, 2.9 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.34 (s, 1H), 2.19 (q, J = 8.4 Hz, 1H), 1.73 (tdd, J = 13.4, 7.9, 4.2 Hz, 3H), 1.35 (td, J = 10.5, 5.8 Hz, 1H)。
I-N-72	401.2	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.62 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.58 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 5.2 Hz, 1H), 6.82 (s, 2H), 3.00 - 2.89 (m, 1H), 2.90 - 2.81 (m, 1H), 2.81 - 2.73 (m, 1H), 2.72 - 2.62 (m, 1H), 2.47 - 2.39 (m, 1H), 2.30 (s, 3H), 2.24 - 2.11 (m, 1H), 0.82 (d, J = 6.2 Hz, 3H)。(一个质子隐蔽在DMSO峰下)。
I-N-73	402.1	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.50 - 9.35 (m, 2H), 8.58 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 3.44 (dt, J = 7.9, 4.0 Hz, 1H), 3.30 (s, 3H), 3.12 - 3.03 (m, 2H), 2.79 (ddd, J = 11.8, 8.8, 3.1 Hz, 2H), 2.07 - 1.98 (m, 2H), 1.75 (dtd, J = 12.2, 8.5, 3.4 Hz, 2H)。
I-N-74	430.2	0.8	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.44 (d, J = 1.2 Hz, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.34 (dd, J = 6.7, 1.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 3.84 - 3.79 (m, 2H), 3.78 (s, 3H), 3.23 - 3.14 (m, 2H), 2.80 - 2.72 (m, 1H), 2.22 - 2.06 (m, 4H)。

[1810]

I-N-75	410.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.54 (s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 8.28 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 1.0 Hz, 1H), 7.57 (d, J = 2.2 Hz, 1H), 7.29 (dd, J = 5.3, 0.5 Hz, 1H), 6.78 (s, 2H), 6.66 (d, J = 1.0 Hz, 1H), 4.34 - 4.11 (m, 4H), 3.59 - 3.44 (m, 2H)。
I-N-76	420.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85 (6H,s), 2.95 (3H,s), 3.2-3.4 (4H,m), 3.6-3.8 (4H,m), 6.8 (1H,brs), 7.47 (1H,d), 8.47 (1H,d), 9.05 (1H,s), 9.15 (1H,s), 9.45 (1H,s), 9.75 (1H,s), 10.0 (1H,brs)。
I-N-77	363.1	1.89*	----------
I-N-78	406.2	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7 (3H,d), 2.95 (3H,s), 3.2-3.4 (4H,m), 3.6-3.8 (4H,m), 4.5 (1H,q), 6.8 (1H,brs), 7.49 (1H,d), 8.47 (1H,d), 8.95 (1H,s), 9.18 (1H,s), 9.40 (1H,s), 9.75 (1H,s), 10.1 (1H,brs)。
I-N-79	391.2	2.32*	----------
I-N-80	410.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 2.99 (3H, br s), 3.18 (2H, m), 3.37-3.44 (4H, m), 3.67 (2H, m), 4.15 (2H, s), 6.80 (2H, br s), 8.32 (1H, d), 8.76 (1H, d), 9.12 (1H, d), 9.51 (1H, s), 9.86 (1H, br s)和 10.19 (1H, s) ppm.
I-N-81	379.2	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.36 (s, 1H), 9.10 (d, J = 2.0 Hz, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.44 (d, J = 6.4 Hz, 1H), 7.49 (d, J = 6.4 Hz, 1H), 6.78 (s, 2H), 4.15 (s, 2H), 3.87 - 3.83 (m, 4H), 3.33 - 3.29 (m, 4H)。
I-N-82	92.2	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.42 (s, 1H), 9.12 (d, J = 1.9 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 6.2 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 6.80 (s, 2H), 4.15 (s, 2H), 3.90 - 3.68 (m, 4H), 3.68 - 3.55 (m, 3H), 2.96 (s, 3H)。

[1811]

I-N-83	393.2	0.53	^{1}H NMR (500 MHz, DMSO-d6) δ 9.92 (s, 1H), 9.46 (s, 1H), 9.06 (dt, J = 2.0, 0.8 Hz, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.21 - 7.16 (m, 1H), 6.77 (s, 2H), 4.73 (d, J = 4.3 Hz, 1H), 4.14 (d, J = 0.7 Hz, 2H), 3.71 (s, 1H), 3.12 (d, J = 11.5 Hz, 2H), 2.77 (t, J = 9.6 Hz, 2H), 1.92 (s, 2H), 1.73 (t, J = 9.2 Hz, 2H)。
I-N-84	377.2	2.38*	----------
I-N-85	405.2	0.69	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.56 (s, 1H), 9.07 (dd, J = 4.3, 2.6 Hz, 1H), 8.82 - 8.77 (m, 1H), 8.25 (s, 1H), 3.38 - 3.36 (m, 4H), 2.84 (d, J = 4.4 Hz, 4H), 2.50 (s, 3H)。
I-N-86	387.1	0.56	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.30 (s, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 2.81 (td, J = 10.9, 5.5 Hz, 1H), 2.71 (td, J = 12.0, 2.4 Hz, 2H), 1.87 (d, J = 12.4 Hz, 2H), 1.66 (qd, J = 12.1, 3.8 Hz, 2H), 3.26 - 3.23 (m, 2H)。
I-N-87	401.1	1.85*	----------
I-N-88	373.0	1.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.82 (s, 2H), 2.93 (dd, J = 6.2, 3.3 Hz, 4H), 2.85 (dd, J = 6.1, 3.2 Hz, 4H)。
I-N-89	378.1	0.97	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.44 (s, 1H), 9.06 (d, J = 1.9 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.15 (s, 2H), 2.95 (d, J = 4.7 Hz, 4H), 2.88 - 2.85 (m, 4H)。

[1812]

I-N-90	408.2	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (d, J = 14.9 Hz, 1H), 9.51 (d, J = 4.6 Hz, 1H), 9.04 (dd, J = 22.0, 2.2 Hz, 1H), 8.67 (dd, J = 24.9, 2.2 Hz, 1H), 8.24 (d, J = 5.3 Hz, 1H), 7.19 (dd, J = 13.7, 5.3 Hz, 1H), 6.76 (d, J = 10.4 Hz, 2H), 4.14 (d, J = 7.0 Hz, 2H), 3.99 - 3.79 (m, 2H), 3.77 - 3.68 (m, 1H), 3.20 (d, J = 11.4 Hz, 1H), 3.16 - 3.00 (m, 1H), 2.90 - 2.73 (m, 1H), 2.71 - 2.53 (m, 3H)。
I-N-91	401.1	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 1.47 (2H, m), 1.82 (3H, m), 2.85 (2H, m), 2.96 (2H, m), 3.66 (2H, m), 6.83 (2H, br s), 7.46 (1H, d), 7.90 (3H, br s), 8.40 (1H, m), 8.76 (1H, s), 9.27 (1H, s), 9.47 (1H, m)和 9.57 (1H, s) ppm.
I-N-92			^{1}H NMR (500 MHz, DMSO-d6) δ 12.39 (s, 1H), 9.81 (s, 1H), 9.45 (d, J = 2.2 Hz, 1H), 9.41 (s, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 5.5 Hz, 1H), 3.45 - 3.40 (m, 2H), 7.40 (d, J = 6.1 Hz, 1H), 6.83 (s, 2H), 3.04 - 2.86 (m, 2H), 2.60 - 2.55 (m, 1H), 2.05 - 1.85 (m, 4H)。
I-N-93	427.2	2.2*	----------
I-N-94	470.2	2.15*	----------
I-N-95	471.2	2.27*	----------
I-N-96	469.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.52 - 9.31 (m, 2H), 8.62 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.81 (s, 2H), 4.63 (s, 4H), 3.27 (s, 4H), 3.13 - 3.02 (m, 2H), 2.76 - 2.66 (m, 2H), 2.14 (dq, J = 8.3, 4.4, 3.8 Hz, 1H), 1.84 - 1.70 (m, 2H), 1.57 - 1.41 (m, 2H)。

[1813]

I-N-97	470.3	0.64	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.14 (s, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.39 (dd, J = 6.5, 1.1 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 3.77 (d, J = 12.8 Hz, 2H), 3.25 - 3.11 (m, 3H), 3.11 - 3.00 (m, 3H), 3.00 - 2.89 (m, 2H), 2.77 (s, 3H), 2.58 - 2.53 (m, 2H), 2.49 - 2.45 (m, 1H), 1.99 - 1.85 (m, 2H), 1.77 - 1.59 (m, 2H)。
I-N-98	459.2	2.43*	----------
I-N-99	483.3	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.53 - 9.46 (m, 2H), 9.34 - 9.23 (m, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.5, 1.0 Hz, 1H), 7.50 (d, J = 6.5 Hz, 1H), 6.84 (s, 2H), 4.70 - 4.42 (m, 3H), 4.04 - 3.90 (m, 2H), 3.89 - 3.74 (m, 3H), 3.24 - 3.09 (m, 1H), 3.10 - 2.90 (m, 2H), 2.46 - 2.39 (m, 1H), 2.33 - 2.12 (m, 3H), 2.00 - 1.73 (m, 2H)。2个质子信号被水隐蔽。
I-N-100	489.2	0.61	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.35 (s, 1H), 9.06 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 7.27 - 7.20 (m, 1H), 3.12 - 3.00 (m, 2H), 3.00 - 2.90 (m, 2H), 2.90 - 2.79 (m, 2H), 2.74 - 2.63 (m, 2H), 2.11 - 2.04 (m, 1H), 2.04 - 1.86 (m, 4H), 1.36 (d, J = 19.8 Hz, 4H)。
I-N-101	493.2	1.4*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.18 (d, J = 1.3 Hz, 1H), 9.08 (d, J = 2.2 Hz, 1H), 8.86 (d, J = 1.3 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 6.8, 1.4 Hz, 1H), 7.54 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 4.44 - 4.35 (m, 2H), 4.10 - 3.98 (m, 4H), 3.29 - 3.17 (m, 4H), 3.03 - 2.92 (m, 1H), 2.19 - 2.10 (m, 2H), 1.99 - 1.88 (m, 2H), 1.39 - 1.26 (m, 1H), 0.92 (d, J = 7.0 Hz, 1H)。

[1814]

I-N-102	493.2	1.4*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.16 (d, J = 1.3 Hz, 1H), 9.12 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 6.9, 1.3 Hz, 1H), 7.56 (q, J = 2.1 Hz, 2H), 7.54 (d, J = 6.9 Hz, 1H), 4.28 (t, J = 5.3 Hz, 2H), 4.06 (dm, J = 13.0 Hz, 2H), 3.33 - 3.19 (m, 4H), 2.99 - 2.93 (m, 1H), 2.14 (d, J = 12.4 Hz, 2H), 1.98 - 1.87 (m, 2H), 1.39 - 1.29 (m, 3H), 0.95 - 0.89 (m, 1H)。
I-N-103	459.2	2.42*	----------
I-N-104	457.3	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.55 (s, 1H), 9.49 (d, J = 2.2 Hz, 1H), 9.23 (d, J = 0.9 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H), 6.83 (s, 2H), 4.20 - 3.93 (m, 2H), 3.91 - 3.79 (m, 2H), 3.30 - 3.09 (m, 1H), 3.03 (t, J = 12.1 Hz, 2H), 2.27 - 2.13 (m, 2H), 1.86 (qd, J = 12.5, 3.7 Hz, 2H)。6个质子的其余信号在水峰下。
I-N-105	441.0	2.26*	----------
I-N-106	484.3	2.29*	----------
I-N-107	457.2	2.24*	----------
I-N-108	463.2	2.55*	----------
I-N-109	469.3	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 - 9.45 (m, 2H), 9.31 (d, J = 1.1 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H), 6.94 - 6.73 (m, 2H), 5.51 - 4.98 (m, 1H), 4.85 (d, J = 9.2 Hz, 2H), 4.83 - 4.51 (m, 1H), 3.93 - 3.66 (m, 6H), 3.09 (t, J = 12.3 Hz, 2H), 2.76 - 2.54 (m, 1H), 2.32 - 1.57 (m, 4H)。(脂族基团信号宽且未限定)。
I-N-110	447.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.56 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (s, 1H), 6.80 (s, 2H), 4.61 (t, J = 6.4 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.70 - 3.51 (m, 1H), 3.44 - 3.20 (m, 4H), 2.60 - 2.45 (m, 4H)。

[1815]

I-N-111	421.2	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (1H, br), 9.68 (1H, s), 9.54 (1H, d, *J* = 5.0 Hz), 8.95 (1 H, d, *J* = 5.0 Hz), 8.55 (1 H, s), 7.37 (1H, t, *J* = 55 Hz), 6.79 (2H, br), 2.88 (3H, s) 3.47-3.22 (8 H, br)。
I-N-112	425.3	1.67*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 9.18 (s, 1H), 8.80 (dd, J = 2.5, 0.5 Hz, 1H), 8.50 (s, 1H), 8.13 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 5.7 Hz, 1H), 6.65 (s, 2H), 4.60 - 4.50 (m, 4H), 3.70 (p, J = 6.4 Hz, 1H), 3.42 - 3.27 (m, 1H), 3.17 (ddd, J = 12.6, 10.4, 2.7 Hz, 1H), 2.76 (ddd, J = 8.1, 6.6, 4.2 Hz, 1H), 2.66 (ddd, J = 11.0, 4.1, 2.5 Hz, 1H), 2.59 - 2.51 (m, 1H), 2.31 - 2.16 (m, 1H), 0.61 (td, J = 5.6, 4.2 Hz, 1H), 0.37 (td, J = 6.8, 5.8 Hz, 1H)。
I-N-113	396.2	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (1H, br), 9.71 (1 H, d, *J* = 2.2 Hz), 9.54 (1H, dd, *J* = 5.0, 2.2 Hz), 9.46 (1 H, s), 8.98 (1H, s), 8.66 (1 H, s), 6.77 (2 H, br), 3.63-3.41 (6 H, br), 3.17 (2 H, br), 2.92 (3 H, s)。
I-N-114	444.3	1.96*	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.41 (s, 1H), 9.57 (d, J = 1.6 Hz, 1H), 9.08 (dd, J = 4.4, 2.4 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 3.0 Hz, 1H), 3.53 - 3.44 (m, 1H), 3.43 - 3.39 (m, 1H), 3.26 - 3.18 (m, 1H), 3.18 - 3.06 (m, 3H), 3.02 (dt, J = 11.3, 2.5 Hz, 1H), 2.99 - 2.92 (m, 1H), 2.92 - 2.85 (m, 1H), 2.85 - 2.78 (m, 1H), 2.74 (s, 3H), 2.71 - 2.66 (m, 1H), 2.63 (d, J = 17.2 Hz, 1H)。
I-N-115	413.2	1.82*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.49 (s, 1H), 9.06 (d, J = 4.5 Hz, 1H), 8.77 (s, 1H), 8.24 (d, J = 5.6 Hz, 1H), 7.24 (d, J = 5.7 Hz, 1H), 3.93 (d, J = 11.2 Hz, 1H), 3.83 - 3.62 (m, 2H), 3.46 - 3.25 (m, 2H), 3.24 - 3.00 (m, 2H), 2.94 (d, J = 11.2 Hz, 1H), 2.83 (d, J = 11.6 Hz, 1H), 2.80 - 2.66 (m, 2H), 2.65 - 2.48 (m, 2H)。

[1816]

I-N-116	413.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (s, 1H), 8.83 - 8.78 (m, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.3, 0.5 Hz, 1H), 6.77 (s, 2H), 3.79 (dm, J = 10.9 Hz, 1H), 3.59 (dd, J = 10.8, 2.8 Hz, 1H), 3.53 (td, 1H), 3.16 - 3.08 (m, 2H), 2.97 (dm, 1H), 2.86 (td, 1H), 2.78 (dm, J = 11.1 Hz, 1H), 2.68 (dm, J = 11.5 Hz, 1H), 2.63 (p, J = 1.8 Hz, 1H), 2.59 - 2.53 (m, 1H), 2.40 (dd, J = 11.5, 3.3 Hz, 1H), 2.36 (p, J = 1.9 Hz, 1H)。
I-N-117	447.1	2.10*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 2.54 - 2.51 (m, 2H), 9.47 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 2.8 Hz, 1H), 6.83 (s, 2H), 4.60 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 4.08 (q, J = 5.3 Hz, 2H), 3.62 - 3.54 (m, 1H), 3.15 - 3.08 (m, 4H)。
I-N-118	375.1	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.34 (m, 8H), 6.83 (2H, br s), 8.32 (1H, m), 8.74 (2H, br s), 8.94 (1H, m), 9.55 (1H, m), 9.61 (1H, s)和 10.32 (1H, s) ppm.
I-N-119	467.3	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 0.6 Hz, 1H), 6.78 (s, 2H), 3.91 - 3.76 (m, 2H), 3.75 - 3.65 (m, 1H), 3.48 (t, J = 7.7 Hz, 1H), 3.32 - 3.12 (m, 4H), 3.09 - 2.92 (m, 1H), 2.80 - 2.66 (m, 2H), 2.65 - 2.54 (m, 2H), 2.19 - 1.97 (m, 2H), 1.84 - 1.63 (m, 1H), 1.09 - 0.97 (m, 2H), 0.90 - 0.77 (m, 2H)。

[1817]

I-N-120	467.3	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 0.6 Hz, 1H), 6.77 (s, 2H), 3.90 - 3.76 (m, 2H), 3.76 - 3.63 (m, 1H), 3.55 - 3.42 (m, 1H), 3.31 - 3.12 (m, 4H), 2.99 (t, J = 7.2 Hz, 1H), 2.77 - 2.66 (m, 2H), 2.63 - 2.54 (m, 2H), 2.17 - 1.95 (m, 2H), 1.79 - 1.64 (m, 1H), 1.08 - 0.99 (m, 2H), 0.89 - 0.78 (m, 2H)。
I-N-121	459.2	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.65-1.73 (2H, m), 2.09 (2H, m), 3.16 (2H, m), 3.38 (5H、m), 3.49 (3H、m), 3.72 (1H, m), 4.02 (2H, m), 6.80 (2H, br s), 8.33 (1H, d), 8.96 (1H, d), 9.46 (1H, s), 9.54 (1H, m), 9.78 (1H, br s)和 10.09 (1H, s) ppm.
I-N-122	445.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.12-2.17 (1H, m), 2.35-2.42 (1H, m), 3.22-3.47 (6H、m), 3.73 掩蔽的信号, 3.95-4.09 (5H、m), 6.81 (2H, br s), 8.33 (1H, d), 8.97 (1H, m), 9.50 (1H, s), 9.54 (1H, d)和 10.09 (2H, m) ppm.
I-N-123	455.3	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (1 H、br), 9.48 (1 H、d, *J* = 5.2 Hz), 9.24 (1 H、m), 8.79 (1 H、br), 8.06 (1 H、d, *J* = 5.2 Hz), 6.77 (2 H、br), 3.92 (2 H、br), 3.35-3.32 (7 H、br), 2.70 (4 H、br), 2.39 (3 H、s), 1.78 (2 H、br), 1.55 (2 H、br)。
I-N-124	461.2	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.1-2.12 (1H,m), 2.4-2.5 (1H,m), 3.2-3.4 (4H,m), 3.6-3.85 (5H,m), 3.9-4.1 (4H,m), 6.78 (2H,brs), 8.35 (1H,s), 8.92 (1H,s), 9.5-9.6 (2H,m), 10.0-10.15 (2H,m)。
I-N-125	445.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.12-2.17 (1H, m), 2.35-2.42 (1H, m), 3.22-3.47 (6H、m), 3.73 掩蔽的信号, 3.95-4.09 (5H、m), 6.81 (2H, br s), 8.32 (1H, d), 8.98 (1H, m), 9.50 (1H, s), 9.54 (1H, d)和 10.09 (2H, m) ppm.

[1818]

I-N-126	391.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.72 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.93 (dd, J = 2.5, 0.7 Hz, 1H), 8.85 (s, 2H), 8.32 (s, 1H), 6.85 (s, 2H), 3.43 - 3.27 (m, 4H), 2.58 - 2.45 (m, 4H)。
I-N-127	433.2	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.64 (2H, t), 2.70 (4H, m), 3.09 (4H, m), 3.27 (3H, s), 3.51 (2H, t, J = 5 Hz), 6.80 (2H, br s), 8.25 (1H, d), 8.77 (1H, m), 9.50 (2H, m)和 10.30 (1H, s) ppm.
I-N-128	500.1	2.13*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.54 (bs, 1H), 9.07 (dd, J = 4.3, 2.5 Hz, 1H), 8.71 (d, J = 2.5 Hz, 1H), 8.34 (bs, 1H), 4.02 - 3.85 (m, 4H), 3.62 (dm, J = 12.6 Hz, 2H), 3.50 - 3.42 (m, 1H), 3.41 - 3.35 (m, 2H), 3.32 - 3.21 (m, 2H), 3.17 - 3.03 (m, 2H), 2.91 (s, 3H), 2.05 (2m, 4H)。
I-N-129	400.2	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 9.05 (dd, J = 2.6, 0.6 Hz, 1H), 8.66 (s, 1H), 8.21 (s, 1H), 6.75 (s, 2H), 6.55 (s, 1H), 3.86 - 3.03 (m, 8H, 在水峰下), 2.95 (s, 3H), 2.94 (s, 3H)。
I-N-130	512.2	2.18*	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.26 (s, 1H), 9.50 (s, 1H), 9.03 (dd, J = 4.3, 2.5 Hz, 1H), 8.68 (dd, J = 2.5, 0.5 Hz, 1H), 8.35 (d, J = 4.1 Hz, 1H), 4.03 - 3.82 (m, 5H), 3.58 - 3.51 (m, 1H), 3.49 - 3.37 (m, 5H), 3.30 - 3.27 (m, 3H), 2.35 (d, J = 3.1 Hz, 1H), 2.18 - 2.09 (m, 1H), 2.09 - 2.01 (m, 2H), 2.01 - 1.87 (m, 2H)。

[1819]

I-N-131	455.2	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.43 (s, 1H), 8.73 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.18 (ddt, J = 7.6, 6.3, 3.7 Hz, 1H), 3.56 (tt, J = 7.9, 3.8 Hz, 1H), 3.13 - 3.01 (m, 2H), 2.79 (ddt, J = 12.2, 8.4, 3.1 Hz, 2H), 2.67 (dd, J = 9.7, 6.3 Hz, 1H), 2.54 - 2.51 (m, 1H), 2.44 - 2.31 (m, 2H), 2.23 (s, 3H), 2.13 - 1.94 (m, 3H), 1.83 - 1.70 (m, 2H), 1.70 - 1.61 (m, 1H)。
I-N-132	473.2	2.52*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.55 (s, 1H), 9.54 - 9.46 (m, 1H), 8.70 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 6.80 (s, 2H), 4.23 (ddt, J = 7.4, 6.3, 3.6 Hz, 1H), 3.64 (dt, J = 8.8, 4.5 Hz, 1H), 3.19 - 3.08 (m, 2H), 3.07 - 2.97 (m, 2H), 2.72 (dd, J = 9.7, 6.2 Hz, 1H), 2.60 - 2.53 (m, 1H), 2.47 - 2.34 (m, 2H), 2.26 (s, 3H), 2.15 - 1.98 (m, 3H), 1.91 - 1.79 (m, 2H), 1.75 - 1.64 (m, 1H)。
I-N-133	441.2	1.78*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 2H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 9.50 (s, 1H), 9.44 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.59 (d, J = 6.0 Hz, 1H), 4.00 - 3.81 (m, 4H), 3.54 (d, J = 28.4 Hz, 4H), 3.29 (d, J = 65.1 Hz, 2H), 2.96 (s, 3H), 2.15 (dd, J = 58.8, 17.3 Hz, 4H)。
I-N-134	512.2	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.54 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.30 (s, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 3.98 - 3.81 (m, 4H), 3.38 - 3.25 (m, 6H), 3.09 (t, J = 4.9 Hz, 4H), 2.22 - 2.11 (m, 6H)。

[1820]

I-N-135	431.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.54 - 9.48 (m, 2H), 8.74 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.07 (q, J = 5.3 Hz, 1H), 3.80 (dd, J = 11.4, 2.9 Hz, 1H), 3.64 - 3.49 (m, 2H), 3.29 - 3.24 (m, 1H), 3.19 - 3.08 (m, 2H), 2.99 (dm, J = 11.9 Hz, 1H), 2.90 - 2.77 (m, 2H), 2.73 (dm, J = 11.8 Hz, 2H), 2.63 - 2.57 (m, 1H), 2.41 (td, J = 11.6, 3.3 Hz, 1H)。
I-N-136	427.2	1.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.51 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 8.99 - 8.94 (m, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 6.76 (s, 2H), 4.51 - 4.43 (m, 1H), 4.07 (s, 2H), 3.98 (dd, J = 11.8, 4.7 Hz, 1H), 3.96 - 3.87 (m, 1H), 3.57 (dd, J = 11.8, 7.0 Hz, 1H), 3.25 - 3.15 (m, 2H), 3.04 (td, J = 12.5, 2.9 Hz, 1H), 2.73 - 2.65 (m, 2H)。
I-N-137	431.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.54 - 9.48 (m, 2H), 8.74 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.07 (q, J = 5.3 Hz, 1H), 3.80 (dd, J = 11.4, 2.9 Hz, 1H), 3.64 - 3.49 (m, 2H), 3.29 - 3.24 (m, 1H), 3.19 - 3.08 (m, 2H), 2.99 (dm, J = 11.9 Hz, 1H), 2.90 - 2.77 (m, 2H), 2.73 (dm, J = 11.8 Hz, 2H), 2.63 - 2.57 (m, 1H), 2.41 (td, J = 11.6, 3.3 Hz, 1H)。
I-N-138	438.2	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.84 (6H, s), 2.33 (3H, s), 2.64 (4H, br d), 3.11 (4H,br s), 6.81 (2H,s), 8.26 (1H,d), 8.815 (1H,d), 9.16 (1H, d), 9.52 (1H,d), 10.46 (1H,s)。
I-N-139	447.1	2.35*	----------
I-N-140	501.1	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.10-2.15 (3H, s), 2.35-2.40 (2H, m), 2.50-2.60 (2H, 被掩蔽), 2.66 (2H, br s), 2.81 (4H, br s), 3.15 (2H, br s), 7.51-7.52 (1H, d), 7.88-7.89 (1H, s), 8.21-8.23 (1H, d), 8.77 (1H, s)。

[1821]

I-N-141	357.0	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 9.31 (d, J = 1.1 Hz, 1H), 8.97 (dd, J = 2.5, 0.5 Hz, 1H), 8.47 (dd, J = 6.6, 1.1 Hz, 1H), 7.53 (d, J = 6.6 Hz,1H), 6.78 (s, 2H), 3.86 - 3.81 (m, 4H), 3.39 - 3.33 (m, 4H)。
I-N-142	463.1	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (s, 1H), 9.34 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.92 (d, J = 2.3 Hz, 1H), 8.56 - 8.43 (m, 1H), 7.57 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.79 - 4.59 (m, 4H), 4.20 (s, 1H), 3.57 (d, J = 6.0 Hz, 5H), 3.08 (s, 4H), 1.85 (s, 6H)。
I-N-143	448.2	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.32 (d, J = 1.0 Hz, 1H), 9.16 (dd, J = 2.1, 0.6 Hz, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.46 (dd, J = 6.5, 1.0 Hz, 1H), 7.55 (d, J = 6.4 Hz, 1H), 6.88 - 6.70 (m, 2H), 4.65 - 4.69 (m, 5H), 4.51 (q, J = 7.2 Hz, 1H), 3.51 (s, 4H), 2.96 (br s, 3H), 1.71 (d, J = 7.2 Hz, 3H)。
I-N-144	480.2	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.45 (s, 1H), 9.15 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 4.87 - 4.67 (m, 4H), 4.42 - 4.27 (br m, 9H), 1.87 (s, 6H)。
I-N-145	466.1	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.48 (s, 1H), 9.19 (dd, J = 2.1, 0.6 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 6.81 (s, 2H), 4.86 - 4.70 (m, 4H), 4.52 (q, J = 7.2 Hz, 1H), 3.71 (5H), 3.41 (s, 4H), 1.73 (d, J = 7.3 Hz, 3H)。
I-N-146	481.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.05-2.12 (4H,m), 2.9 (6H,s) , 3.15-3.22 (4H,m) , 3.55-3.62 (1H,m) , 8.29 (1H,d), 8.96 (1H,d), 9.50-9.53 (1H,m), 9.65 (1H,s), 10.42 (1H,s)。
I-N-147	457.1	2.1*	----------

[1822]

I-N-148	564.2	2.42*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.88-1.92 (2H,m), 1.96-2.05 (2H,m), 2.06-2.15 (4H,m), 2.77-2.83 (6H,m), 3.1-3.22 (6H,m), 3.47-3.60 (3H,m), 3.85-3.95 (1H,m), 8.29 (1H,d), 8.96 (1H,d), 9.40 (1H,s), 9.50-9.53 (1H,m), 9.65 (1H,s), 10.42 (1H,s).
I-N-149	473.2	2.60*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.53 (dd, J = 4.9, 2.5 Hz, 1H), 9.51 (s, 1H), 9.40 (s, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 2.8 Hz, 1H), 6.82 (s, 2H), 4.01 (d, J = 12.9 Hz, 2H), 3.73 (t, J = 12.0 Hz, 2H), 3.56 (d, J = 12.4 Hz, 2H), 3.21 (t, J = 6.1 Hz, 2H), 3.13 (d, J = 7.7 Hz, 5H), 2.08 (d, J = 5.7 Hz, 2H), 1.90 (d, J = 11.8 Hz, 2H), 1.56 (q, J = 18.7, 14.9 Hz, 2H).
I-N-150	486.2	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.49 (s, 1H), 8.75 (d, J = 2.6 Hz, 1H), 8.28 (d, J = 2.9 Hz, 1H), 6.82 (s, 2H), 3.47 (br s, 6H), 3.19 - 2.94 (m, 5H), 2.86 - 2.78 (m, 2H), 2.82 (s, 3H), 1.86 (d, J = 12.8 Hz, 4H), 1.52 (dd, J = 16.7, 8.1 Hz, 2H).
I-N-151	486.2	1.96*	----------
I-N-152	354.0	2.59*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.61 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.20 (s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 6.77 (s, 2H), 3.32 (t, J = 5.4 Hz, 4H), 1.77 - 1.69 (m, 4H), 1.65 (td, J = 6.3, 3.5 Hz, 2H).
I-N-153	460.2	2.01*	----------
I-N-154	469.2	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.42-1.50 (2H, m), 1.72-1.81 (4H, m), 1.96-2.04 (5H, m), 2.14 (3H, s), 2.61 (2H, m), 2.81 (2H, m), 3.07 (2H, m), 3.40-3.47 (1H, m), 3.67-3.72 (1H, m), 6.77 (2H, br s), 7.17 (1H, d), 8.20 (1H, d), 8.73 (1H, d), 9.44 (1H, s), 9.49 (1H, m)和 9.91 (1H, br s) ppm.

[1823]

I-N-155	523.2	2.37*	^{1}H NMR (500 MHz，DMSO-d6) δ 2.02-2.18 (4H,m)，3.12-3.22 (4H,m)，3.26-3.40 (8H,m)，3.57-3.63 (1H,m)，3.62-3.68 (4H,m)，8.27 (1H,d)，8.95 (1H,d)，9.48-9.52 (1H,m)，9.64 (1H,s)，10.42 (1H,s)。
I-N-156	486.2	1.97*	^{1}H NMR (500 MHz，甲醇-d4) δ 2.09-2.20 (2H，m)，2.41 (2H，s)，2.52-2.57 (1H，m)，2.70-2.82 (2H，m)，2.93-2.97 (1H，m)，3.17-3.22 (3H，m)，3.40-3.45 (1H，m)，3.88-3.97 (1H，m)，8.18 (1H，d)，8.71 (1H，dd)，9.58 (1H，s)。
I-N-157	486.2	2.03*	----------
I-N-158	523.1	2.25*	^{1}H NMR (500 MHz，CDCl3) δ 1.92-2.05 (3H、m)，2.07-2.12 (2H，m)，3.26-3.28 (4H、m)，3.45 (2H，m)，3.61-3.63 (4H、m)，5.89 (2H，s)，8.25 (1H，d)，8.54 (1H，dd)，8.61 (1H，d)，9.70 (1H，s)，10.25 (1H，s)。
I-N-159	479.1	2.34*	----------
I-N-160	472.1	1.96*	----------
I-N-161	354.0	1.70*	----------
I-N-162	354.0	1.63*	----------
I-N-163	429.1	1.93*	^{1}H NMR (500 MHz，DMSO-d6) δ 1.52-1.62 (2H，m)，1.12-1.18 (1H，m)，2.22-2.25 (1H，m)，2.32-2.37 (1H，m)，2.85-2.92 (1H，m)，2.94-2.98 (1H，m)，3.03-3.18 (2H，m)，3.22-3.27 (1H，m)，3.95 (1H，被掩蔽)，6.85 (2H，br s)，8.29 (1H，d)，8.81 (1H，d)，9.48 (1H，dd)，9.55 (1H，s)，10.42 (1H，s)。
I-N-164	441.2	2.02*	^{1}H NMR (500 MHz，DMSO-d6) δ 1.70-1.76 (2H，m)，1.94-1.97 (2H，m)，2.24 (3H、s)，2.75-2.81 (4H、m)，3.04-3.08 (2H，m)，3.53-3.57 (3H、m)，4.10-4.15 (1H，m)，6.77 (2H，br s)，7.18 (1H，d)，8.21 (1H，d)，8.75 (1H，d)，9.42 (1H，s)，9.49 (1H，m)和 9.86 (1H，br s) ppm。

[1824]

I-N-165	452.0	1.48*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.64 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 7.16 (s, 1H), 6.80 (s, 2H), 3.45 (ddt, J = 12.2, 7.5, 3.8 Hz, 1H), 3.25 - 3.10 (m, 4H), 3.07 (s, 3H), 2.23 - 2.16 (m, 2H), 2.10 - 1.98 (m, 2H)。
I-N-166	536.1	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (5H,m), 2.47 (3H,s), 3.12-3.32 (7H,m), 3.48-3.53 (2H,m), 3.65-3.71 (1H,m), 3.85-3.92 (4H,m), 8.27 (1H,d), 8.91 (1H,d), 9.51-9.53 (1H,m), 9.65 (1H,s), 9.72 (1H,brs), 10.43 (1H,s)。
I-N-167	487.2	2.38*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.60 (s, 1H), 9.05 (dd, J = 4.4, 2.5 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 2.9 Hz, 1H), 3.76 (t, J = 5.8 Hz, 2H), 3.65 (dt, J = 9.1, 4.8 Hz, 1H), 3.28 - 3.22 (m, 2H), 3.16 (dt, J = 11.4, 2.6 Hz, 2H), 2.83 (t, J = 5.8 Hz, 2H), 2.72 (d, J = 6.9 Hz, 4H), 2.19 (dt, J = 13.0, 4.0 Hz, 2H), 2.07 - 1.96 (m, 2H), 1.90 - 1.84 (m, 4H)。
I-N-168	458.2	1.70*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.62 (s, 1H), 8.29 (d, J = 2.5 Hz, 1H), 6.81 (s, 2H), 4.30 - 4.08 (m, 4H), 4.07 - 3.92 (m, 1H), 3.77 (s, 2H), 3.08 (dt, J = 10.8, 4.7 Hz, 4H)。
I-N-169	493.1	2.51*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.01-2.12 (2H,m), 2.12-2.18 (2H,m), 2.22-2.28 (2H,m), 3.16-3.21 (4H,m), 3.38-3.46 (1H,m), 3.92-3.97 (4H,m), 5.8 (2H,brs), 8.29 (1H,d), 8.93 (1H,d), 9.50-9.53 (1H,m), 9.63 (1H,s), 10.41 (1H,s)。
I-N-170	505.1	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.18 (3H,m), 2.98-3.08 (2H,m), 3.25-3.31 (4H,m), 3.57-3.71 (8H,m), 6.82 (2H,brs), 7.5 (1H,d), 8.42 (1H,d), 8.81 (1H,d), 9.44 (1H,s), 9.54-9.57 (1H,m), 9.80 (1H,s)。

[1825]

I-N-171	500.1	2.31*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.57 - 9.47 (m, 2H), 8.80 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H), 6.82 (s, 2H), 4.12 (s, 2H), 3.86 (s, 2H), 3.56 (s, 2H), 3.42 (s, 1H), 3.24 (s, 1H), 3.12 (s, 4H), 2.92 (s, 3H), 2.11 (s, 1H), 1.88 (s, 2H), 1.63 - 1.45 (m, 2H)。
I-N-172	488.1	1.8*	----------
I-N-173	501.0	2.26*	----------
I-N-174	502.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.15-2.30 (4H, m), 2.65-2.75 (1H, br s), 2.78-2.88 (1H, br s), 3.02-3.14 (5H, m), 3.55-3.65 (2H, br s), 3.70-3.75 (1H, br s), 3.82-3.90 (3H, br s), 4.30-4.38 (1H, br s), 6.80 (2H, s), 8.27 (1H, d), 8.82 (1H, d), 9.49 (1H, dd), 9.55 (1H, d), 10.40 (1H, s)。
I-N-175	536.0	2.26*	----------
I-N-176	461.0	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 0.94-1.03 (4H, m), 2.80-2.83 (1H, m), 3.37 (4H, m), 3.42 (4H, m), 6.79 (2H, s), 7.51-7.52 (1H, d), 8.44-8.45 (1H, d), 8.88 (1H, d), 9.32 (1H, s), 9.55 (1H, dd), 9.77 (1H, s)。
I-N-177	505.0	2.08*	----------
I-N-178	435.0	1.9*	----------
I-N-179	491.0	2.03*	----------
I-N-180	478.0	1.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.66 - 1.70 (2H, m), 1.80 - 1.85 (2H, m), 2.59 (4H, brs), 3.12 (4H, brs), 3.58 - 3.64 (1H, m), 4.48 - 4.52 (2H, m), 3.58 - 3.62 (2H, m), 6.78 (2H, s), 8.24 (1H, s), 8.71 (1H, s), 9.08 (1H, s), 9.49 (1H, s), 10.36 (1H, s)。
I-N-181	486.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85-2.03 (2H, m), 2.06-2.13 (1H, m), 2.86 (3H, d), 3.11-3.13 (4H, m), 3.19-3.24 (1H, m), 3.63-3.68 (3H, m), 3.75-3.80 (1H, m), 3.82-3.85 (1H, m), 4.63-4.65 (2H, m), 6.80 (2H, br s), 8.30 (1H, d), 8.90 (1H, d), 9.51-9.53 (1H, dd), 9.56 (2H, m), 10.37 (1H, s)。

[1826]

I-N-182	429.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.52-1.62 (2H, m), 1.12-1.18 (1H, m), 2.22-2.25 (1H, m), 2.32-2.37 (1H, m), 2.85-2.92 (1H, m), 2.94-2.98 (1H, m), 3.03-3.18 (2H, m), 3.22-3.27 (1H, m), 3.95 (1H, 被掩蔽), 6.85 (2H, br s), 8.29 (1H, d), 8.81 (1H, d), 9.48 (1H, dd), 9.55 (1H, s), 10.42 (1H, s)。
I-N-183	441.4	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.77-1.82 (2H, m), 1.99 (2H, m), 2.23 (3H, m), 2.37 (3H, m), 2.93 (4H, m), 3.68 (2H, m), 6.77 (2H, br s), 7.19 (1H, d, J = 5Hz), 8.20 (1H, d), 8.80 (1H, m), 9.41 (1H, s), 9.41 (1H, m)和 9.79 (1H, br s) ppm.
I-N-184	457.1	2.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.60 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 8.99 (dd, J = 2.6, 0.7 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 7.83 (d, J = 3.3 Hz, 1H), 7.68 (d, J = 3.3 Hz, 1H), 6.80 (s, 2H), 3.40 - 3.32 (m, 1H), 3.27 - 3.22 (m, 2H), 3.16 (d, J = 11.7 Hz, 2H), 2.30 - 2.20 (m, 2H), 2.12 (d, J = 12.5 Hz, 2H)。
I-N-185	500.0	2.16*	----------
I-N-186	429.0	1.97*	^{1}H NMR (500MHz, DMSO-d6) δ 1.52-1.62 (1H, m), 2.11-2.17 (1H, m), 2.22-2.25 (1H, m), 2.32-2.37 (1H, m), 2.85-2.88 (1H, m), 2.90-2.92 (1H, m), 3.02-3.05 (1H, m), 3.10-3.13 (1H, m), 3.22-3.27 (1H, m), 3.93-3.95 (2H, m), 6.79 (2H, br s), 8.29 (1H, d), 8.81 (1H, d), 9.48 (1H, dd), 9.55 (1H, s), 10.42 (1H, s)。
I-N-187	486.0	2.19*	^{1}H NMR (500 MHz, CDCl3) δ 10.34 (s, 1H), 9.69 (s, 1H), 8.54-8.55 (dd, 1H), 8.46 (d, 1H), 8.23 (d, 1H), 5.89 (s, 2H), 3.90 (s, 4H), 3.48 (s, 2H), 3.18 (s, 4H), 2.71 (s, 4H), 1.86 (s, 4H)。

[1827]

I-N-188	518.0	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.80-1.87 (2H, m), 2.20-2.25 (2H, m), 2.81 (3H, s), 2.92-2.97 (2H, m), 3.33 (3H, s), 3.48-3.56 (8H, m), 6.80 (2H, s), 7.45 (1H, m), 8.41 (1H, d), 8.90 (1H, d), 9.31 (1H, s), 9.53-9.55 (1H, d), 9.73 (1H, s)。
I-N-189	459.0	2.36*	^{1}H NMR (500 MHz, DMSO-d6)δ 1.85-1.88 (2H, m), 2.17-2.19 (2H, m), 3.14-3.21 (3H, m), 3.27-3.30 (2H, m), 3.53-3.55 (2H, m), 3.73-3.76 (2H, m), 4.04-4.07 (2H, m), 6.75-6.6.85 (2H, s), 7.41-7.44 (1H, m), 7.54-7.56 (1H, m), 7.72-7.74 (1H, d), 7.99-8.00 (1H, d), 8.29 (1H, d), 8.94 (1H, d), 9.41 (1H, s), 9.52-9.54 (1H, m), 9.60-9.80 (1H, m), 10.05 (1H, s)。
I-N-190	434.0	0.6	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.90 (s, 0.5H), 9.62 (d, 1H), 9.1-9.07 (m, 1H), 8.88 (d, 1H), 8.38 (d, 1H), 7.62 (d, 1H), 3.92-3.85 (m, 2H), 3.51-3.45 (m, 1H), 3.15 - 3.08 (m, 2H), 3.06 (s, 3H), 2.35 - 2.26 (m, 4H)
I-N-191	486.2	1.89*	----------
I-N-192	533.0	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (1H, s), 9.48 (1H, s), 9.08 (1H, d), 8.68 (1H, d), 8.28 (1H, d), 6.77 (2H, brs), 3.08 – 3.19 (6H, m), 2.80 (3H, s), 1.85 – 1.88 (2H, m), 1.76 – 1.81 (2H, m), 1.70 – 1.73 (2H, m), 1.52 – 1.55 (2H, m) (n.b 一些信号被宽水峰掩蔽)。
I-N-193	500.1	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.53 (s, 1H), 9.51 (dd, J = 4.7, 2.5 Hz, 1H), 8.94 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 6.81 (s, 2H), 3.92 (s, 2H), 3.59 (d, J = 4.7 Hz, 4H), 3.45 (s, 2H), 3.17 - 3.00 (m, 4H), 2.88 (s, 3H), 1.93 (dtd, J = 15.7, 8.3, 7.6, 3.8 Hz, 1H), 1.74 (d, J = 12.1 Hz, 2H), 1.55 (qd, J = 12.1, 4.4 Hz, 2H)。

[1828]

I-N-194	472.1	1.85*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 9.04-9.05 (dd, 1H), 9.70 (d, 1H), 8.18 (d, 1H), 3.92 (s, 2H), 3.68-3.71 (m, 5H), 3.49 (m, 2H), 3.18-3.20 (m, 4H), 2.42 (s, 3H)。
I-N-195	477.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.50-9.51 (dd, 1H), 9.39 (s, 1H), 8.91 (d, 1H), 8.26 (d, 1H), 7.23-7.24 (d, 1H), 6.76 (s, 2H), 4.93-4.97 (m, 1H), 4.84-4.88 (m, 2H), 4.73-4.76 (m, 2H), 3.35 (s, 4H), 3.03 (s, 4H)。
I-N-196	544.1	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.97-2.18 (9H,m), 2.92-3.00 (2H,m), 3.30-3.50 (5H,m), 3.55-3.65 (3H,m), 3.67-3.72 (2H,m), 4.22-4.26 (1H,m), 6.70-6.88 (2H,m), 7.45 (1H,d), 8.40 (1H,d), 8.78 (1H,s), 9.45 (1H,s), 9.52-9.54 (1H,m), 9.8 (1H,brs), 10.35 (1H,s)。
I-N-197	475.1	2.83*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.69 (s, 1H), 9.20 (dd, 1H), 9.11 (dd, 1H), 8.76 (dd, 1H), 8.36 - 8.22 (m, 1H), 7.51 (dd, 1H), 3.98 (d, 2H), 3.71 (br t, 2H), 3.52 (s, 2H), 3.19 - 3.16 (m, 2H), 3.13 (dd, 2H), 2.59 (tt, 2H), 2.11 - 2.05 (m, 1H), 1.98 (d, 2H), 1.62 (qd, 2H)。
I-N-198	468.1	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.46-9.49 (m, 2H), 8.94 (d, 1H), 7.20 (d, 1H), 6.76 (s, 2H), 3.90-3.95 (m, 1H), 3.80-3.87 (m, 2H), 3.60-3.67 (m, 1H), 3.29 (s, 3H), 3.15-3.25 (m, 1H), 2.85-3.00 (m, 4H), 2.20-2.30 (m, 2H), 2.10-2.15 (m, 1H), 1.80-1.90 (m, 2H)。
I-N-199	468.2	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 9.46-9.49 (m, 2H), 8.94 (d, 1H), 7.20 (d, 1H), 6.76 (s, 2H), 3.90-3.95 (m, 1H), 3.80-3.87 (m, 2H), 3.60-3.67 (m, 1H), 3.29 (s, 3H), 3.15-3.25 (m, 1H), 2.85-3.00 (m, 4H), 2.20-2.30 (m, 2H), 2.10-2.15 (m, 1H), 1.80-1.90 (m, 2H)。

[1829]

I-N-200	476.1	1.9*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.97-2.12 (4H,m), 2.92-3.00 (2H,m), 3.44-3.56 (1H,m), 3.60-3.67 (2H,m), 4.75-4.79 (2H,m), 4.83-4.86 (2H,m), 6.80 (2H,brs), 7.50 (1H,d), 8.42 (1H,d), 8.81-8.83 (1H,m), 9.47 (1H,s), 9.54-9.58 (1H,m), 9.8 (1H,brs)。
I-N-201	495.0	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.46 (s, 1H), 8.84 - 8.80 (m, 1H), 8.30 (d, J = 2.6 Hz, 1H), 6.79 (s, 2H), 5.07 - 4.97 (m, 1H), 4.85 (dd, J = 8.1, 7.0 Hz, 2H), 4.75 (dd, J = 7.1, 6.1 Hz, 2H), 3.45 (dd, J = 6.1, 3.4 Hz, 4H), 3.18 - 3.12 (m, 4H)。
I-N-202	379.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.42 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.83 (dd, J = 18.1, 2.1 Hz, 2H), 7.79 (d, J = 5.1 Hz, 1H), 6.74 (s, 2H), 1.87 (ddd, J = 10.6, 8.2, 5.3 Hz, 1H), 1.11 - 0.93 (m, 4H)。
I-N-203	526.1	2.26*	----------
I-N-204	514.0	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.55 (s, 1H), 9.51-9.52 (dd, 1H), 9.38-9.46 (m, 1H), 8.88 (d, 1H), 8.30 (d, 1H), 6.80 (s, 2H), 4.56-4.61 (m, 1H), 3.92-3.95 (m, 1H), 3.82-3.85 (m, 1H), 3.70-3.80 (m, 2H), 3.55-3.58 (m, 1H), 3.08-3.20 (m, 5H), 2.98-3.05 (m, 1H), 2.89-2.95 (m, 1H), 212-2.15 (m, 1H), 1.78-1.90 (m, 3H), 1.50-1.65 (m, 2H), ,25-1.28 (t, 3H)。
I-N-205	514.0	2.23*	----------
I-N-206	514.1	2.18*	----------
I-N-207	500.1	2.09*	----------

[1830]

I-N-208	478.2	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.99-2.10 (2H,m), 2.18-2.25 (2H,m), 2.95-3.05 (2H,m), 3.32 (3H,s), 3.40-3.50 (4H,m), 3.62-3.68 (2H,m), 3.75-3.78 (2H,m), 6.80 (2H,brs), 7.55 (1H,d), 8.43 (1H,d), 8.81-8.82 (1H,m), 9.48 (1H,s), 9.54-9.57 (1H,m), 9.8 (1H,brs)。
I-N-209	385.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.53 (dd, 1H), 9.09 (s, 1H), 8.74 (d, 1H), 8.40 (dd, 1H), 7.42 (d, 1H), 6.75 (s, 2H), 4.02 (s, 2H), 3.75 (br t, 2H), 3.48 (br t, 1H), 2.94 (s, 3H)。
I-N-210	406.0	1.65*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 9.33 (d, J = 0.9 Hz, 1H), 8.86 - 8.81 (m, 1H), 8.47 (dd, J = 6.2, 0.9 Hz, 1H), 7.64 (d, J = 6.3 Hz, 1H), 6.80 (s, 2H), 3.77 - 3.71 (m, 4H), 3.46 - 3.40 (m, 8H)。
I-N-211	542.1	2.02*	----------
I-N-212	403.1	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.51 (s, 1H), 9.50 (t, 1H), 8.54 (d, 1H), 8.31 (d, 1H), 6.76 (br s, 2H), 3.71 (s, 2H), 3.53 - 3.50 (m, 2H), 3.46 - 3.44 (m, 2H), 3.01 (s, 3H)。
I-N-213	471.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.52 (s, 1H), 9.50 (dd, 1H), 8.99 (d,1H), 8.28 (d, 1H), 6.79 (br s, 2H), 3.38 (t, 2H), 3.22 (d, 2H), 3.12 - 3.02 (m, 4H), 2.26 (t, 2H), 1.98 - 1.92 (m, 2H), 1.89 - 1.82 (m, 1H), 1.68 (dd, 2H), 1.52 (qd, 2H)。
I-N-214	500.1	2.49*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.49-9.56 (m, 2H), 8.77 (d, 1H), 8.27 (d, 1H), 6.80 (s, 2H), 4.02-4.25 (m, 2H), 3.80-3.90 (m, 1H), 3.70-3.80 (m, 2H), 3.35-3.45 (m, 1H), 3.05-3.20 (m, 4H), 2.88-2.90 (m, 1H), 2.19 (s, 2H), 1.90-205 (m, 2H), 1.60-1.80 (m, 3H), 1.50-1.55 (s, 1H), 1.30-1.40 (m, 1H)。

[1831]

I-N-215	448.1	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.62-1.70 (2H,m), 1.96-2.03 (2H,m), 2.20-2.28 (1H,m), 3.00-3.08 (5H,m), 3.28 (2H,d), 3.62-3.68 (2H,m), 6.80 (2H,brs), 7.48 (1H,d), 8.42 (1H,d), 8.97 (1H,d), 9.32 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs)。
I-N-216	441.0	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.53 (dd, 1H), 9.29 (s, 1H), 8.88 (d, 1H), 8.43-8.45 (dd, 1H), 7.57-7.58 (d, 1H), 6.79 (s, 2H), 3.45-3.50 (m, 2H), 3.45 (s, 2H), 3.30-3.45 (m, 2H), 2.78 (s, 3H), 1.97-2.08 (m, 4H)。
I-N-217	411.1	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.40 - 9.34 (m, 1H), 8.99 - 8.92 (m, 1H), 8.43 (dd, J = 6.3, 0.9 Hz, 1H), 7.52 (d, J = 6.4 Hz, 1H), 6.78 (s, 2H), 3.95 - 3.85 (m, 2H), 3.77 - 3.70 (m, 1H), 3.62 (d, J = 12.5 Hz, 1H), 3.15 - 3.05 (m, 1H), 2.87 (td, J = 12.3, 3.5 Hz, 1H), 2.77 (dd, J = 12.1, 10.9 Hz, 1H), 2.37 - 2.21 (m, 2H), 2.09 (dddd, J = 12.8, 9.8, 7.7, 4.0 Hz, 1H), 1.63 - 1.52 (m, 1H)。
I-N-218	368.1	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.73 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.46 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 5.1, 0.6 Hz, 1H), 2.38 (s, 3H), 2.36 (s, 3H)。
I-N-219	407.0	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.85 (s, 1H), 9.48 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.24 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.59 (d, J = 1.3 Hz, 1H), 6.66 (s, 2H)。
I-N-220	370.1	2.63*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.48 (dd, J = 4.8, 2.6 Hz, 1H), 9.26 (d, J = 0.9 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 1.5, 0.7 Hz, 1H), 8.10 (dd, J = 7.4, 1.4 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.65 (s, 2H), 3.80 (t, J = 6.5 Hz, 2H), 1.90 - 1.77 (m, 4H), 1.54 (s, 6H)。

[1832]

I-N-221	434.0	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (1H, s), 9.53 (1H, dd), 9.35 (1H, s), 9.00 (1H, dd), 8.45 (1H, dd), 7.57 (1H, d), 6.79 (2H, brs), 3.92 (1H, d), 3.52 – 3.58 (2H, m), 3.16 – 3.21 (1H, t), 2.99 (3H, s), 2.88 – 2.93 (1H, m), 2.30 – 2.33 (1H, m), 1.83 – 1.93 (2H, m), 1.67 – 1.71 (1H, m)。
I-N-222	411.1	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.52 (dd,1H), 9.01 (s, 1H), 8.74 (d, 1H), 8.38 (dd, 1H), 7.44 (d, 1H), 6.74 (s, 2H), 4.24 (d, 1H), 4.20 (d, 1H), 3.87 (d, 1H), 3.84 - 3.78 (m, 1H), 3.53 - 3.48 (m, 1H), 3.41 - 3.36 (m, 1H), 3.18 (dd, 1H), 1.95 - 1.90 (m, 2H), 1.84 - 1.74 (m, 1H), 1.47 - 1.38 (m, 1H)。
I-N-223	353.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.26 (3H, s), 6.47 (1H, m), 6.70 (2H, br s), 7.59 (1H, m), 7.94 (1H, m), 8.48 (1H, m), 8.60 (1H, m), 9.41 (1H, m), 9.79 (1H, s)和 10.14 (1H, s) ppm.
I-N-224	425.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (s, 1H), 8.92 (d, J = 1.1 Hz, 1H), 8.71 (d, J = 2.5 Hz, 1H), 8.33 (dd, J = 6.9, 1.2 Hz, 1H), 7.45 (d, J = 6.9 Hz, 1H), 6.73 (s, 2H), 3.97 - 3.90 (m, 1H), 3.72 - 3.63 (m, 1H), 3.50 (ddd, J = 13.8, 11.4, 5.6 Hz, 2H), 3.10 (ddd, J = 13.4, 10.7, 2.7 Hz, 1H), 3.00 (dd, J = 9.9, 1.7 Hz, 1H), 2.74 (d, J = 0.7 Hz, 3H), 2.71 (dt, J = 7.5, 4.1 Hz, 1H), 2.63 - 2.53 (m, 1H), 1.94 - 1.84 (m, 1H), 1.59 (dtd, J = 13.7, 10.1, 3.6 Hz, 1H)。
I-N-225	352.9	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.32 (3H, s), 6.46 (1H, m), 6.73 (2H, br s), 7.64 (1H, m), 8.37-8.40 (2H, m), 8.76 (1H, m), 9.40-9.42 (2H, m)和 11.10 (1H, s) ppm.

[1833]

I-N-226	398.1	2.0*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 9.44 (s, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.14 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 4.39 (s, 4H), 2.86 - 2.80 (m, 4H), 2.02 (t, J = 5.5 Hz, 4H)。
I-N-227	502.0	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 10.20 (s, 1H), 9.56 (s, 1H), 9.51 (dd, 1H), 8.91 (d, 1H), 8.30 (d, 1H), 6.80 (br s, 2H), 4.80-4.85 (m, 1H), 4.32 (m, 1H), 4.01-4.09 (m, 2H), 3.88-3.91 (m, 1H), 3.70-3.76 (m, 2H), 3.57-3.62 (m, 1H), 3.49-3.53 (t, 1H), 3.42-3.45 (d, 1H), 3.20 (m, 3H), 3.11 (s, 2H), 2.83 (s, 3H)。
I-N-228	472.0	2.06*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.11 (s, 1H), 9.52-9.54 (m, 2H), 9.07 (dd, 1H), 8.32 (d, 1H), 6.80 (br s, 2H), 4.22-4.24 (m, 2H), 4.15 (s, 2H), 3.99-4.00 (t, 2H), 3.25-3.70 (m, 8H), 2.29-237 (s, 2H)。
I-N-229	459.0	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.51-9.52 (dd, 2H), 8.67 (d, 1H), 8.30 (d, 1H), 6.80 (br s, 2H), 3.54 (s, 2H), 3.22-3.28 (m, 2H), 3.02-3.08 (m, 2H), 2.81 (s, 3H), 2.02-2.07 (m, 4H)。
I-N-230	439.0	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 9.36 (s, 1H), 8.93 - 8.88 (m, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.19 (d, J = 5.4 Hz, 1H), 6.76 (d, J = 4.5 Hz, 2H), 4.34 (t, J = 5.1 Hz, 1H), 3.84 (tt, J = 12.1, 3.9 Hz, 1H), 3.48 - 3.44 (m, 1H), 3.27 - 3.21 (m, 2H), 2.80 (td, J = 12.2, 2.2 Hz, 2H), 2.25 (dd, J = 8.6, 7.5 Hz, 2H), 2.09 - 1.91 (m, 4H), 1.69 - 1.62 (m, 2H)。
I-N-231	453.1	2.01*	1H NMR (500 MHz, DMSO-d6) δ 9.52-9.55 (m, 2H), 9.15 (d, 1H), 8.90 (d, 1H), 8.41-8.43 (m, 1H), 7.50 (d, 1H), 6.77 (s, 2H), 3.40 (m, 4H), 3.23 (s, 2H), 2.80 (s, 3H), 2.20-2.25 (m, 2H), 1.74-1.77 (m, 2H), 1.63-1.71 (m, 4H)。

[1834]

I-N-232	429.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.54 (s, 1H), 9.50 (dd, 1H), 8.48 (d, 1H), 8.30 (d, 1H), 6.76 (s, 2H), 3.78 - 3.56 (m, 5H), 3.50 - 3.45 (m, 1H), 3.29 - 3.23 (m, 1H), 2.02 - 1.94 (m, 2H), 1.92 - 1.84 (m, 1H), 1.54 - 1.45 (m, 1H)。
I-N-233	440.1	1.7*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.52-9.53 (dd, 1H), 9.32 (d, 1H), 8.93 (d, 1H), 8.47-8.48 (dd, 1H), 7.57-7.58 (d, 1H), 6.80 (s, 2H), 4.03-4.06 (dd, 1H), 3.66-3.69 (m, 1H), 3.45-3.50 (m, 1H), 3.23-3.26 (m, 1H), 3.06-3.15 (m, 4H), 2.97-3.03 (m, 1H), 2.95-2.97 (m, 4H), 2.62-2.65 (m, 1H)。
I-N-234	429.1	1.75*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.66 (s, 1H), 9.52-9.53 (dd, 1H), 9.24 (d, 1H), 8.96-8.97 (dd, 1H), 8.40-8.42 (dd, 1H), 7.51-7.52 (d, 1H), 6.80 (s, 2H), 4.51-4.54 (dd, 1H), 3.96-3.98 (m, 1H), 3.56-3.58 (m 2H), 3.18-3.23 (m, 2H), 3.02 (s, 3H), 2.77 (s, 3H)。
I-N-235	439.1	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.26 (s, 1H), 8.85 (dd, J = 2.6, 0.5 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.21 (dd, J = 5.3, 0.5 Hz, 1H), 6.77 (s, 2H), 3.23 - 3.16 (m, 2H), 2.89 (dd, J = 13.1, 11.0 Hz, 2H), 2.72 (t, J = 0.7 Hz, 3H), 2.26 (dd, J = 8.4, 7.4 Hz, 2H), 2.14 (td, J = 12.7, 4.2 Hz, 2H), 1.97 (t, J = 7.9 Hz, 2H), 1.47 (d, J = 12.4 Hz, 2H)。
I-N-236	439.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.61 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.21 (d, J = 1.1 Hz, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.42 (dd, J = 6.7, 1.1 Hz, 1H), 7.51 (d, J = 6.7 Hz, 1H), 6.78 (s, 2H), 3.41 - 3.32 (m, 4H), 3.27 (s, 2H), 2.73 (s, 3H), 2.29 (d, J = 1.1 Hz, 2H), 1.77 (dtdd, J = 17.2, 10.7, 7.1, 3.8 Hz, 4H)。
I-N-237	367.1	2.11*	----------

[1835]

I-N-238	413.1	1.72*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.84 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.47 - 9.40 (m, 1H), 9.00 (dd, J = 2.6, 0.6 Hz, 1H), 8.45 (dd, J = 6.2, 0.9 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 6.78 (s, 2H), 4.42 - 4.34 (m, 1H), 4.18 (dddd, J = 10.9, 8.6, 5.0, 3.7 Hz, 1H), 3.98 - 3.94 (m, 1H), 3.75 - 3.64 (m, 2H), 3.52 (d, J = 12.4 Hz, 1H), 3.35 (ddd, J = 13.3, 12.0, 3.5 Hz, 1H), 3.02 - 2.89 (m, 2H)。
I-N-239	416.1	2.27*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.49 (q, J = 2.3 Hz, 2H), 8.61 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 3.0 Hz, 1H), 6.79 (s, 2H), 4.44 (s, 4H), 3.00 (dd, J = 6.8, 4.1 Hz, 4H), 2.04 (t, J = 5.4 Hz, 4H)。
I-N-240	458.1	1.88*	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.48 (s, 1H0, 9.07-9.09 (d, 1H), 8.77 (d, 1H), 8.43-8.44 (d, 1H), 3.91-3.96 (m, 1H), 3.62-3.68 (m, 1H), 3.53-3.56 (m, 1H), 3.30-3.45 (m, 4H), 3.25-3.28 (m, 1H), 2.88-3.04 (m, 5H)。
I-N-241	424.1	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.05-2.15 (4H,m), 3.15-3.20 (2H,m), 3.23-3.32 (1H,m), 3.62-3.68 (2H,m), 6.80 (2H,brs), 7.52 (1H,d), 8.42 (1H,d), 8.87 (1H,d), 9.38 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs), 9.79 (1H,s)。
I-N-242	372.0	1.85*	----------
I-N-243	448.0	1.96*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (1H, s), 9.54 (1H, dd), 9.44 (1H, s), 8.88 (1H, d), 8.50 (1H, dd), 7.62 (1H, d), 6.81 (2H, brs), 3.59 – 3.63 (2H, m), 3.17 – 3.22 (2H, m), 2.97 (3H, s), 2.37 – 2.42 (2H, m), 1.78 – 1.81 (2H, m), 1.53 (3H, s)。
I-N-244	425.0	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.52-9.53 (dd, 1H),9.34 (s, 1H), 8.99 (d, 1H), 8.43-8.44 (d, 1H), 7.50-7.52 (d, 1H),6.78 (s, 2H), 4.47-4.50 (m, 1H), 3.62-3.78 (m, 2H), 2.94-2.97 (m, 2H), 2.86 (t, 1H), 2.18-2.22 (m, 2H),2.81-2.83 (m, 1H), 2.64-2.78 (m, 2H), 1.35-1.47 (m, 1H)。

[1836]

I-N-245	468.1	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.51-9.53 (dd, 1H), 9.31 (d, 1H), 8.94 (d, 1H), 8.44-8.45 (dd,1H), 7.54-7.55 (d, 1H), 4.50-4.55 (m, 1H) 3.91-3.96 (m, 1H), 3.62-3.68 (m, 1H), 3.25-3.30 (m, 1H), 2.90-3.15 (m, 4H), 2.50-2.80 (m, 4H)。1.03-1.06 (t, 6H)。
I-N-246	360.1	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.82-1.92 (4H,m), 3.6-3.7 (4H,m), 6.85 (2H,s), 8.45 (1H,d), 8.59 (1H,s), 8.80-8.82 (1H,m), 9.48-9.53 (2H,m)。
I-N-247	447.1	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.48 (s, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.1, 0.7 Hz, 1H), 7.54 (d, J = 6.1 Hz, 1H), 6.81 (s, 2H), 3.70 - 3.63 (m, 1H), 3.57 (d, J = 12.1 Hz, 1H), 3.47 (tdd, J = 9.8, 6.7, 3.0 Hz, 1H), 3.40 - 3.33 (m, 2H), 3.33 - 3.29 (m, 1H), 3.12 (td, J = 11.5, 3.0 Hz, 1H), 3.02 (td, J = 12.0, 3.0 Hz, 1H), 2.95 (dd, J = 12.0, 10.2 Hz, 1H), 2.36 (dddd, J = 12.6, 9.3, 5.8, 3.6 Hz, 1H), 1.97 (dtd, J = 12.5, 10.3, 8.2 Hz, 1H)。
I-N-248	431.0	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.55 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.30 (d, J = 2.5 Hz, 1H), 6.79 (s, 2H), 4.43 (t, J = 8.6 Hz, 1H), 4.20 (ddd, J = 12.1, 9.5, 4.4 Hz, 1H), 3.99 (dd, J = 8.9, 5.0 Hz, 1H), 3.73 (dt, J = 13.0, 2.6 Hz, 1H), 3.42 - 3.31 (m, 1H), 3.23 (dd, J = 11.4, 3.9 Hz, 1H), 3.07 - 2.99 (m, 3H)。
I-N-249	441.0	1.76*	----------
I-N-250	424.0	1.90*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.58 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.68 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 1.8 Hz, 1H), 6.85 (s, 2H), 3.60 - 3.42 (m, 8H)。

[1837]

I-N-251	439.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.47-9.48 (dd, 1H), 9.45 (s, 1H), 8.80 (d, 1H), 8.22 (d, 1H), 7.17 (d, 1H), 6.77 (s, 2H), 3.93 (s, 2H), 3.63 (s, 2H), 2.87 (m, 4H), 1.93-1.95 (m, 4H), 1.78 (s, 3H)。
I-N-252	434.1	1.91*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 9.51 (s, 1H), 9.26 (s, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.41 (d, J = 6.1 Hz, 1H), 7.54 (d, J = 6.2 Hz, 1H), 6.81 (s, 2H), 3.51 (m, 6H), 1.46 (s, 6H)。
I-N-253	397.9	2.05*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.51-9.52 (d, 1H), 9.48 (s, 1H), 9.25 (s, 1H), 8.83 (d, 1H), 7.51-7.53 (d, 1H), 6.78 (s, 2H), 4.43 (d, 2H), 4.31 (d, 2H), 3.55 (s, 2H), 3.08 (m, 2H), 1.87-1.89 (m, 2H), 1.65-1.67 (m, 2H)。
I-N-254	399.1	1.72*	----------
I-N-255	411.2	1.8*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.54 (dd, 1H), 9.27 (s, 1H), 8.90 (d, 1H), 8.88 (br s, 2H), 8.40 (dd, 1H), 7.46 (d, 1H), 6.80 (s, 2H), 3.34 - 3.25 (m, 6H), 3.12 (t, 2H), 1.91 (t, 2H), 1.83 - 1.73 (m, 4H)。
I-N-256	439.1	1.89*	1H NMR (500 MHz, DMSO-d6) (TFA salt) δ 2.37 (3H,s), 3.43-3.48 (4H,m), 3.63-3.67 (4H,m), 6.80 (2H,brs), 7.57 (1H,d), 8.48 (1H,d), 9.02 (1H,d), 9.37 (1H,s), 9.53-9.56 (1H,m), 9.63 (1H,brs), 9.77 (1H,s)。
I-N-257	453.1	2.05*	^{1}H NMR (500 MHz, DMSO) δ 9.60 (d, 1H), 9.53 (ddd, 1H), 9.19 (t, 1H), 8.90 (t, 1H), 8.41 (dt, 1H), 7.50 (dd, 1H), 6.78 (s, 2H), 3.50 (t, 1H), 3.43 - 3.31 (m, 6H), 3.27 (s, 1H), 1.94 (d, 3H), 1.90 (t, 1H), 1.81 (t, 1H), 1.74 - 1.70 (m, 4H)。

[1838]

I-N-258	411.1	1.8*	^{1}H NMR (500 MHz, DMSO) δ 9.79 (s, 1H), 9.52 (dd, 1H), 9.37 (s, 1H), 8.96 (d, 1H), 8.43 (d, 1H), 7.51 (d,1H), 6.78 (s, 2H), 3.92 - 3.87 (m, 2H), 3.72 (d, 1H), 3.60 (d, 1H), 3.10 (td, 1H), 2.87 (td, 1H), 2.77 (t, 1H), 2.35 - 2.23 (m, 2H), 2.13 - 2.06 (m, 1H), 1.61 - 1.54 (m, 1H)。
I-N-259	326.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.99 (s, 1H), 9.52-9.54 (d, 1H), 9.16 (d, 1H), 8.87 (m, 1H), 8.81 (s, 1H), 7.90 (d, 1H), 7.08 (d, 1H), 6.74 (s, 2H), 4.22 (d, 3H)。
I-N-260	439.1	2.4*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.41 (3H,s), 3.43-3.47 (4H,m), 3.53-3.57 (4H,m), 6.80 (2H,brs), 7.51 (1H,d), 8.45 (1H,d), 8.87 (1H,d), 9.37 (1H,s), 9.52-9.56 (1H,m), 9.63 (1H,brs), 9.77 (1H,s)。
I-N-261	433.1	2.29*	^{1}H NMR (500 MHz, DMSO-d6)δ 10.37 (s, 1H), 9.53 (s, 1H), 9.47-9.49 (dd, 1H), 8.86 (d, 1H), 8.27 (s,1H), 6.79 (s, 2H), 3.64-3.66 (m, 7H), 3.05-3.07 (m, 4H)。
I-N-262	453.2	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.51 (dd, J = 4.7, 2.6 Hz, 1H), 9.40 (d, J = 1.1 Hz, 1H), 9.19 (dd, J = 2.6, 0.8 Hz, 1H), 8.44 (dd, J = 6.7, 1.1 Hz, 1H), 7.53 (d, J = 6.7 Hz, 1H), 6.79 (s, 2H), 3.71 - 3.60 (m, 2H), 3.51 (t, J = 6.7 Hz, 2H), 3.21 (td, J = 12.8, 3.9 Hz, 2H), 3.08 - 2.94 (m, 2H), 2.01 (d, J = 6.9 Hz, 5H), 1.81 (p, J = 6.8 Hz, 2H), 1.42 (dd, J = 12.6, 2.2 Hz, 2H)。
I-N-263	354.1	1.34*	^{1}H NMR (500 MHz, DMSO) δ 9.74 (s, 1H), 9.60 (s, 1H), 9.46 (dd, J = 4.8, 2.5 Hz, 1H), 8.84 (s, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.27 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H), 6.67 (s, 1H), 2.27 (s, 3H)。
I-N-264	371.0	2.49*	在 d6-DMSO 中运行

[1839]

I-N-265	438.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6)δ 2.02-2.18 (4H,m), 2.37 (3H,s), 3.21-3.27 (2H,m), 3.30-3.37 (1H,m), 3.68-3.75 (2H,m), 6.80 (2H,brs), 7.58 (1H,d), 8.48 (1H,d), 8.87 (1H,d), 9.33 (1H,s), 9.53-9.56 (1H,m), 9.72 (1H,brs)。
I-N-266	387.2	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.63 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.22 (d, J = 1.1 Hz, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.40 (dd, J = 6.6, 1.1 Hz, 1H), 7.49 (d, J = 6.6 Hz, 1H), 6.77 (s, 2H), 3.49 (dtt, J = 11.8, 7.5, 3.6 Hz, 3H), 3.26 (s, 3H), 3.26 - 3.12 (m, 2H), 2.09 - 1.92 (m, 2H), 1.80 - 1.61 (m, 2H)。
I-N-267	413.1	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.41 (s, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 6.77 (s, 2H), 3.32 (s, 2H), 3.16 (dt, J = 12.0, 3.3 Hz, 2H), 2.68 (td, J = 11.8, 2.4 Hz, 2H), 2.18 (s, 6H), 1.79 (dd, J = 13.3, 3.6 Hz, 2H), 1.63 (s, 1H), 1.49 - 1.41 (m, 2H)。
I-N-268	424.1	1.93*	^{1}H NMR (500 MHz, DMSO-d6)δ 2.02-2.13 (2H,m), 2.14-2.24 (2H,m), 3.21-3.27 (2H,m), 3.38-3.42 (1H,m), 3.68-3.75 (2H,m), 6.80 (2H,brs), 7.58 (1H,d), 8.48 (1H,d), 8.85 (1H,d), 9.22 (1H,s), 9.33 (1H,s), 9.53-9.55 (1H,m), 9.72 (1H,brs)。
I-N-269	367.1	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.36 (s, 1H), 9.33 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.73 (d, J = 5.1 Hz, 1H), 6.74 (s, 2H), 2.38 (d, J = 1.0 Hz, 3H), 2.04 (d, J = 1.0 Hz, 3H)。
I-N-270	374.1	2.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.51 (s, 1H), 9.49 (dd, 1H), 8.77 (d, 1H), 8.24 (d, 1H), 6.79 (s, 2H), 3.03 (br t, 4H), 1.80 - 1.76 (m, 4H), 1.669 - 1.65 (m, 2H)。

[1840]

I-N-271	475.1	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.01-2.12 (2H,m), 2.12-2.18 (2H,m), 2.22-2.28 (2H,m), 2.92-3.02 (2H,m), 3.38-3.46 (2H,m), 3.52-3.60 (3H,m), 3.92-3.97 (4H,m), 6.82 (2H,brs), 7.45-7.48 (1H,m), 8.40 (1H,brs), 8.80 (1H,d), 9.45-9.50 (1H,m),9.53- 9.56 (1H,m), 9.83 (1H,s)。
I-N-272	459.1	2.38*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.83 (2H, m), 2.02 (2H, m), 3.19 (3H、s), 2.30 (4H、m), 2.89-2.91 (2H, m), 3.25 (2H, m), 3.70 (2H, m), 6.80 (2H, br s), 8.24 (1H, d), 8.71 (1H, d), 9.49 (2H, m)和 10.31 (1H, br s) ppm.
I-N-273	562.1	2.25*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.0-2.2 (10H,m), 2.90-3.05 (3H,m), 3.35-3.42 (2H,m), 3.42-3.53 (3H,m), 3.60-3.68 (1H,m), 3.75-3.79 (2H,m), 4.30-4.33 (1H,m), 8.28 (1H,d), 8.94 (1H,d), 9.50-9.53 (1H,m), 9.66 (1H,s), 10.23 (1H,brs), 10.43 (1H,s)。
I-N-274	473.0	2.03*	----------
I-N-275	417.1	1.96*	^{1}H NMR (500 MHz, 甲醇-d4) δ1.03 (s, 1H), 9.52 (d, 1H), 9.05 (d, 1H), 8.72 (d, 1H), 8.36 (d, 1H), 3.85-3.91 (m, 4H), 3.35-3.40 (masked, 4H), 2.15 (s, 3H)。
I-N-276	443.0	2.24*	----------
I-N-277	443.1	2.1*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 6.80 (s, 2H), 4.60 (dd, J = 12.1, 2.7 Hz, 1H), 3.75 (d, J = 8.1 Hz, 1H), 3.15 - 3.06 (m, 2H), 3.05 - 2.89 (m, 3H), 2.33 - 2.26 (m, 2H), 1.93 (dt, J = 13.5, 4.7 Hz, 1H), 1.75 (p, J = 4.1 Hz, 2H), 1.51 - 1.40 (m, 1H)。
I-N-278	459.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.53-9.55 (d, 1H), 9.48-9.49 (dd, 1H), 8.88 (d, 1H), 8.29 (d, 1H), 6.80 (s, 2H), 4.71-4.76 (m, 4H), 4.17-4.23 (m, 1H), 3.75(m, 2H), 3.741-3.43 (m, 2H), 3.05-3.07 (m, 2H)。

[1841]

I-N-279	443.1	2.09*	^{1}H NMR (500 MHz, DMSO) δ 10.39 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 2.7 Hz, 1H), 6.84 - 6.74 (m, 2H), 4.63 - 4.56 (m, 1H), 3.74 (d, J = 11.3 Hz, 1H), 3.15 - 3.06 (m, 2H), 3.05 - 2.89 (m, 3H), 2.29 (dd, J = 9.7, 4.8 Hz, 2H), 1.93 (dt, J = 13.5, 4.6 Hz, 1H), 1.75 (dq, J = 10.2, 4.4 Hz, 2H), 1.51 - 1.40 (m, 1H)。
I-N-280	443.1	2.1*	^{1}H NMR (500 MHz, DMSO) δ 10.38 (s, 1H), 9.56 (s, 1H), 9.49 (dd, J = 4.8, 2.5 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 2.7 Hz, 1H), 6.78 (s, 2H), 4.63 - 4.56 (m, 1H), 3.75 (q, J = 8.5 Hz, 1H), 3.17 - 3.06 (m, 2H), 3.06 - 2.89 (m, 3H), 2.29 (t, J = 7.3 Hz, 2H), 1.93 (dq, J = 13.4, 4.5, 4.0 Hz, 1H), 1.81 - 1.71 (m, 2H), 1.45 (dtd, J = 14.2, 9.5, 4.7 Hz, 1H)。
I-N-281	376.0	2.87*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.28 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.35 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.41 (s, 1H), 3.52 - 3.45 (m, 4H), 2.12 - 2.04 (m, 4H)。
I-N-282	400.0	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.52 (dd, J = 4.8, 2.5 Hz, 1H), 9.28 (d, J = 1.1 Hz, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.39 (dd, J = 6.6, 1.0 Hz, 1H), 7.48 (d, J = 6.5 Hz, 1H), 6.78 (s, 2H), 3.65 (dt, J = 13.2, 3.4 Hz, 2H), 3.30 (d, J = 13.4 Hz, 6H), 2.98 (td, J = 12.5, 2.5 Hz, 2H), 1.91 - 1.67 (m, 3H), 1.66 - 1.46 (m, 2H)。
I-N-283	353.1	1.75*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (d, J = 0.6 Hz, 1H), 9.58 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.80 (d, J = 1.1 Hz, 1H), 7.50 (dd, J = 5.0, 0.6 Hz, 1H), 7.08 (t, J = 1.1 Hz, 1H), 6.70 (s, 2H), 2.01 (d, J = 1.1 Hz, 3H)。

[1842]

I-N-284	392.1	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.48-9.49 (m, 1H), 9.19 (s, 1H), 8.78 (d, 1H), 8.36 (s, 1H), 6.80 (s, 2H), 4.45-4.48 (m, 1H), 3.78-3.80 (m, 1H), 3.70-3.73 (m, 1H), 3.41-3.45 (m, 1H), 3.35-3.37 (m, 1H), 2.10-2.15 (m, 1H), 1.88-1.93 (m, 1H)。
I-N-285	401.0	2.4*	----------
I-N-286	431.1	2.25*	----------
I-N-287	454.0	2.11*	----------
I-N-288	440.3	2.16*	----------
I-N-289	500.0	2.2*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.50-1.60 (1H, m), 1.75-1.95 (2H, m), 2.01-2.12 (2H, m), 2.70-2.90 (5H, m), 3.00-3.15 (5H, m), 3.20-3.45 (2H, m), 3.85-3.97 (2H, m), 4.40-4.45 (1H, m), 6.85-6.93 (2H, br s), 8.28 (1H, d), 8.94 (1H, d), 9.51-9.53 (2H, dd), 9.60-9.70 (1H, s), 10.30-10.33 (1H, s)。
I-N-290	427.0	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.52-9.54 (dd, 1H), 9.09 (d, 1H), 8.94 (dd, 1H), 8.36-8.38 (dd, 1H), 6.77 (s, 2H), 3.74-3.77 (m, 2H), 3.11-3.18 (m, 1H), 2.90-3.05 (m, 2H), 2.71 (s, 3H), 2.55 (s, 3H), 1.95-1.98 (m, 1H), 1.77-1.79 (m, 2H), 1.46-1.51 (m, 1H)。
I-G-1	482.3	0.63	^{1}H NMR (500 MHz, MeOD) δ 9.52 (d, J = 1.2 Hz, 1H), 9.06 (dd, J = 4.3, 2.5 Hz, 1H), 8.88 (dd, J = 2.6, 0.5 Hz, 1H), 8.34 (dd, J = 6.6, 1.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 4.77 (s, 2H), 4.36 (s, 2H), 3.78 (dm, J = 13.0 Hz, 2H), 3.57 (s, 2H), 3.22 - 3.01 (m, 5H), 2.95 (s, 3H), 2.20 (dm, J = 12.2 Hz, 2H), 1.91 (dm, 2H)。
I-G-2	427.2	0.65	^{1}H NMR (500 MHz, MeOD) δ 9.60 (s, 1H), 9.02 (dd, J = 2.6, 0.6 Hz, 1H), 9.00 (dd, J = 4.3, 2.5 Hz, 1H), 8.21 (d, J = 5.4 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 3.29 (dt, J = 11.6, 2.6 Hz, 2H), 3.20 (s, 3H), 3.03 (s, 3H), 2.95 (tt, J = 11.7, 3.8 Hz, 1H), 2.87 (td, J = 12.1, 2.3 Hz, 2H), 2.25 (qd, 2H), 1.87 (dm, 2H)。

[1843]

I-G-3	516.2	0.77	^{1}H NMR (500 MHz, MeOD) δ 10.65 (s, 1H), 9.81 (d, J = 1.3 Hz, 1H), 9.21 (dd, J = 2.6, 0.8 Hz, 1H), 9.04 (dd, J = 4.3, 2.6 Hz, 1H), 8.30 (s, 1H), 4.57 - 4.28 (m, 2H), 3.75 - 3.65 (m, 2H), 3.69 - 3.45 (m, 4H), 3.25 - 3.07 (m, 4H), 3.03 (dt, J = 12.2, 3.6 Hz, 1H), 3.00 (s, 3H), 2.40 - 2.23 (m, 2H), 1.91 (dm, J = 12.7 Hz, 2H)。
I-G-4	500.2	0.72	^{1}H NMR (500 MHz, MeOD) δ 10.67 (s, 1H), 9.69 (d, J = 0.6 Hz, 1H), 9.20 (dd, J = 2.7, 0.6 Hz, 1H), 9.01 (dd, J = 4.3, 2.6 Hz, 1H), 8.16 (d, J = 3.0 Hz, 1H), 7.58 (d, J = 2.8 Hz, 1H), 3.74 (t, J = 5.1 Hz, 2H), 3.72 - 3.65 (m, 2H), 3.34 - 3.28 (m, 2H), 3.18 (tt, J = 12.0, 2.4 Hz, 2H), 3.06 - 2.95 (m, 1H), 2.60 - 2.45 (m, 4H), 2.38 (s, 3H), 2.36 - 2.25 (m, 2H), 1.91 - 1.79 (m, 2H)。
I-G-5	516.2	2.34*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.66 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 9.03 (d, J = 2.2 Hz, 1H), 8.32 - 8.24 (m, 1H), 6.85 (s, 2H), 4.47 (dd, J = 115.4, 12.9 Hz, 2H), 3.48 (d, J = 10.4 Hz, 2H), 3.40 (t, J = 13.5 Hz, 1H), 3.20 (d, J = 10.8 Hz, 2H), 3.10 - 2.94 (m, 6H), 2.85 (d, J = 2.9 Hz, 3H), 2.12 (dd, J = 43.1, 13.1 Hz, 2H), 1.84 - 1.73 (m, 2H)。
I-G-6	514.2	2.28*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7-1.8 (2H,m), 2.1-2.25 (4H,m), 2.85-3.0 (4H,m), 3.05-3.12 (3H,m), 3.2-3.3 (3H,m), 3.4-3.55 (3H,m), 3.6-3.75 (2H,m), 4.05-4.15 (1H,m), 6.8 (2H,brs), 8.28 (1H,d), 9.25 (1H,d), 9.5-9.6 (2H,m), 9.7 (1H,d), 10.63-10.66 (1H,m)。
I-G-7	526.2	2.21*	^{1}H NMR (500 MHz, DMSO-d6, 370 K) δ 10.50 (s, 1H), 9.62 (s, 1H), 9.27 (dd, J = 4.7, 2.4 Hz, 1H), 8.19 (d, J = 2.7 Hz, 1H), 6.53 (s, 2H), 3.78 - 3.67 (m, 2H), 3.22 (tm, J = 11.6 Hz, 2H), 3.09 (dm, 2H), 3.02 - 2.83 (m, 8H), 2.29 - 2.14 (m, 3H), 1.96 - 1.84 (m, 2H), 1.83 - 1.64 (m, 2H)。

[1844]

I-G-8	457.1	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7-1.75 (2H,m), 2.05-2.15 (2H,m), 2.2-2.28 (2H,m), 2.4-2.5 (1H,m), 3.03-3.18 (4H,m), 3.95 (2H,t), 4.25 (2H,t), 8.28 (1H,d), 9.38 (1H,d), 9.47-9.50 (1H,m), 9.7 (1H,s), 10.65 (1H,s)。
I-G-9	514.0	2.40*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.23 (3H,t), 1.75-1.81 (2H,m), 2.05-2.20 (2H,m), 2.97-3.1 (5H,m), 3.15-3.25 (4H,m), 3.4-3.57 (3H,m), 4.35-4.4 (1H,m), 4.6-4.65 (1H,m), 8.28 (1H,d), 9.18 (1H,d), 9.48-9.56 (2H,m), 9.68 (1H,s), 10.65 (1H,s)。
I-G-10	526.2	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.5-1.6 (1H,m), 1.70-1.81 (3H,m), 1.90-2.25 (5H,m), 2.90-3.1 (4H,m), 3.18-3.37 (4H,m), 3.4-3.5 (1H,m), 3.6-3.9 (3H,m), 3.9-4.0 (1H,m), 6.6-6.85 (2H,m), 8.26 (1H,d), 9.1-9.2 (1H,m), 9.47-9.51 (2H,m), 9.68 (1H,s), 10.1 (1H,brs), 10.67 (1H,s)。
I-G-11	514.2	2.30*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.78-1.84 (2H,m), 2.00-2.18 (4H,m), 2.28-2.4 (2H,m), 2.45-2.55 (1H,m), 2.70-2.80 (1H,m), 2.80-2.90 (6H,m), 3.05-3.12 (2H,m), 3.12-3.22 (3H,m), 4.35-4.4 (1H,m), 4.6-4.65 (1H,m), 6.78 (2H,brs), 8.28 (1H,d), 9.35 (1H,d), 9.48-9.50 (1H,m), 9.70 (1H,s), 9.75-9.85 (1H,m), 10.67-10.69 (1H,m)。
I-G-12	486.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.80 (2H,m), 2.08-2.15 (2H,m), 2.92-3.00 (1H,m), 3.05-3.25 (8H,m), 3.72-3.78 (2H,m), 3.80-3.85 (2H,m), 6.79 (2H,brs), 8.23 (1H,d), 8.72 (2H,brs), 9.15 (1H,d), 9.48 (1H,d), 9.65 (1H,s), 10.63 (1H,s)。
I-G-13	526.1	2.62*	^{1}H NMR (500 MHz, CDCl3) δ 0.57 (4H, br s), 1.82-1.85 (2H, d), 2.03 (21H, s), 2.33-2.35 (2H, m), 2.60-2.85 (4H, m), 3.13-3.15 (2H, m), 3.24-3.29 (2H, m), 3.70 (4H, br s), 5.84 (2H, s), 8.20 (2H, d), 8.48-8.49 (1H, d), 9.34 (1H, d), 9.80 (1H, s), 10.6 (1H, s)。

[1845]

I-G-14	498.4	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.68 (s, 1H), 9.47-9.48 (dd, 1H), 9.35 (dd, 1H), 8.25-8.26 (d, 1H), 6.79 (s, 2H), 4.69 (s, 4H), 4.41 (s, 2H), 4.10 (s, 2H), 3.10-3.13 (m, 2H), 3.02-3.05 (m, 2H), 2.45-2.50 (m, 2H), 2.04-2.08 (m, 2H), 1.72- 1.75 (m, 2H)。
I-G-15	528.2	2.43*	----------
I-G-16	516.3	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.95 (3H,m), 2.10-2.25 (2H,m), 2.78-2.85 (5H,m), 2.90-3.00 (1H,m), 3.02-3.15 (5H,m), 3.17-3.26 (2H,m), 3.43-3.52 (2H,m), 8.27-8.29 (1H,m), 9.22 (1H,s), 9.27 (1H,d), 9.48-9.53 (1H,m), 9.68-9.71 (1H,m), 10.64-10.68 (1H,s)。
I-G-18	526.2	2.30*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.90 (2H,m), 2.10-2.22 (2H,m), 2.70-2.82 (1H,m), 2.85-2.93 (4H,m), 2.96-3.12 (3H,m), 3.12-3.22 (2H,m), 3.23-3.35 (2H,m), 3.40-3.55 (2H,m), 3.59-3.75 (2H,m), 3.78-3.90 (2H,m), 6.75-6.90 (1H,m), 8.28 (1H,d), 9.37 (1H,d), 9.48-9.53 (1H,m), 9.69 (1H,s), 9.74-9.88 (1H,m), 10.66 (1H,s)。
I-G-19	473.2	2.78*	----------
I-G-20	514.2	2.14*	----------
I-G-21	487.1	2.31*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.68-1.75 (2H, m), 2.01-2.14 (2H, m), 2.35-2.40 (1H, 被掩蔽), 3.05-3.15 (4H, m), 3.24 (3H, s), 3.71-3.74 (1H, m), 4.05-4.12 (2H, m), 4.22-4.24 (1H, m), 4.41-4.44 (1H, m), 6.70-7.00 (2H, br s), 8.29 (1H, d), 9.36 (1H, dd), 9.47-9.49 (1H, dd), 9.67 (1H, s), 10.62 (1H, s)。
I-G-22	500.2	2.23*	----------
I-G-23	486.1	2.04*	----------
I-G-24	500.2	2.14*	----------

[1846]

I-G-25	525.2	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.22-2.25 (2H, m), 2.35-2.50 (6H, masked), 2.87 (3H, s), 3.05-3.25 (4H, m), 3.30-3.35 (2H, m),4.70-4.80 (2H, m), 6.77-6.92 (2H, br s), 8.32 (1H, d), 8.69 (1H, dd), 9.51-9.53 (1H, dd), 9.64 (1H, s), 9.80-9.95 (1H, br s), 10.37 (1H, s)。
I-G-26	502.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.77-1.83 (4H, m), 2.10-2.18 (2H, m), 2.36-2.42 (1H, m), 2.78-2.80 (6H, m), 3.05-3.09 (6H, m), 3.18-3.22 (2H, m), 6.80 (2H, br s), 8.16-8.18 (1H, m), 8.27 (1H, d), 9.34-9.36 (2H, m), 9.49-9.50 (1H, d), 9.67 (1H, s), 10.62 (1H, s)。
I-G-27	514.2	2.19*	----------
I-G-28	512.2	2.2*	----------
I-G-29	445.0	2.37*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.74-1.77 (2H, m), 2.05-2.15 (2H, m), 2.88-2.91 (4H, m), 3.03-3.05 (2H, m), 3.11 (3H, s), 3.15-3.22 (2H, m), 6.79 (1H, s), 8.25 (1H, d), 9.34 (1H, dd), 9.47-9.49 (1H, dd), 9.68 (1H, s), 10.66 (1H, s)。
I-G-30	489.2	2.12*	----------
I-G-31	502.1	2.33*	----------
I-G-32	542.3	2.14*	^{1}H NMR (500 MHz, 甲醇-d4) δ 1.87 (2H, m), 2.27-2.33 (2H, m), 2.55 (4H, m), 2.97-3.03 (1H, m), 3.18 (2H, m), 3.70-3.85 (4H, m), 4.67-4.70 (2H, m), 4.75-4.78 (2H, m), 8.16 (1H, d), 9.00 (1H, dd), 9.17 (1H, dd), 9.68 (1H, s), 10.65 (1H, s)。
I-G-33	432.1	2.07*	----------
I-G-34	486.1	2.07*	----------
I-G-35	540.2	2.74*	----------
I-G-36	487.0	2.34*	----------
I-G-37	473.1	2.04*	----------
I-G-38	526.2	2.39*	----------
I-G-40	489.2	2.45*	----------

[1847]

I-G-41	473.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.87 (2H, m), 2.25 (2H, m), 2.61 (1H, m), 3.84 (1H, m), 4.10 (1H, m), 4.28 (1H, m), 4.55 (1H, m), 4.62 (1H, m), 4.80 (3H, masked), 8.32 (1H, d), 9.05 (1H, dd), 9.24 (1H, d), 9.69 (1H, s), 10.56 (1H, s)。
I-G-42	500.2	2.11*	----------
I-G-43	526.0	2.43*	----------
I-G-44	512.0	2.18*	----------
I-G-45	500.0	2.14*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.14-1.17 (3H, m), 1.83-1.86 (2H, m), 2.22-2.34 (2H, m), 2.37-2.45 (1H, m), 2.75-2.88 (3H, m), 2.92-3.12 (2H, m), 3.11-3.20 (3H, m), 3.28-3.335 (1H, 被掩蔽), 4.01-4.08 (1H, m), 4.46-4.54 (1H, m), 8.14 (1H, s), 8.99-9.00 (1H, m), 9.19 (1H, m), 9.67 (1H, s)。
I-G-46	512.1	2.15*	----------
I-G-47	514.2	2.37*	----------
I-G-48	504.1	2.15*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.81 (s, 1H), 9.46 (dd, J = 4.7, 2.5 Hz, 1H), 9.35 (s, 1H), 8.24 (s, 1H), 6.79 (s, 2H), 3.58 - 3.44 (m, 6H), 2.95 - 2.84 (m, 3H), 2.68 (dt, J = 22.8, 4.7 Hz, 4H), 2.40 (s, 1H), 2.21 - 2.11 (m, 2H), 1.77 - 1.70 (m, 2H)。
I-G-49	512.1	2.29*	----------
I-G-50	514.2	2.38*	----------
I-G-51	512.1	2.03*	----------
I-G-52	526.2	2.46*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72-1.76 (1H, m), 1.83-1.85 (1H, m), 1.92-1.98 (3H, m), 2.05-2.12 (2H, m), 2.15-2.25 (1H, m), 2.80 (3H, s), 2.89 (1H, m), 3.05-3.25 (7H, m), 3.45-3.47 (2H, m), 4.78-4.80 (2H, m), 6.82 (2H, br s), 8.27 (1H, d), 9.27 (1H, d), 9.49-9.51 (1H, dd), 9.68 (1H, s), 10.65 (1H, s)。
I-G-53	512.1	2.18*	----------

[1848]

I-G-54	514.2	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.81 (s, 1H), 9.53 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 6.81 (s, 2H), 4.50 (d, J = 14.0 Hz, 2H), 3.46 (d, J = 11.7 Hz, 2H), 3.28 - 3.10 (m, 4H), 3.10 - 2.89 (m, 4H), 2.83 (s, 3H), 2.30 (ddd, J = 13.1, 8.9, 3.4 Hz, 2H), 1.86 - 1.67 (m, 2H), 1.40 (s, 3H)。
I-G-55	496.2	2.17*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.67 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 9.25 (s, 1H), 8.04 (s, 1H), 6.78 (s, 2H), 3.64 (d, J = 37.4 Hz, 4H), 3.16 - 3.07 (m, 1H), 3.01 - 2.87 (m, 3H), 2.70 - 2.56 (m, 5H), 2.41 (s, 6H), 2.23 - 2.09 (m, 2H), 1.77 - 1.67 (m, 2H), 1.19 (t, J = 7.3 Hz, 1H)。
I-G-56	482.2	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.73 (s, 1H), 9.50 (dd, J = 4.8, 2.6 Hz, 1H), 9.38 - 9.30 (m, 1H), 8.08 (d, J = 0.8 Hz, 1H), 6.83 (s, 2H), 3.61 (dt, J = 26.1, 5.2 Hz, 4H), 2.97 (tt, J = 11.8, 3.6 Hz, 3H), 2.85 (dt, J = 23.8, 5.0 Hz, 4H), 2.46 (s, 5H), 2.28 - 2.15 (m, 2H), 1.77 (dd, J = 12.2, 3.4 Hz, 2H)。
I-G-57	540.0	2.69*	----------
I-G-58	540.0	2.57*	----------
I-G-59	554.0	2.45*	----------
I-G-60	568.0	2.58*	----------
I-G-61	500.2	2.14*	----------
I-G-62	498.0	2.17*	----------
I-G-63	487.0	2.17*	----------
I-G-64	554.0	2.75*	----------
I-G-65	512.0	2.41*	^{1}H NMR (500 MHz, DMSO-d6) δ 0.64-0.78 (2H, m), 1.75-1.88 (2H, m), 2.05-2.24 (3H, m), 2.34-2.35 (3H, m), 2.50-2.55 (1H, 被掩蔽), 2.61-2.63 (1H, m), 2.71-2.74 (1H, m), 3.05-3.20 (6H, m), 4.07-4.09 (1H, m), 6.79 (2H, s), 8.26 (1H, d), 9.45 (1H, d), 9.48 (1H, dd), 9.69 (1H, s), 10.68 (1H, s)。

[1849]

I-G-66	542.1	2.41*	^{1}H NMR (500 MHz, DMSO) δ 10.71 (d, J = 19.7 Hz, 1H), 9.82 (d, J = 12.7 Hz, 1H), 9.47 (dt, J = 4.7, 2.9 Hz, 1H), 9.31 (s, 1H), 8.24 (d, J = 1.0 Hz, 1H), 6.80 (s, 2H), 4.54 - 4.23 (m, 1H), 3.73 (dt, J = 31.9, 5.7 Hz, 2H), 3.59 - 3.50 (m, 2H), 2.96 - 2.79 (m, 9H), 2.20 (dd, J = 26.6, 13.3 Hz, 2H), 1.87 (d, J = 13.8 Hz, 3H), 1.76 (d, J = 12.7 Hz, 2H), 1.65 (tt, J = 10.1, 4.8 Hz, 1H)。
I-G-67	474.4	2.42*	----------
I-G-68	542.0	2.42*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.05-1.25 (2H, m), 1.71-1.78 (2H, m), 1.95-1.98 (2H, m), 2.05-2.25 (3H, m), 2.340-2.45 (2H, 被掩蔽), 2.60 (1H, m), 2.95-3.10 (4H、m), 3.15-3.22 (2H, m), 3.35-3.40 (1H, m), 4.04-4.08 (2H, m), 4.15-4.27 (3H、m), 4.52-4.55 (1H, m), 6.80 (2H, br s), 8.27 (1H, d), 9.22 (1H, dd), 9.48-9.50 (1H, dd), 9.67 (1H, s), 9.90-10.00 (1H, s), 10.62 (1H, s)。
I-G-69	528.1	2.30*	^{1}H NMR (500 MHz, DMSO) δ 10.54 (s, 1H), 9.75 (s, 1H), 9.33 - 9.28 (m, 2H), 8.22 (s, 1H), 6.58 (s, 2H), 3.55 (t, J = 11.6 Hz, 2H), 2.26 - 2.11 (m, 4H), 3.01 - 2.93 (m, 3H), 2.80 (s, 2H), 2.47 (d, J = 11.4 Hz, 2H), 1.96 (s, 1H), 1.77 (d, J = 13.6 Hz, 3H), 2.39 - 2.34 (m, 1H), 2.68 - 2.60 (m, 2H)。
I-G-70	512.0	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.70-1.80 (2H, m), 1.81-1.97 (2H, m), 2.05-2.15 (2H, m), 2.40-2.50 (2H, 被掩蔽), 2.55-2.60 (1H, m), 2.78-2.83 (2H, m), 2.85-3.05 (2H, m), 3.10-3.20 (2H, m), 3.72-3.74 (1H, m), 3.96-3.98 (1H, m), 4.51 (1H, m), 5.05 (1H, m), 6.79 (2H, s), 8.25 (1H, m), 9.31 (1H, d), 9.35 (1H, d), 9.45 (1H, m), 9.67 (1H, d), 10.60 (1H, d)。

[1850]

I-G-71	512.0	2.11*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.70-1.80 (2H, m), 1.81-1.97 (2H, m), 2.05-2.15 (2H, m), 2.40-2.50 (1H, 被掩蔽), 2.55-2.60 (1H, m), 2.78-2.83 (2H, m), 2.85-3.05 (2H, m), 3.72-3.74 (1H, m), 3.96-3.98 (1H, m), 4.51 (1H, m), 5.05 (1H, m), 6.79 (2H, s), 8.25 (1H, m), 9.31 (1H, d), 9.35 (1H, d), 9.45 (1H, m), 9.67 (1H, d), 10.60 (1H, d)。
I-G-72	499.1	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.68 (s, 1H), 9.47-9.48 (dd, 1H), 9.35 (dd, 1H), 8.25-8.26 (d, 1H), 6.79 (s, 2H), 4.69 (s, 4H), 4.41 (s, 2H), 4.10 (s, 2H), 3.10-3.13 (m, 2H), 3.02-3.05 (m, 2H), 2.45-2.50 (m, 2H), 2.04-2.08 (m, 2H), 1.72- 1.75 (m, 2H)。
I-G-73	493.0	2.63*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.67 (s, 1H), 9.48-9.50 (dd, 1H), 9.27 (dd, 1H), 8.28 (d, 1H), 6.80 (be s, 2H), 4.76 (m, 2H), 4.38 (m, 2H), 3.14 (m, 2H), 3.08-3.11 (m, 2H), 2.55-2.60 (m, 1H), 2.03-2.15 (m, 2H), 1.82-1.84 (m, 2H)。
I-G-74	475.1	2.42*	----------
I-G-75	501.0	2.5*	----------
I-G-76	482.1	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.61 (s, 1H), 9.67 (s, 1H), 9.48-9.50 (dd, 1H), 9.30 (dd, 1H), 8.28 (d, 1H), 6.80 (br s, 2H), 4.55-4.56 (m, 1H), 4.46-4.49 (m, 1H), 4.21-4.25 (m, 1H),4.07-4.11 (m, 1H), 3.81-3.85 (m, 1H), 3.05-3.17 (m, 4H), 2.50-2.55 (被掩蔽, 1H), 2.03-2.09 (m, 2H), 1.75-1.81 (m, 2H)。
I-G-77	439.1	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.45 (d, J = 1.0 Hz, 1H), 9.02 (dd, J = 2.6, 0.6 Hz, 1H), 8.44 (dd, J = 6.5, 1.1 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.21 (t, J = 7.6 Hz, 2H), 3.89 (t, J = 7.7 Hz, 2H), 3.58 (dt, J = 12.3, 3.2 Hz, 2H), 3.02 (td, J = 12.5, 2.5 Hz, 2H), 2.59 - 2.52 (m, 1H), 2.26 - 2.16 (m, 2H), 2.06 - 1.94 (m, 2H), 1.80 - 1.72 (m, 2H)。

[1851]

I-G-78	469.1	1.99*	----------
I-G-79	483.0	2.12*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (d, J = 1.0 Hz, 1H), 9.00 (dd, J = 2.5, 0.6 Hz, 1H), 8.46 (dd, J = 6.5, 1.1 Hz, 1H), 7.58 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.17 - 4.11 (m, 1H), 4.00 (dd, J = 8.8, 1.2 Hz, 1H), 3.80 (d, J = 9.9 Hz, 1H), 3.68 (dd, J = 10.0, 1.2 Hz, 1H), 3.60 (dt, J = 12.5, 3.3 Hz, 2H), 3.18 (s, 3H), 3.06 - 2.98 (m, 2H), 2.57 (ddt, J = 11.7, 8.3, 4.2 Hz, 1H), 2.06 - 1.94 (m, 2H), 1.83 - 1.75 (m, 2H), 1.42 (s, 3H)。
I-G-80	475.1	2.24*	----------
I-G-81	464.1	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 9.44 (d, J = 1.0 Hz, 1H), 8.96 (dd, J = 2.5, 0.5 Hz, 1H), 8.46 (dd, J = 6.5, 1.1 Hz, 1H), 7.57 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.55 - 4.41 (m, 2H), 4.19 (t, J = 9.4 Hz, 1H), 4.05 (dd, J = 9.6, 6.1 Hz, 1H), 3.81 (tt, J = 9.1, 6.1 Hz, 1H), 3.64 - 3.56 (m, 2H), 3.02 (td, J = 12.4, 2.6 Hz, 2H), 2.61 - 2.52 (m, 1H), 2.04 - 1.90 (m, 2H), 1.80 (dd, J = 30.8, 12.9 Hz, 2H)。
I-G-82	457.1	2.04*	----------
I-G-83	453.1	2.21*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (d, J = 1.5 Hz, 1H), 9.53 (ddd, J = 4.9, 2.6, 1.0 Hz, 1H), 9.46 (dd, J = 2.5, 1.1 Hz, 1H), 9.06 - 9.01 (m, 1H), 8.46 (ddd, J = 6.4, 2.5, 1.1 Hz, 1H), 7.57 (dd, J = 6.6, 1.7 Hz, 1H), 6.80 (s, 2H), 3.62 (dt, J = 12.8, 3.2 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 3.05 (td, J = 12.5, 2.4 Hz, 2H), 2.77 (tt, J = 11.5, 3.9 Hz, 1H), 2.05 (qd, J = 12.7, 3.9 Hz, 2H), 1.96 - 1.86 (m, 2H), 1.85 - 1.75 (m, 4H)。

[1852]

I-G-84	495.1	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.84 (q, J = 1.7 Hz, 1H), 9.54 (ddd, J = 4.7, 2.6, 2.0 Hz, 1H), 9.45 (q, J = 1.6 Hz, 1H), 9.06 - 8.96 (m, 1H), 8.46 (ddd, J = 6.5, 2.6, 1.2 Hz, 1H), 7.61 - 7.52 (m, 1H), 6.80 (s, 2H), 4.55 (d, J = 6.1 Hz, 1H), 4.52 - 4.34 (m, 2H), 3.82 (s, 1H), 3.71 - 3.24 (m, 6H), 3.11 - 2.99 (m, 2H), 2.76 (dddd, J = 21.0, 17.3, 12.3, 6.9 Hz, 1H), 2.21 (t, J = 6.9 Hz, 1H), 2.13 - 1.97 (m, 3H), 1.82 (td, J = 13.2, 6.7 Hz, 2H)。
I-G-85	469.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.79 (s, 1H), 9.54 (dd, J = 4.8, 2.5 Hz, 1H), 9.41 (d, J = 1.1 Hz, 1H), 8.97 - 8.90 (m, 1H), 8.45 (dd, J = 6.6, 1.1 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 6.80 (s, 2H), 3.68 - 3.54 (m, 8H), 3.50 (t, J = 4.5 Hz, 2H), 3.16 - 2.94 (m, 3H), 2.07 - 1.96 (m, 2H), 1.81 - 1.71 (m, 2H)。
I-G-86	535.0	2.12*	----------
I-G-87	542.0	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 11.28 (1H, brs), 10.56 (0.4H, s), 10.52 (0.6H, s), 9.66 0.4H, s), 9.63 (0.6H, s), 9.44 (1H, d), 9.22 (0.4H, d), 8.99 (0.6H, d), 8.38 (1H, dd), 4.72 (0.6H, brs), 4.58 (0.4H, brs), 3.96 – 3.99 (2H, m), 3.20 – 3.40 (8H, m), 3.11 – 3.12 (2H, m), 1.98 – 2.15 (7H, m), 1.77 – 1.80 (2H, m)。
I-G-88	481.1	1.86*	----------
I-G-89	517.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.16 (s, 1H), 9.64 (s, 1H), 9.47 (dd, J = 4.8, 2.5 Hz, 1H), 9.06 (dd, J = 2.5, 0.6 Hz, 1H), 8.23 (d, J = 5.2 Hz, 1H), 7.21 (dd, J = 5.2, 0.6 Hz, 1H), 6.77 (s, 2H), 4.59 - 4.52 (m, 1H), 4.43 (dd, J = 9.5, 4.9 Hz, 1H), 4.31 (tt, J = 8.4, 5.0 Hz, 1H), 4.20 (dd, J = 10.4, 8.5 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.14 - 3.08 (m, 2H), 3.07 (s, 3H), 2.75 (tdd, J = 11.9, 6.5, 2.4 Hz, 2H), 2.48 (dt, J = 11.8, 4.0 Hz, 1H), 2.14 - 2.00 (m, 2H), 1.76 (dt, J = 12.5, 3.0 Hz, 2H)。

[1853]

I-G-90	481.1	1.96*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.83 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 9.44 (d, J = 1.1 Hz, 1H), 8.98 (d, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.5, 1.1 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 6.80 (s, 2H), 4.49 - 4.38 (m, 3H), 4.33 (dd, J = 10.0, 1.7 Hz, 1H), 4.14 (dd, J = 11.3, 1.7 Hz, 1H), 3.96 (dd, J = 11.2, 1.7 Hz, 1H), 3.61 - 3.54 (m, 2H), 3.01 (tt, J = 12.5, 3.2 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.59 - 2.52 (m, 1H), 1.97 (qq, J = 12.5, 4.8, 4.3 Hz, 2H), 1.81 - 1.73 (m, 2H)。
I-G-91	483.1	2.18*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (d, J = 0.9 Hz, 1H), 9.04 - 8.98 (m, 1H), 8.43 (dd, J = 6.4, 1.0 Hz, 1H), 7.54 (d, J = 6.4 Hz, 1H), 6.80 (s, 2H), 4.40 (ddd, J = 9.1, 6.5, 1.3 Hz, 1H), 4.30 (tt, J = 6.5, 4.0 Hz, 1H), 4.11 - 3.99 (m, 2H), 3.70 - 3.66 (m, 1H), 3.56 (d, J = 12.5 Hz, 2H), 3.43 (qd, J = 7.0, 2.3 Hz, 2H), 3.05 - 2.96 (m, 2H), 2.61 - 2.52 (m, 1H), 1.99 (qt, J = 12.6, 3.5 Hz, 2H), 1.79 (q, J = 12.8, 11.8 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H)。
I-G-92	556.0	2.37*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.67 (s, 1H), 9.49-9.50 (dd, 1H), 9.19 (d, 1H), 8.28 (d, 1H), 6.81 (s, 2H), 4.30-4.90 (m, 7H), 2.98-3.21 (m, 10H), 2.15-2.20 (m, 2H), 1.78-1.80 (m, 2H), 1.58 (m, 3H)。
I-G-93	483.1	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 - 9.83 (m, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.45 (dd, J = 2.2, 1.1 Hz, 1H), 9.02 (t, J = 2.5 Hz, 1H), 8.44 (dd, J = 6.4, 1.1 Hz, 1H), 7.56 (dd, J = 6.5, 1.6 Hz, 1H), 6.79 (s, 2H), 3.99 (dtt, J = 37.7, 4.6, 2.3 Hz, 1H), 3.71 - 3.43 (m, 5H), 3.41 - 3.27 (m, 1H), 3.25 (d, J = 11.0 Hz, 3H), 3.05 (tq, J = 12.4, 2.5 Hz, 2H), 2.78 (qt, J = 11.6, 3.9 Hz, 1H), 2.12 - 1.76 (m, 6H)。

[1854]

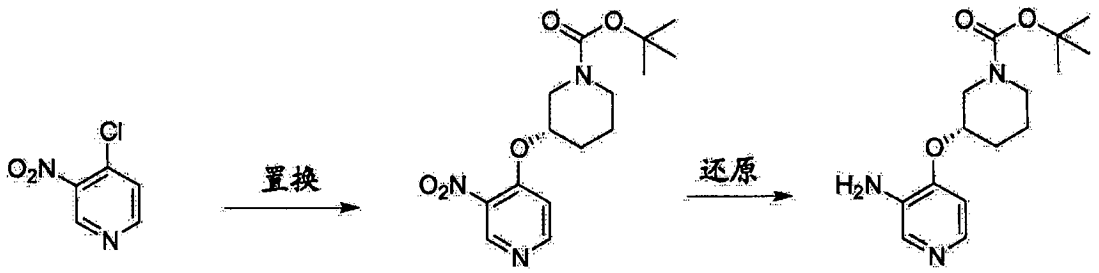
I-G-94	483.0	2.07*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.87 (d, J = 1.5 Hz, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 9.46 (dd, J = 2.2, 1.0 Hz, 1H), 9.02 (t, J = 2.7 Hz, 1H), 8.44 (dd, J = 6.4, 1.0 Hz, 1H), 7.55 (dd, J = 6.5, 1.6 Hz, 1H), 6.80 (s, 2H), 3.99 (dtt, J = 37.8, 4.5, 2.3 Hz, 1H), 3.71 - 3.43 (m, 5H), 3.40 - 3.27 (m, 1H), 3.25 (d, J = 10.9 Hz, 3H), 3.03 (dddd, J = 12.9, 8.3, 3.9, 2.3 Hz, 2H), 2.77 (qt, J = 11.0, 3.7 Hz, 1H), 2.12 - 1.86 (m, 4H), 1.80 (dt, J = 13.6, 6.9 Hz, 2H)。
I-G-95	516.1	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.48 (s, 1H), 10.64 (s, 1H), 9.68 (s, 1H), 9.50 (dd, 1H), 9.17 (dd, 1H), 8.28 (d, 1H), 6.81 (s, 2H), 4.54 (d, 1H), 4.31 (d, 1H), 3.79 - 3.69 (m, 5H), 3.53 (s, 3H), 3.36 - 3.30 (m, 1H), 3.24 - 3.18 (m, 2H), 3.09 - 3.01 (m, 3H), 2.21 - 2.07 (m, 2H), 1.79 (br d, 2H)。
I-G-96	555.2	2.13*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.67 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 9.29 - 9.18 (m, 1H), 8.26 (d, J = 2.4 Hz, 1H), 6.79 (s, 2H), 3.65 - 3.50 (m, 4H), 3.38 (s, 1H), 3.19 (t, J = 11.7 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 11.7 Hz, 1H), 2.82 (d, J = 31.4 Hz, 3H), 2.65 (p, J = 1.9 Hz, 1H), 2.55 (s, 1H), 2.37 (p, J = 1.9 Hz, 1H), 2.30 - 2.19 (m, 7H), 2.18 - 2.06 (m, 2H), 1.78 - 1.69 (m, 2H), 1.25 (s, 2H)。
I-G-98	501.0	2.44*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.63 (s,1H), 9.67 (s, 1H), 9.47-9.49 (dd, 1H), 9.38 (dd, 1H), 8.28 (d, 1H), 6.80 (s, 2H), 4.27-4.30 (m, 1H),3.93-3.97 (m, 2H), 3.61-3.64 (m, 1H), 3.49-3.51 (m, 2H), 3.30 (s, 3H), 3.15-3.16 (m, 2H), 3.10-3.11 (m, 2H), 2.80-2.83 (m, 1H), 2.35-2.40 (被掩蔽, 1H), 2.00-2.10 (m, 2H), 1.70-1.80 (m, 2H)。
I-G-99	501.1	2.45*	----------

[1855] (*) 表示保留时间,它是使用上文实验材料和方法部分中所述的 HPLC 方法 B 测定的。对于其余全部化合物,保留时间是使用 HPLC 方法 A 测定的。

[1856] 制备例 0-1 :(S)-3-((3- 氨基吡啶 -4- 基) 氧基) 哌啶 -1- 甲酸叔丁酯

[1857] 方案 7

[1858]



[1859] 步骤 1 :(3S)-3-[(3- 硝基 -4- 吡啶基) 氧基] 哌啶 -1- 甲酸叔丁酯

[1860] 将氢化钠 (492.0mg,12.30mmol) 加入到 (3S)-3- 羟基哌啶 -1- 甲酸叔丁酯 (2.095g,10.41mmol) 在 THF(20mL) 中的溶液中,将该反应体系在 0℃搅拌 15 分钟。加入 4- 氯 -3- 硝基 - 吡啶 (1.5g,9.461mmol) 在 THF(10mL) 中的混悬液,将该反应体系在 2 小时内缓慢地温至环境温度。用水使反应停止,使该混合物分配在 EtOAc 与盐水之间。用盐水洗涤合并的有机萃取物,干燥 ($MgSO_4$),过滤,真空浓缩。通过柱色谱法纯化残余物 (ISCO Companion,80g 柱,用 0 — 100% EtOAc/ 石油醚洗脱),得到 (3S)-3-[(3- 硝基 -4- 吡啶基) 氧基] 哌啶 -1- 甲酸叔丁酯,为淡黄色固体 (2.65g,87% 收率,93% ee)。MS(ES+)324.1.

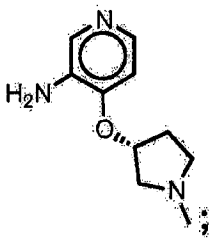
[1861] 步骤 2 :(S)-3-((3- 氨基吡啶 -4- 基) 氧基) 哌啶 -1- 甲酸叔丁酯

[1862] 将 C 上 Pd(10%,湿的, Degussa)(1g,0.9397mmol) 加入到搅拌的 (3S)-3-[(3- 硝基 -4- 吡啶基) 氧基] 哌啶 -1- 甲酸叔丁酯 (2.65g,8.196mmol) 在 EtOAc(30mL)/EtOH(15mL) 中的溶液中。将该反应体系放入氢气气氛中,在环境温度搅拌 16 小时。通过经 C 盐垫过滤除去催化剂,真空浓缩滤液,得到小标题化合物,为灰白色固体 (2.46g, >100% 收率)。MS(2ES+)587.3.

[1863] 使用制备例 0-1 制备了如下氨基吡啶类 :

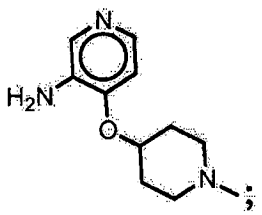
[1864] (R)-4-((1- 甲基吡咯烷 -3- 基) 氧基) 吡啶 -3- 胺 :

[1865]



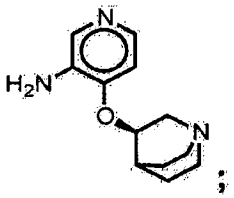
[1866] 4-((1- 甲基哌啶 -4- 基) 氧基) 吡啶 -3- 胺 :

[1867]



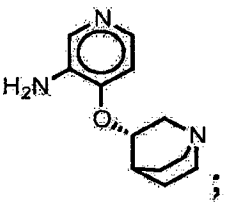
[1868] (R)-4-(奎宁环 -3- 基氧基) 吡啶 -3- 胺 :

[1869]



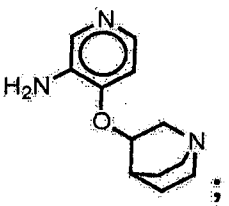
[1870] (S)-4-(奎宁环-3-基氧基)吡啶-3-胺：

[1871]



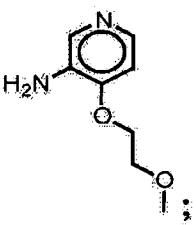
[1872] 4-(奎宁环-3-基氧基)吡啶-3-胺：

[1873]



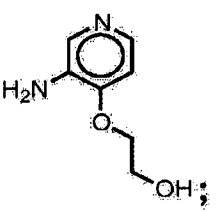
[1874] 4-(2-甲氧基乙氧基)吡啶-3-胺：

[1875]



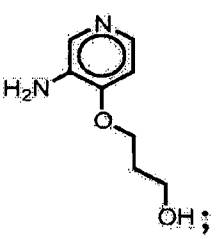
[1876] 2-((3-氨基吡啶-4-基)氧基)乙醇：

[1877]



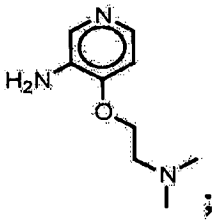
[1878] 3-((3-氨基吡啶-4-基)氧基)丙-1-醇：

[1879]



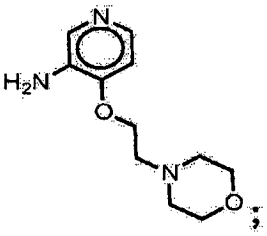
[1880] 4-(2-(二甲基氨基)乙氧基)吡啶-3-胺：

[1881]



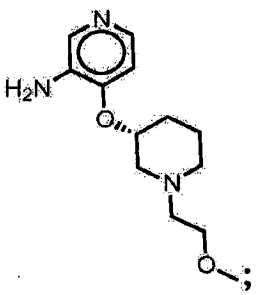
[1882] 4-(2-吗啉代乙氧基)吡啶-3-胺：

[1883]



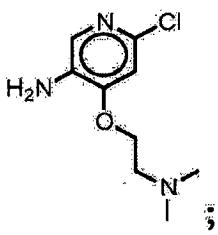
[1884] (R)-4-((1-(2-甲氧基乙基)哌啶-3-基)氧基)吡啶-3-胺：

[1885]



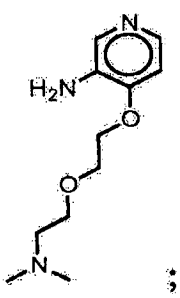
[1886] 6-氯-4-(2-(二甲基氨基)乙氧基)吡啶-3-胺：

[1887]



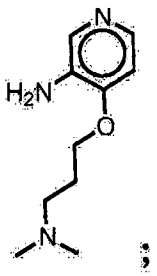
[1888] 4-(2-(2-(二甲基氨基)乙氧基)乙氧基)吡啶-3-胺：

[1889]



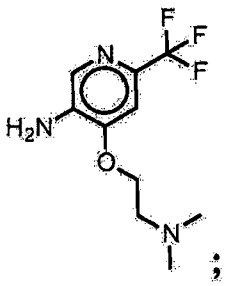
[1890] 4-(3-(二甲基氨基)丙氧基)吡啶-3-胺：

[1891]



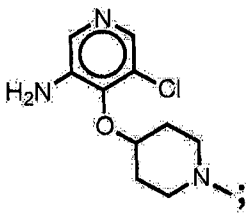
[1892] 4-(2-(二甲基氨基)乙氧基)-6-(三氟甲基)吡啶-3-胺：

[1893]



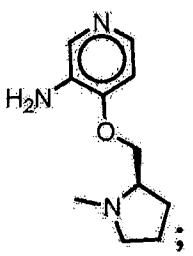
[1894] 5-氯-4-((1-甲基哌啶-4-基)氧基)吡啶-3-胺：

[1895]



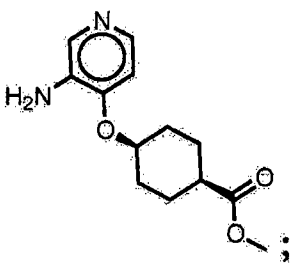
[1896] (R)-4-((1-甲基吡咯烷-2-基)甲氧基)吡啶-3-胺：

[1897]



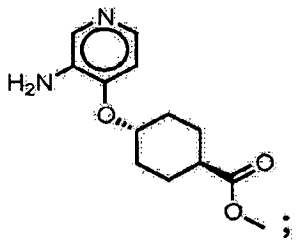
[1898] (1s,4s)-甲基4-((3-氨基吡啶-4-基)氧基)环己烷甲酸酯：

[1899]



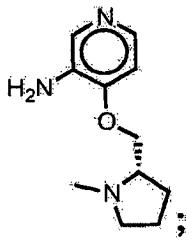
[1900] (1r,4r)-4-((3-氨基吡啶-4-基)氧基)环己烷甲酸甲酯：

[1901]



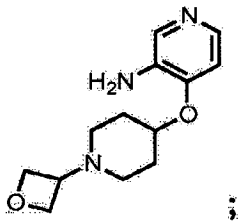
[1902] (S)-4-((1-甲基吡咯烷-2-基)甲氧基)吡啶-3-胺：

[1903]



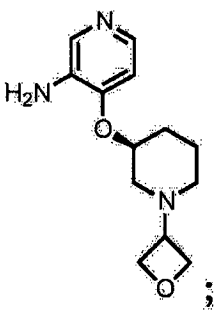
[1904] 4-((1-(氧杂环丁烷-3-基)哌啶-4-基)氧基)吡啶-3-胺：

[1905]



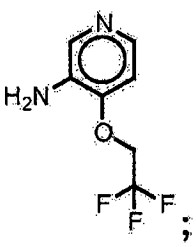
[1906] (S)-4-((1-(氧杂环丁烷-3-基)哌啶-4-基)氧基)吡啶-3-胺：

[1907]



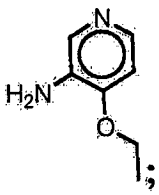
[1908] 4-(2,2,2-三氟乙氧基)吡啶-3-胺：

[1909]



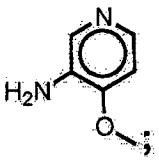
[1910] 4- 乙氧基吡啶 -3- 胺：

[1911]



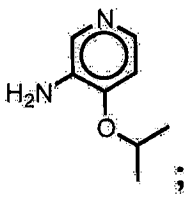
[1912] 4- 甲氧基吡啶 -3- 胺：

[1913]



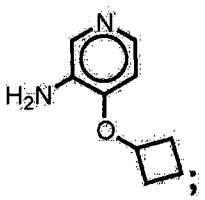
[1914] 4- 异丙氧基吡啶 -3- 胺：

[1915]



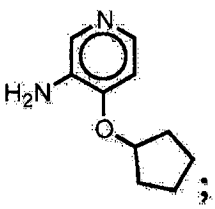
[1916] 4- 环丁氧基吡啶 -3- 胺：

[1917]



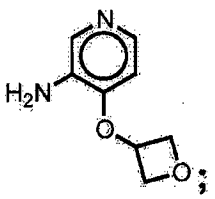
[1918] 4-（环戊基氧基）吡啶 -3- 胺：

[1919]



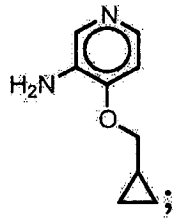
[1920] 4-（氧杂环丁烷 -3- 基氧基）吡啶 -3- 胺：

[1921]



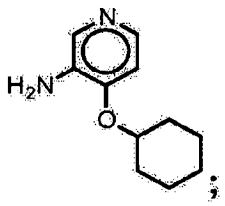
[1922] 4-（环丙基甲氧基）吡啶 -3- 胺：

[1923]



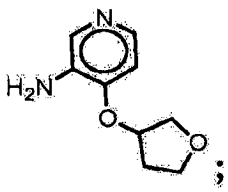
[1924] 4-(环己基氧基)吡啶-3-胺：

[1925]



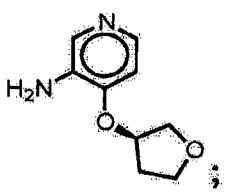
[1926] 4-((四氢呋喃-3-基)氧基)吡啶-3-胺：

[1927]



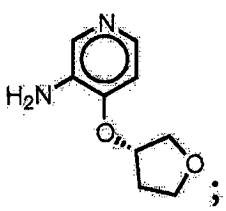
[1928] (R)-4-((四氢呋喃-3-基)氧基)吡啶-3-胺：

[1929]



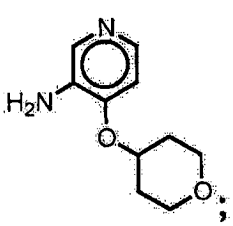
[1930] (S)-4-((四氢呋喃-3-基)氧基)吡啶-3-胺：

[1931]



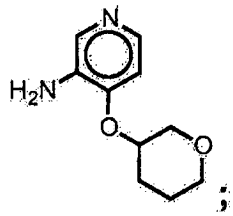
[1932] 4-((四氢-2H-吡喃-4-基)氧基)吡啶-3-胺：

[1933]



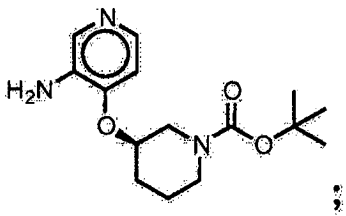
[1934] 4-((四氢-2H-吡喃-3-基)氧基)吡啶-3-胺：

[1935]



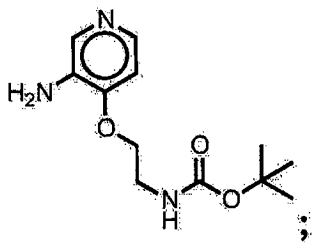
[1936] (R)-叔丁基3-((3-氨基吡啶-4-基)氧基)哌啶-1-甲酸酯：

[1937]



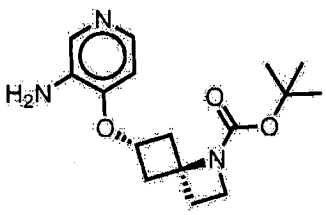
[1938] 叔丁基(2-((3-氨基吡啶-4-基)氧基)乙基)氨基甲酸酯：

[1939]



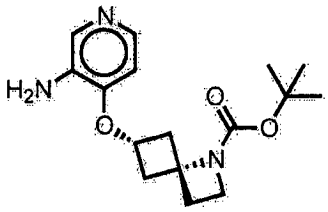
[1940] (4r,6s)-叔丁基6-((3-氨基吡啶-4-基)氧基)-1-氮杂螺[3.3]庚烷-1-甲酸酯：

[1941]



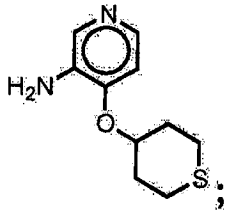
[1942] (4s,6r)-叔丁基6-((3-氨基吡啶-4-基)氧基)-1-氮杂螺[3.3]庚烷-1-甲酸酯：

[1943]



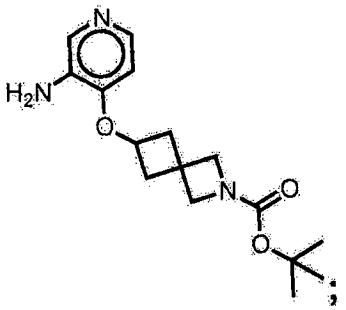
[1944] 4-((四氢-2H-噻喃-4-基)氧基)吡啶-3-胺：

[1945]



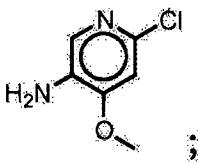
[1946] 叔丁基 6-((3- 氨基吡啶 -4- 基) 氧基)-2- 氮杂螺 [3.3] 庚烷 -2- 甲酸酯 :

[1947]



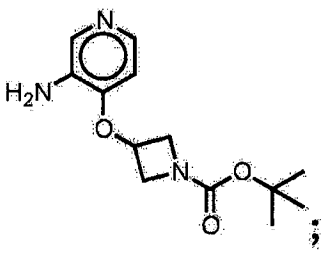
[1948] 6- 氯 -4- 甲氧基吡啶 -3- 胺 :

[1949]



[1950] 叔丁基 3-((3- 氨基吡啶 -4- 基) 氧基) 氮杂环丁烷 -1- 甲酸酯 :

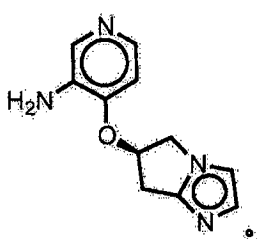
[1951]



且

[1952] (R)-4-((6,7- 二氢 -5H- 吡咯并 [1,2-a] 咪唑 -6- 基) 氧基) 吡啶 -3- 胺 :

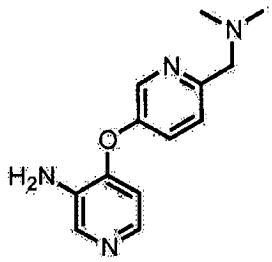
[1953]



[1954] 氨基吡啶类的其它制备例

[1955] 制备例 0-2 :4-((6-((二甲基氨基) 甲基) 吡啶 -3- 基) 氧基) 吡啶 -3- 胺

[1956]



[1957] 步骤 1 :6-((二甲基氨基)甲基)吡啶 -3- 醇

[1958] 将 6-(氨基甲基)吡啶 -3- 醇 (150mg,1.208mmol)、甲酸 (1mL,26.51mmol)、甲醛 (1mL,36.30mmol) 在 100℃加热过夜。真空浓缩混合物,得到 6-((二甲基氨基)甲基)吡啶 -3- 醇,未经进一步纯化,将其用于下一步骤中。

[1959] 步骤 2 :N,N- 二甲基 -1-(5-((3- 硝基吡啶 -4- 基)氧基)吡啶 -2- 基)甲胺

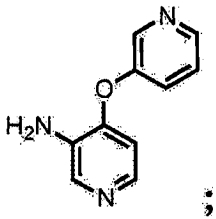
[1960] 向 6-((二甲基氨基)甲基)吡啶 -3- 醇在 DMF(5mL) 中的溶液中添加 K_2CO_3(834.8mg,6.040mmol) 并在 RT 搅拌混合物 10 分钟,然后添加 4- 氯 -3- 硝基 - 吡啶 (191.5mg,1.208mmol)。在 RT 搅拌混合物 60 小时。将反应混合物分配在 EtOAc 和 NH_4Cl 饱和水溶液之间。将合并的有机萃取物用盐水洗涤,干燥 ($MgSO_4$) 并真空浓缩,得到油状物,通过 SCX 柱纯化所述油状物,得到 N,N- 二甲基 -1-(5-((3- 硝基吡啶 -4- 基)氧基)吡啶 -2- 基)甲胺,为无色油状物。MS(ES+)275.1.

[1961] 步骤 3 :4-((6-((二甲基氨基)甲基)吡啶 -3- 基)氧基)吡啶 -3- 胺

[1962] 在 RT 在氢气 (气球) 下,将 N,N- 二甲基 -1-(5-((3- 硝基吡啶 -4- 基)氧基)吡啶 -2- 基)甲胺 (150mg,0.5469mmol)、Pd/C(10%)(58.20mg,0.5469mmol) 在 MeOH(15mL) 中搅拌过夜。过滤出催化剂并真空浓缩滤液,得到标题产物,为透明油状物。MS(ES+)245.2.

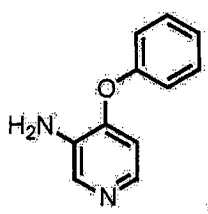
[1963] 使用制备例 0-2 的步骤 2 和步骤 3 合成了下面的氨基吡啶 :

[1964] 4-(吡啶 -3- 基氧基)吡啶 -3- 胺 :

[1965]  以及 ;

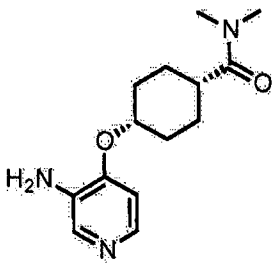
[1966] 4- 苯氧基吡啶 -3- 胺 :

[1967]



[1968] 制备例 0-3 :(1s,4s)-4-((3- 氨基吡啶 -4- 基)氧基)-N,N- 二甲基环己烷甲酰胺

[1969]



[1970] 步骤 1 :4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酸

[1971] 在 RT 搅拌甲基 4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酸酯 (250.0mg, 0.8920mmol)(根据制备例 0-1 的步骤 1 中所述方法类似的方法制备) 的 THF(2.748mL)、水 (2.748mL) 和 MeOH(1.5mL) 溶液并用氢氧化锂一水合物 (水 (1))(224.6mg,5.352mmol) 处理。在 RT 搅拌混合物过夜,然后减压浓缩以除去有机物。在冰浴中冷却水溶液,然后用 HCl(5.352mL,1M,5.352mmol) 酸化至 pH 4-5。然后添加乙酸乙酯并分离层。再用乙酸乙酯 (2x 5mL) 萃取含水层,将合并的有机层用 $MgSO_4$ 干燥并真空浓缩,得到 4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酸,为黄色油状物。未经进一步纯化,将其用于下一步骤。MS(ES+)267.0.

[1972] 步骤 2 :N,N- 二甲基 -4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酰胺

[1973] 将 TBTU(630.0mg,1.962mmol) 和二甲基胺 (1.784mL 的 2M,3.568mmol) 添加到 4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酸 (475mg,1.784mmol) 和 DIPEA(253.6mg, 341.8μL,1.962mmol) 在 THF(9.500mL) 中的溶液中并将得到的溶液在 RT 搅拌过夜。将反应混合物分配在 EtOAc 和水之间,将合并的有机萃取物用 $MgSO_4$ 干燥并真空浓缩。通过硅胶柱色谱法纯化残余物,用 0-100% EtOAc/ 石油醚洗脱,使用 ISCO 柱 companion 系统 (12g 柱)。将清洁的级分合并并真空浓缩,得到 N,N- 二甲基 -4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酰胺,为浅黄色油状物。(180mg,34%)。MS(ES+)294.3.

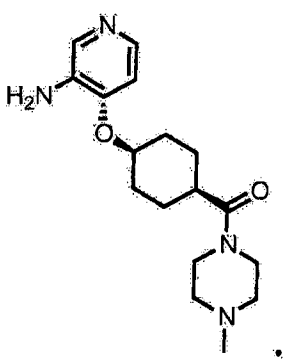
[1974] 步骤 3 :(1s,4s)-4-((3- 氨基吡啶 -4- 基) 氧基)-N,N- 二甲基环己烷甲酰胺

[1975] 将 C 上 Pd(10 %, 湿的, Degussa)(65.31mg,0.06137mmol) 加入 N,N- 二甲基 -4-[(3- 硝基 -4- 吡啶基) 氧基] 环己烷甲酰胺 (180mg,0.6137mmol) 在甲醇 (6.300mL) 中的溶液中,并在氢气氛围下搅拌反应混合物过夜。滤出催化剂并真空浓缩滤液,得到标题产物,为黄色油状物 (160mg,99%),MS(ES+)264.3.

[1976] 根据与制备例 0-3 中所述方法类似的方法,合成了下面的氨基吡啶 :

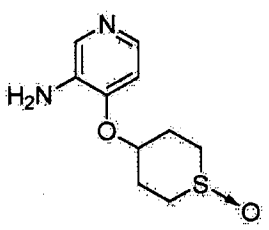
[1977] ((1s,4s)-4-((3- 氨基吡啶 -4- 基) 氧基) 环己基)(4- 甲基哌嗪 -1- 基) 甲酮 :

[1978]

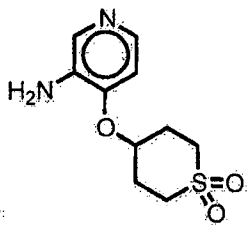


[1979] 制备例 0-4 :4-((3-氨基吡啶 -4- 基) 氧基) 四氢 -2H- 噻喃 1- 氧化物和 4-((3- 氨基吡啶 -4- 基) 氧基) 四氢 -2H- 噻喃 1,1- 二氧化物

[1980]



和



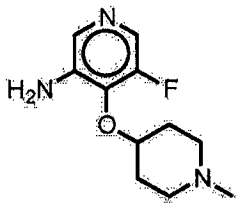
[1981] 在 RT,将一定量的 mCPBA(513.0mg,2.081mmol) 加入 3- 硝基 -4-((四氢 -2H- 噻喃 -4- 基) 氧基) 吡啶 (根据与制备例 0-1 中所述方法类似的方法制备)(400mg,1.665mmol) 在 DCM(10mL) 中的溶液。在 RT 搅拌混合物过夜,然后添加 5mL 的 $NaHCO_3$ 饱和水溶液和 5mL 的 $Na_2S_2O_3$ 饱和水溶液。在 RT 将混合物搅拌 30 分钟,分配在 DCM 和水之间。将合并的有机萃取物用盐水洗涤,干燥 ($MgSO_4$) 并真空浓缩得到油状物,将其溶于 MeOH(15mL)。添加 Pd/C 10% (177.2mg,1.665mmol) 并氢化混合物 (H^2 气球) 过夜。滤出催化剂并真空浓缩滤液,得到“亚砜和砜氨基吡啶”中间体的 1/1 混合物,未经进一步纯化,将其用于下一步骤中。

[1982] MS(ES+)227.1(亚砜) ;以及

[1983] MS(ES+)243.1(砜)。

[1984] 制备例 0-5 :5- 氟 -4-((1- 甲基哌啶 -4- 基) 氧基) 吡啶 -3- 胺

[1985]



[1986] 步骤 1 :2- 溴 -5- 氟 -4-((1- 甲基哌啶 -4- 基) 氧基)-3- 硝基吡啶

[1987] 在 0 ℃,将 NaH(86.67mg,2.167mmol) 分批加入 1- 甲基哌啶 -4- 醇 (192.0mg,1.667mmol) 在 THF(5.000mL) 中的溶液中,并将得到的溶液搅拌 15 分钟,然后添加 THF(5.000mL) 中的 2,4- 二溴 -5- 氟 -3- 硝基 - 吡啶 (500mg,1.667mmol),并在 RT 将反应混合物搅拌过夜。将反应混合物分配在水 (10mL) 和乙酸乙酯 (10mL) 之间。将合并的有机萃取物用 $MgSO_4$ 干燥并真空浓缩。通过硅胶柱色谱法纯化残余物,用乙酸乙酯 / 石油醚 (24g 柱,0-100% EtOAc) 洗脱,使用 ISCO 柱 companion 系统。将产物级分合并并真空浓缩,得到产物,为黄色油状物,放置使其固化 (125mg)。MS(ES+)334.0336.0.

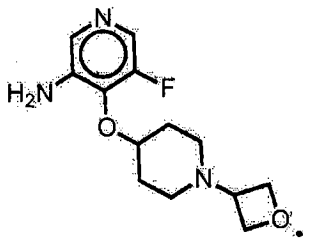
[1988] 步骤 2 :5- 氟 -4-((1- 甲基哌啶 -4- 基) 氧基) 吡啶 -3- 胺

[1989] 将 2- 溴 -5- 氟 -4-[(1- 甲基 -4- 哌啶基) 氧基]-3- 硝基 - 吡啶 (96mg,0.2873mmol)、$ZnBr_2$(12.94mg,3.080 μL,0.05746mmol) 和 C 上 Pd,湿的,Degussa(31mg) 在甲醇 (5mL) 中的溶液用氢气冲洗,抽真空 (3x),然后在氢气氛围下搅拌过夜。通过 C 盐垫滤出催化剂,用甲醇和乙酸乙酯混合物洗涤,并真空浓缩滤液,得到浅黄色油状物,未经进一步纯化,将其用于下一步骤中。MS(ES+)226.1。

[1990] 使用制备 0-5 的步骤 1 和步骤 2，制备了下面的氨基吡啶：

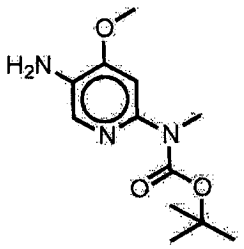
[1991] 5- 氟 -4-((1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 氧基) 吡啶 -3- 胺：

[1992]



[1993] 制备例 0-6：(5- 氨基 -4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸叔丁酯

[1994]



[1995] 步骤 1：叔丁基 (5- 碘 -4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸酯

[1996] 将氢化钠 (37.70mg，0.9425mmol) 加入叔丁基 N-(5- 碘 -4- 甲氧基 -2- 吡啶基) 氨基甲酸酯 (300mg，0.8568mmol) 在 DMF(3mL) 中的搅拌混合物中并在 0℃将反应搅拌 15 分钟。添加 MeI(145.9mg，63.99 μL，1.028mmol) 并在 1 小时期间让反应升温至环境温度。通过添加水淬灭混合物，用 EtOAc 稀释并分离层。将有机层用饱和 $NaHCO_3$ 水溶液 (x1)、盐水 (x 2) 洗涤，干燥 ($MgSO_4$)、过滤并真空浓缩。通过柱色谱法纯化残余物 (ISCO Companion，40g 柱，用 0 ～ 30% EtOAc/ 石油醚洗脱，载入 DCM)，得到叔丁基 (5- 碘 -4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸酯，为无色油状物 (269mg，86% 收率)。MS(ES+-t-Bu)309.4.

[1997] 步骤 2：叔丁基 (5-((二苯基亚甲基) 氨基)-4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸酯

[1998] 将 $Pd_2(dba)_3$(33.70mg，0.03680mmol) 和 Xantphos(42.58mg，0.07359mmol) 加入密封管，该密封管含有二噁烷 (2.5mL) 中的叔丁基 N-(5- 碘 -4- 甲氧基 -2- 吡啶基)-N- 甲基 - 氨基甲酸酯 (268mg，0.7359mmol)、二苯基甲亚胺 (173.4mg，160.6 μL，0.9567mmol) 和 Cs_2CO_3(719.4mg，2.208mmol)。将反应置于氮气氛围下并在 100℃加热 4 小时。在 RT，通过 C 盐过滤反应混合物并真空浓缩滤液。通过柱色谱法 (ISCOCompanion，40g 柱，用 0 ～ 30% EtOAc/ 石油醚洗脱，载入 DCM) 纯化残余物，得到叔丁基 (5-((二苯基亚甲基) 氨基)-4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸酯，为黄色固体 (213mg，69% 收率)。MS(ES+)418.2.

[1999] 步骤 3：叔丁基 (5- 氨基 -4- 甲氧基吡啶 -2- 基)(甲基) 氨基甲酸酯

[2000] 将 HCl(100 μL of 2M，0.2000mmol) 加入叔丁基 N-[5-(亚二苯甲基氨基)-4- 甲氧基 -2- 吡啶基]-N- 甲基 - 氨基甲酸酯 (212mg，0.5078mmol) 在 THF(2mL) 中的搅拌的溶液中并在环境温度搅拌反应 18 小时。过滤分离得到的沉淀并在环境温度再搅拌滤液 6 小时。用 1M HCl 稀释反应并用 Et_2O(x 3) 萃取。添加 $NaHCO_3$ 饱和水溶液使水层变成碱性并用 DCM(x 3) 萃取。干燥合并的有机萃取物 ($MgSO_4$)、过滤并真空浓缩，得到叔丁基 (5- 氨基 -4- 甲氧

基吡啶 -2- 基）（甲基）氨基甲酸酯，为红色油状物 (98.2mg，76％收率）。MS(ES+)254.1.

[2001] 使用与实施例 1 或实施例 3a 类似的方法合成了如下化合物：

[2002] (S)-2- 氨基 -6- 氟 -N-(4-((1- 甲基吡咯烷 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-1）；

[2003] (R,S)-2- 氨基 -6-（氰基甲基）-N-(4-（哌啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-2）；

[2004] 2- 氨基 -N-(4-((6-((二甲基氨基）甲基）吡啶 -3- 基）氧基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-3）；

[2005] 2- 氨基 -6- 氟 -N-(4- 甲氧基吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-4）；

[2006] (R)-2- 氨基 -6- 氟 -N-(4-（奎宁环 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-5）；

[2007] (R,S)-2- 氨基 -6- 氟 -N-(4-（奎宁环 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-6）；

[2008] 2- 氨基 -6- 氟 -N-(4-（吡啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-7）；

[2009] 4-((3-(2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰氨基）吡啶 -4- 基）氧基）环己烷甲酸（化合物 I-0-8）；

[2010] (S)-2- 氨基 -6- 氟 -N-(4-((1-（氧杂环丁烷 -3- 基）哌啶 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-9）；

[2011] (S)-2- 氨基 -6- 氟 -N-(4-（奎宁环 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-10）；

[2012] 2- 氨基 -6- 氟 -N-(4-((1-（氧杂环丁烷 -3- 基）哌啶 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-11）；

[2013] 2- 氨基 -6- 氟 -N-(4-((1- 甲基哌啶 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-12）；

[2014] (1r,4r)- 甲基 4-((3-(2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰氨基）吡啶 -4- 基）氧基）环己烷甲酸酯（化合物 I-0-13）；

[2015] 2- 氨基 -N-(4- 乙氧基吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-14）；

[2016] (R,S)-2- 氨基 -6- 氟 -N-(4-((四氢呋喃 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-15）；

[2017] (S)-2- 氨基 -N-(4-((6,7- 二氢 -5H- 吡咯并 [1,2-a] 咪唑 -6- 基）氧基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-16）；

[2018] 2- 氨基 -N-(4-(((1s,4s)-4-（二甲基氨基甲酰基）环己基）氧基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-17）；

[2019] (1s,4s)- 甲基 4-((3-(2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰氨基）吡啶 -4- 基）氧基）环己烷甲酸酯（化合物 I-0-18）；

[2020] 2- 氨基 -6- 氟 -N-(4-(((1s,4s)-4-(4- 甲基哌嗪 -1- 羰基）环己基）氧基）吡

啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-19) ;

[2021] 2- 氨基 -6-(1- 氰基丙基)-N-(4- 甲氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-20) ;

[2022] 2- 氨基 -6-(1- 氰基乙基)-N-(4- 甲氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-21) ;

[2023] (R,S)-2- 氨基 -6-(氰基甲基)-N-(4-(奎宁环 -3- 基氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-22) ;

[2024] 2- 氨基 -6-(氰基甲基)-N-(4-((1- 甲基哌啶 -4- 基) 氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-23) ;

[2025] 2- 氨基 -6-(氰基甲基)-N-(4-(2-(二甲基氨基) 乙氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-24) ;

[2026] 2- 氨基 -6-(氰基甲基)-N-(4- 苯氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-25) ;

[2027] 2- 氨基 -6-(氰基甲基)-N-(4- 甲氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-26) ;

[2028] 2- 氨基 -N-(6- 氯 -4- 甲氧基吡啶 -3- 基)-6-(氰基甲基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-27) ;

[2029] 2- 氨基 -6-(氰基甲基)-N-(4- 乙氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-28) ;

[2030] 2- 氨基 -6-(氰基甲基)-N-(4-(2- 甲氧基乙氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-29) ;

[2031] 2- 氨基 -6-(氰基甲基)-N-(4-((四氢 -2H- 吡喃 -4- 基) 氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-30) ;

[2032] (R)-2- 氨基 -6-(氰基甲基)-N-(4-((四氢呋喃 -3- 基) 氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-31) ;

[2033] 2- 氨基 -6-(氰基甲基)-N-(4-(环丙基甲氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-32) ;

[2034] 2- 氨基 -6-(氰基甲基)-N-(4-(2- 羟基乙氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-33) ;

[2035] 2- 氨基 -6-(氰基甲基)-N-(4-(2,2,2- 三氟乙氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-34) ;

[2036] 2- 氨基 -6-(氰基甲基)-N-(4- 异丙氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-35) ;

[2037] 2- 氨基 -6-(氰基甲基)-N-(4- 环丁氧基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-36) ;

[2038] (R,S)-2- 氨基 -6-(氰基甲基)-N-(4-((四氢呋喃 -3- 基) 氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-37) ;

[2039] 2- 氨基 -6-(氰基甲基)-N-(4-(氧杂环丁烷 -3- 基氧基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-0-38) ;

[2040] 2-氨基-6-(氰基甲基)-N-(4-(环己基氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-39);

[2041] 2-氨基-6-(氰基甲基)-N-(4-(3-羟基丙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-40);

[2042] 2-氨基-6-(氰基甲基)-N-(4-((四氢-2H-吡喃-3-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-41);

[2043] (S)-2-氨基-6-(氰基甲基)-N-(4-((四氢呋喃-3-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-42);

[2044] 2-氨基-6-(氰基甲基)-N-(4-(环戊基氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-43);

[2045] 2-氨基-6-氟-N-(4-((1-氧化四氢-2H-噻喃-4-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-44);

[2046] 2-氨基-N-(4-((1,1-二氧化四氢-2H-噻喃-4-基)氧基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-45);

[2047] 2-氨基-6-氯-N-(5-氯-4-((1-甲基哌啶-4-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-46);

[2048] 2-氨基-6-氯-N-(4-(2-(2-(二甲基氨基)乙氧基)乙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-47);

[2049] 2-氨基-6-氯-N-(4-(2-(二甲基氨基)乙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-48);

[2050] (R)-2-氨基-6-氯-N-(4-((1-甲基吡咯烷-2-基)甲氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-49);

[2051] (S)-2-氨基-6-氯-N-(4-((1-甲基吡咯烷-2-基)甲氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-50);

[2052] 2-氨基-6-氯-N-(4-((1-甲基哌啶-3-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-51);

[2053] 2-氨基-6-氯-N-(4-(3-(二甲基氨基)丙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-52);

[2054] 2-氨基-6-氯-N-(4-(3-羟基丙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-53);

[2055] (R)-2-氨基-6-氯-N-(4-((四氢呋喃-3-基)氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-54);

[2056] 2-氨基-6-氯-N-(4-(2-甲氧基乙氧基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-55);

[2057] 2-氨基-6-氯-N-(4-乙氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-56);

[2058] 2-氨基-6-氯-N-(4-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-0-57);

[2059] (S)-2-氨基-6-氯-N-(4-((四氢呋喃-3-基)氧基)吡啶-3-基)吡唑并[1,5-a]

嘧啶 -3- 甲酰胺（化合物 I-0-58）；

[2060] 2- 氨基 -6- 氯 -N-(4-(2,2,2- 三氟乙氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-59）；

[2061] 2- 氨基 -6- 氯 -N-(4-(2- 吗啉代乙氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-60）；

[2062] 2- 氨基 -6- 氯 -N-(4-((四氢 -2H- 吡喃 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-61）；

[2063] 2- 氨基 -6- 氯 -N-(4-(奎宁环 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-62）；

[2064] (R)-2- 氨基 -6- 氯 -N-(4-((1- 甲基吡咯烷 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-63）；

[2065] 2- 氨基 -6- 氯 -N-(4-((1- 甲基哌啶 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-64）；

[2066] 2- 氨基 -6- 氯 -N-(4-((四氢 -2H- 吡喃 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-65）；

[2067] 2- 氨基 -6- 氯 -N-(4-(2- 羟基乙氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-66）；

[2068] (S)-2- 氨基 -6- 氯 -N-(4-((1-(2- 甲氧基乙基）哌啶 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-67）；

[2069] 2- 氨基 -6- 氯 -N-(6- 氯 -4-(2-（二甲基氨基）乙氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-68）；

[2070] (S)-2- 氨基 -6- 氯 -N-(4-((1- 甲基吡咯烷 -3- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-69）；

[2071] 2- 氨基 -6- 氯 -N-(4-（吡啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-70）；

[2072] 2- 氨基 -6- 氯 -N-(4-(2-（二甲基氨基）乙氧基）-6-（三氟甲基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-71）；

[2073] 2- 氨基 -N-(4-（叔丁氧基）吡啶 -3- 基）-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-88）；

[2074] 2- 氨基 -6- 氟 -N-(5- 氟 -4-((1- 甲基哌啶 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-89）；

[2075] 2- 氨基 -6- 氟 -N-(5- 氟 -4-((1-（氧杂环丁烷 -3- 基）哌啶 -4- 基）氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-91）；以及

[2076] 2- 氨基 -6- 氟 -N-(4-（氧杂环丁烷 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-92）。

[2077] 使用与实施例 2 类似的方法制备了如下化合物：

[2078] N-(4-(2- 氮杂螺 [3.3] 庚 -6- 基氧基）吡啶 -3- 基）-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-72）；

[2079] 2- 氨基 -N-(4-（氮杂环丁烷 -3- 基氧基）吡啶 -3- 基）-6- 氯吡唑并 [1,5-a] 嘧

啶 -3- 甲酰胺（化合物 I-0-73）；

[2080] (S)-2- 氨基 -6- 氯 -N-(4-（哌啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-74）；

[2081] 2- 氨基 -6- 氯 -N-(4-（哌啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-75）；

[2082] (S)-2- 氨基 -6- 氯 -N-(4-（吡咯烷 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-76）；

[2083] (R)-2- 氨基 -6- 氯 -N-(4-（吡咯烷 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-77）；

[2084] N-(4-((4s,6r)-1- 氮杂螺 [3.3] 庚 -6- 基氧基）吡啶 -3- 基）-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-78）；

[2085] N-(4-((4r,6s)-1- 氮杂螺 [3.3] 庚 -6- 基氧基）吡啶 -3- 基）-2- 氨基 -6- 氯吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-79）；

[2086] 2- 氨基 -6- 氯 -N-(4-（哌啶 -4- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-80）；

[2087] (R)-2- 氨基 -6- 氯 -N-(4-（哌啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-81）；

[2088] 2- 氨基 -N-(4-（氮杂环丁烷 -3- 基氧基）吡啶 -3- 基）-6-（氰基甲基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-82）；

[2089] 2- 氨基 -N-(4-(2- 氨基乙氧基）吡啶 -3- 基）-6-（氰基甲基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-83）；

[2090] 2- 氨基 -6-（氰基甲基）-N-(4-（哌啶 -4- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-84）；

[2091] (S)-2- 氨基 -6- 氟 -N-(4-（哌啶 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-85）；

[2092] (S)-2- 氨基 -6-（氰基甲基）-N-(4-（吡咯烷 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-86）；

[2093] (R)-2- 氨基 -6-（氰基甲基）-N-(4-（吡咯烷 -3- 基氧基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-87）；以及

[2094] 2- 氨基 -6- 氟 -N-(4- 甲氧基 -6-（甲基氨基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-0-90）。

[2095] 化合物分析数据

[2096]

化合物编号	LCMS ES +	LCMS (Rt 分)	HNMR
I-O-1	372.2	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 10.4-10.6 (s, 1H), 10.05-10.15 (s, 1H), 9.64 (s, 1H), 9.54-9.56 (dd, 1H), 8.91 (s, 1H), 8.47-8.48 (d, 1H), 7.52 (s, 1H), 6.79 (s, 2H), 5.50-5.60 (m, 1H), 4.10-4.15 (s< 1H), 3.85-3.95 (s, 2H), 3.20-3.60 (m, 3H), 2.93 (s, 3H), 2.80-2.90 (s, 1H)。
I-O-2	393.1	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 2.0, 0.7 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.75 (s, 2H), 4.63 - 4.53 (m, 1H), 4.15 (d, J = 0.7 Hz, 2H), 3.20 - 3.11 (m, 1H), 2.85 - 2.75 (m, 2H), 2.69 - 2.61 (m, 1H), 2.17 - 2.05 (m, 1H), 1.86 - 1.70 (m, 2H), 1.59 - 1.44 (m, 1H)。
I-O-3	423.0	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.71 (s, 1H), 9.50 (dd, J = 4.7, 2.5 Hz, 1H), 8.77 (dd, J = 2.9, 0.6 Hz, 1H), 8.73 - 8.66 (m, 1H), 8.39 (d, J = 5.8 Hz, 1H), 7.91 (dd, J = 8.5, 2.9 Hz, 1H), 7.69 (dd, J = 8.6, 0.7 Hz, 1H), 7.22 (d, J = 5.8 Hz, 1H), 6.77 (s, 2H), 4.50 (s, 2H), 2.84 (s, 6H)。

[2097]

I-O-4	303.1	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 4.03 (2H, s), 6.71 (2H, s), 7.15-7.16 (1H, dd), 8.22-8.23 (1H, s), 8.87 (1H, d), 9.44 91H, s), 9.45-9.46 (1H, m), 9.96 (1H, s)。
I-O-5	398.0	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.83 - 8.79 (m, 1H), 8.50 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 6.82 (s, 2H), 5.30 (d, J = 4.2 Hz, 1H), 3.98 (ddd, J = 14.0, 8.3, 2.2 Hz, 1H), 3.50 - 3.24 (m, 5H), 2.68 - 2.63 (m, 1H), 2.28 (s, 1H), 2.10 - 2.01 (m, 1H), 1.95 (d, J = 7.2 Hz, 2H)。
I-O-6	398.2	0.64	----------
I-O-7	366.1	0.63	^{1}H NMR (500 MHz, DMSO-d6)δ 6.80-6.90 (2H, s), 7.23-7.24 (1H, d), 7.62-7.65 (1H, dd), 7.87-7.89 (1H, m), 8.43-8.44 (1H, d), 8.61-8.63 (1H, d), 8.72-8.76 (1H, m), 9.50 (1H, d), 8.78 (1H, (1H, s), 10.48 (1H, s)
I-O-8	415.3	0.43	^{1}H NMR (500 MHz, DMSO-d6) δ 12.20 (s, 1H), 10.34 (s, 1H), 9.62 (d, J = 0.9 Hz, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 6.3 Hz, 1H), 7.74 (d, J = 6.3 Hz, 1H), 6.76 (s, 2H), 6.51 (s, 1H), 4.90 (s, 1H), 2.22 (dd, J = 12.4, 4.0 Hz, 2H), 2.15 - 2.01 (m, 2H), 1.81 - 1.53 (m, 4H)。
I-O-9	428.3	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.68 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 8.82 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 6.5 Hz, 1H), 7.77 (d, J = 6.8 Hz, 1H), 6.80 (s, 2H), 5.16 (s, 1H), 4.68 - 4.65 (m, 5H), 4.57 (s, 1H), 4.15 (s, 1H), 3.30 (s, 1H), 2.96 (s, 1H), 2.20 (s, 2H), 1.92 (s, 2H)。

[2098]

I-O-10	398.0	0.61	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.54 (s, 1H), 9.48 (dd, J = 4.8, 2.5 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.07 (d, J = 5.5 Hz, 1H), 6.76 (s, 2H), 4.72 (dt, J = 7.3, 3.1 Hz, 1H), 3.38 (ddd, J = 14.3, 7.9, 2.1 Hz, 1H), 2.92 - 2.82 (m, 1H), 2.82 - 2.64 (m, 3H), 2.22 (q, J = 3.2 Hz, 1H), 2.01 (ddt, J = 13.0, 9.8, 4.0 Hz, 1H), 1.75 - 1.66 (m, 1H), 1.66 - 1.55 (m, 1H), 1.51 - 1.42 (m, 1H).
I-O-11	428.2	0.59	^{1}H NMR (500 MHz, DMSO-d6) δ 2.2-2.36 (4H, m), 3.25 掩蔽的信号, 4.39 (1H, m), 4.73-4.78 (4H, m), 5.18 (1H, m), 6.81 (2H, br s), 7.71 (1H, m), 8.55 (1H, m), 8.78 (1H, m), 9.56 (1H, m), 9.66 (1H, s) 和 10.18 (1H, br s) ppm
I-O-12	386.1	0.59	----------
I-O-13	429.2	0.78	^{1}H NMR (500 MHz, DMSO-d6) δ 1.40-1.76 (4H, m), 2.07 (2H, m), 2.21 (2H, m), 2.63 (1H, m), 3.65 (3H, s), 4.91 (1H, m), 6.76 (2H, br s), 7.73 (1H, m), 8.50 (1H, m), 8.92 (1H, s), 9.52 (1H, m), 9.62 (1H, m)和 10.34 (1H, s) ppm
I-O-14	317.1	0.60	----------
I-O-15	359.1	1.86*	----------
I-O-16	395.0	0.55	^{1}H NMR (500 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.67 (s, 1H), 9.57 - 9.43 (m, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.52 (dd, J = 6.1, 2.5 Hz, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.69 - 7.59 (m, 2H), 6.77 (s, 2H), 6.09 (d, J = 5.7 Hz, 1H), 4.82 (dd, J = 13.3, 5.3 Hz, 1H), 4.62 (dd, J = 13.4, 1.1 Hz, 1H), 3.94 (dd, J = 18.2, 6.2 Hz, 1H), 3.53 (d, J = 18.2 Hz, 1H).
I-O-17	442.2	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 1.67 (2H, m), 1.85-2.00 (4H, m), 2.12 (2H, m), 2.84 (4H, m), 3.09 (3H, s), 5.22 (1H, m), 6.80 (2H, br s), 7.75 (1H, m), 8.56 (1H, m), 9.11 (1H, m), 9.52 (1H, m), 9.69 (1H, s)和 10.09 (1H, s) ppm

[2099]

I-O-18	429.2	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 1.75-1.84 (4H, m), 1.91-2.03 (4H, m), 2.57 掩蔽的信号, 3.58 (3H, s), 4.92 (1H, s), 6.54 (1H, s), 6.78 (2H, br s), 7.26 (1H, m), 8.21 (1H, m), 8.68 (1H, m), 9.51 (2H, m)和 9.81 (1H, s) ppm
I-O-19	497.3	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 1.68 (2H, m), 1.85-1.98 (4H, m), 2.12 (2H, m), 2.84 (3H, s), 2.91 (1H, m), 4.42 掩蔽的信号, 5.24 (1H, m), 6.81 (2H, br s), 7.72 (1H, m), 8.57 (1H, m), 9.03 (1H, m), 9.53 (1H, m), 9.70 (1H, s)和 10.05 (1H, s) ppm
I-O-20	352.1	0.69	^{1}H NMR (500 MHz, 甲醇-d4) δ 1.2 (3H,t), 1.2-2.0 (2H,m), 3.8 (1H,t), 4.45 (3H,s), 7.7 (1H,d), 8.4-8.6 (3H,m), 8.7 (1H,s), 8.9 (1H,s), 9.7 (1H,s),
I-O-21	338.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.7 (3H,d), 4.3 (3H,s), 4.55 (1H,q), 6.68-6.8 (2H,m), 7.2 (0.5H,d), 7.5 (0.5H,d), 7.7 (1H,d), 8.15 (1H,d), 8.8 (1H,s), 9.2 (1H,s), 9.7 (1H,s), 10.5 (1H,s)。
I-O-22	419.0	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 10.07 (d, J = 2.7 Hz, 1H), 9.70 (s, 1H), 9.13 (dd, J = 1.6, 0.9 Hz, 1H), 8.61 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 6.81 (s, 2H), 5.33 (d, J = 5.4 Hz, 1H), 4.13 (s, 2H), 4.03 - 3.93 (m, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.39 (m, 3H), 3.31 - 3.22 (m, 1H), 2.65 (m, 1H), 2.44 (m, 1H), 2.14 - 1.90 (m, 3H)。
I-O-23	407.2	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 1.9, 0.8 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.22 (d, J = 5.6 Hz, 1H), 6.74 (s, 2H), 4.68 (dq, J = 8.5, 4.6, 4.2 Hz, 1H), 4.20 - 4.10 (m, 2H), 2.81 - 2.66 (m, 2H), 2.35 - 2.24 (m, 2H), 2.21 (s, 3H), 2.12 - 2.00 (m, 2H), 1.89 - 1.76 (m, 2H)。

[2100]

I-O-24	381.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.60 (s, 1H), 9.12 (d, J = 2.0 Hz, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 6.1 Hz, 1H), 7.58 (d, J = 5.7 Hz, 1H), 6.79 (s, 2H), 4.80 (d, J = 4.6 Hz, 2H), 4.14 (s, 2H), 3.77 - 3.70 (m, 2H), 2.94 (s, 6H)。
I-O-25	386.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.76 (d, J = 0.8 Hz, 1H), 9.08 (dd, J = 1.9, 0.8 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.42 (dd, J = 6.3, 0.8 Hz, 1H), 7.67 - 7.54 (m, 2H), 7.49 - 7.37 (m, 3H), 7.12 (d, J = 6.3 Hz, 1H), 6.79 (s, 2H), 4.07 (s, 2H)。
I-O-26	324.1	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.62 (s, 1H), 9.09 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 6.7 Hz, 1H), 7.67 (d, J = 6.5 Hz, 1H), 6.76 (s, 2H), 4.27 (s, 3H), 4.14 (s, 2H)。
I-O-27	358.0	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.27 (s, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 7.29 (s, 1H), 6.71 (s, 2H), 4.12 (s, 2H), 4.08 (s, 3H)。
I-O-28	338.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.63 (s, 1H), 9.11 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 6.4 Hz, 1H), 7.64 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.51 (q, J = 7.0 Hz, 2H), 4.14 (s, 2H), 1.63 (t, J = 7.0 Hz, 3H)。
I-O-29	368.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.10 (dt, J = 1.5, 0.7 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.57 (dd, J = 6.4, 1.0 Hz, 1H), 7.68 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 4.72 - 4.53 (m, 2H), 4.22 - 4.11 (m, 2H), 4.02 - 3.86 (m, 2H), 3.42 (s, 3H)。

[2101]

I-O-30	394.2	0.60	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.68 (d, J = 1.0 Hz, 1H), 9.11 (dt, J = 1.6, 0.7 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.58 (dd, J = 6.6, 1.1 Hz, 1H), 7.83 (d, J = 6.7 Hz, 1H), 6.78 (s, 2H), 5.23 (tt, J = 7.9, 3.9 Hz, 1H), 4.15 (s, 2H), 4.02 (ddd, J = 11.4, 5.9, 3.9 Hz, 2H), 3.66 (ddd, J = 11.5, 8.3, 3.1 Hz, 2H), 2.23 - 2.10 (m, 2H), 1.88 (dtd, J = 12.2, 8.1, 3.8 Hz, 2H)。
I-O-31	380.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.63 (d, J = 1.0 Hz, 1H), 9.08 (dt, J = 1.6, 0.8 Hz, 1H), 8.60 - 8.53 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.75 (s, 2H), 5.56 (ddd, J = 5.7, 3.7, 1.8 Hz, 1H), 4.16 (d, J = 0.8 Hz, 2H), 4.13 - 3.98 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.50 - 2.40 (m, 1H), 2.29 - 2.18 (m, 1H)。
I-O-32	364.1	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.65 (d, J = 1.0 Hz, 1H), 9.11 (dd, J = 1.9, 0.8 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.59 - 8.48 (m, 1H), 7.60 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.34 (d, J = 7.2 Hz, 2H), 4.14 (s, 2H), 1.50 (pt, J = 7.5, 4.7 Hz, 1H), 0.86 - 0.74 (m, 2H), 0.58 - 0.46 (m, 2H)。
I-O-33	354.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.10 (dd, J = 1.9, 0.8 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 6.4 Hz, 1H), 7.67 (d, J = 6.4 Hz, 1H), 6.76 (s, 2H), 5.07 (s, 1H), 4.50 (t, J = 4.8 Hz, 2H), 4.15 (s, 2H), 4.00 (t, J = 4.7 Hz, 2H)。
I-O-34	392.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.72 (d, J = 0.7 Hz, 1H), 9.09 (dt, J = 2.0, 0.7 Hz, 1H), 8.58 (dd, J = 6.2, 0.8 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 6.3 Hz, 1H), 6.77 (s, 2H), 5.27 (q, J = 8.4 Hz, 2H), 4.22 - 4.14 (m, 2H)。

[2102]

I-O-35	352.2	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.69 - 10.33 (m, 1H), 9.64 (d, J = 5.6 Hz, 1H), 9.23 - 9.02 (m, 1H), 8.80 - 8.64 (m, 1H), 8.55 (t, J = 6.5 Hz, 1H), 7.72 (t, J = 5.7 Hz, 1H), 6.76 (s, 2H), 5.19 (hept, J = 6.6 Hz, 1H), 4.29 - 4.03 (m, 2H), 1.67 - 1.44 (m, 6H)。
I-O-36	364.1	0.71	^{1}H NMR (500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.11 (dt, J = 1.6, 0.7 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 6.4, 1.0 Hz, 1H), 7.46 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 5.29 - 5.13 (m, 1H), 4.14 (s, 2H), 2.73 - 2.59 (m, 2H), 2.40 - 2.27 (m, 2H), 2.03 - 1.91 (m, 1H), 1.80 (dtt, J = 10.9, 9.8, 8.3 Hz, 1H)。
I-O-37	380.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.64 (d, J = 0.9 Hz, 1H), 9.10 (dd, J = 1.9, 0.8 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.58 - 8.52 (m, 1H), 7.66 (d, J = 6.4 Hz, 1H), 6.77 (s, 2H), 5.57 (ddd, J = 5.6, 3.5, 1.7 Hz, 1H), 4.16 (d, J = 0.9 Hz, 2H), 4.13 - 4.00 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.49 - 2.40 (m, 1H), 2.32 - 2.19 (m, 1H)。
I-O-38	366.0	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.67 (d, J = 0.8 Hz, 1H), 9.11 (dt, J = 1.9, 0.7 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 6.3, 0.9 Hz, 1H), 7.32 (d, J = 6.3 Hz, 1H), 6.77 (s, 2H), 5.75 (tt, J = 5.8, 4.4 Hz, 1H), 5.14 (ddd, J = 7.8, 5.9, 1.1 Hz, 2H), 4.80 (ddd, J = 7.8, 4.4, 1.0 Hz, 2H), 4.16 - 4.11 (m, 2H)。
I-O-39	392.2	0.79	^{1}H NMR (500 MHz, DMSO-d6) δ 10.36 (s, 1H), 9.67 (d, J = 1.0 Hz, 1H), 9.12 (dt, J = 2.0, 0.7 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.55 (dd, J = 6.6, 1.1 Hz, 1H), 7.77 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.03 (tt, J = 8.0, 3.6 Hz, 1H), 4.20 - 4.12 (m, 2H), 2.15 - 2.01 (m, 2H), 1.96 - 1.83 (m, 2H), 1.83 - 1.69 (m, 2H), 1.66 - 1.38 (m, 4H)。

[2103]

I-O-40	368.1	0.52	^{1}H NMR (500 MHz, DMSO-d6) δ 10.38 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.09 (dd, J = 1.9, 0.9 Hz, 1H), 8.69 - 8.47 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.77 (s, 2H), 4.52 (t, J = 5.8 Hz, 2H), 4.15 (d, J = 0.8 Hz, 2H), 3.81 (q, J = 7.0, 6.5 Hz, 2H), 2.14 (p, J = 6.0 Hz, 2H)。
I-O-41	394.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.69 (d, J = 1.0 Hz, 1H), 9.10 (dt, J = 1.6, 0.7 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.55 (dd, J = 6.5, 1.1 Hz, 1H), 7.76 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.03 (H, J = 3.7, 3.2 Hz, 1H), 4.16 (d, J = 0.7 Hz, 2H), 3.97 - 3.85 (m, 2H), 3.83 - 3.74 (m, 1H), 3.69 (ddd, J = 11.3, 8.1, 3.1 Hz, 1H), 2.16 (tt, J = 9.2, 4.7 Hz, 1H), 2.11 - 1.92 (m, 2H), 1.73 - 1.59 (m, 1H)。
I-O-42	380.1	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.63 (d, J = 0.9 Hz, 1H), 9.09 (dd, J = 2.0, 0.8 Hz, 1H), 8.59 - 8.55 (m, 2H), 7.68 (d, J = 6.5 Hz, 1H), 6.75 (s, 2H), 5.57 (ddd, J = 5.9, 3.8, 1.7 Hz, 1H), 4.16 (d, J = 0.9 Hz, 2H), 4.13 - 3.99 (m, 3H), 3.93 (td, J = 8.4, 4.3 Hz, 1H), 2.50 - 2.41 (m, 1H), 2.27 - 2.21 (m, 1H)。
I-O-43	378.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.64 (d, J = 1.0 Hz, 1H), 9.11 (dt, J = 1.9, 0.7 Hz, 1H), 8.63 - 8.49 (m, 2H), 7.68 (d, J = 6.6 Hz, 1H), 6.78 (s, 2H), 5.39 (dq, J = 5.8, 3.7, 2.9 Hz, 1H), 4.20 - 4.12 (m, 2H), 2.20 - 2.07 (m, 2H), 2.07 - 1.95 (m, 2H), 1.96 - 1.84 (m, 2H), 1.83 - 1.66 (m, 2H)。

[2104]

I-O-44	405.0	0.5	^{1}H NMR (500 MHz, DMSO-d6) δ 9.95 (s, 1H), 9.69 (d, J = 1.0 Hz, 1H), 9.54 (dd, J = 4.7, 2.5 Hz, 1H), 8.77 - 8.69 (m, 1H), 8.58 (dd, J = 6.5, 1.1 Hz, 1H), 7.77 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 5.34 - 5.26 (m, 1H), 3.10 (td, J = 13.7, 12.2, 3.0 Hz, 2H), 3.01 - 2.90 (m, 2H), 2.55 (m, 2H), 2.14 (dd, J = 15.1, 4.3 Hz, 2H)。
I-O-45	421.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.68 (d, J = 0.9 Hz, 1H), 9.55 (dd, J = 4.7, 2.5 Hz, 1H), 8.83 (dd, J = 2.5, 0.7 Hz, 1H), 8.58 (dd, J = 6.5, 1.0 Hz, 1H), 7.76 (d, J = 6.6 Hz, 1H), 6.82 (s, 2H), 5.34 - 5.27 (m, 1H), 3.50 (ddd, J = 14.4, 10.8, 3.7 Hz, 2H), 3.39 - 3.32 (m, 2H), 2.50 - 2.34 (m, 4H)。
I-O-46	436.1	0.8	^{1}H NMR (500MHz, 甲醇-d4) δ 2.10 (6H, m), 2.27 (3H, s), 2.90 (2H, m), 4.75 (1H, m), 8.28 (1H, s), 8.75 (1H, d), 9.02 (1H, m)和 9.61 (1H, s) ppm
I-O-47	420.1	0.65	^{1}H NMR (500 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.48 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.77 (s, 2H), 4.37 - 4.31 (m, 2H), 3.95 - 3.89 (m, 2H), 3.60 (t, J = 6.0 Hz, 2H), 2.36 (t, J = 6.0 Hz, 2H), 2.07 (s, 6H)。
I-O-48	376.1	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.48 (s, 1H), 9.42 (d, J = 2.3 Hz, 1H), 8.62 - 8.56 (m, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.19 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.30 (t, J = 5.6 Hz, 2H), 2.84 (t, J = 5.6 Hz, 2H), 2.26 (s, 6H)。
I-O-49	402.1	0.73	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72 (3H, m), 2.09 (1H, m), 2.28 (1H, m), 2.39 (3H, s), 2.79 (1H, m), 2.97 (1H, m), 4.00 (1H, m), 4.25 (1H, m), 6.79 (2H, br s), 7.18 (1H, m), 8.19 (1H, m), 8.54 (1H, m), 9.42 (1H, d), 9.47 (1H, s)和 9.81 (1H, s) ppm

[2105]

I-O-50	402.2	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 1.72 (3H, m), 2.11 (1H, m), 2.27 (1H, m), 2.39 (3H, s), 2.78 (1H, m), 2.97 (1H, m), 4.00 (1H, m), 4.25 (1H, m), 6.79 (2H, br s), 7.19 (1H, m), 8.20 (1H, m), 8.54 (1H, m), 9.42 (1H, m), 9.47 (1H, s)和 9.81 (1H, s) ppm
I-O-51	402.1	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 9.98 (s, 1H), 9.53 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 8.18 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.69 (s, 1H), 2.92 (s, 1H), 2.59 - 2.47 (m, 1H), 2.35 - 2.12 (m, 2H), 2.33 (s, 3H), 2.07 (d, J = 5.5 Hz, 1H), 1.91 (s, 1H), 1.73 - 1.51 (m, 2H)。
I-O-52	390.1	0.68	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.51 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 4.22 (t, J = 5.9 Hz, 2H), 2.16 (s, 6H), 2.06 (p, J = 6.6 Hz, 2H)。
I-O-53	365.1	0.59	^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.61 (s, 1H), 9.47 (d, J = 2.2 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.52 (d, J = 6.4 Hz, 1H), 7.60 (d, J = 6.4 Hz, 1H), 6.81 (s, 2H), 4.47 (t, J = 5.9 Hz, 2H), 3.77 (s, 2H), 2.12 (p, J = 6.2 Hz, 2H)。
I-O-54	375.0	0.66	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.29 (s, 1H), 9.61 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 6.5 Hz, 1H), 7.56 (d, J = 6.6 Hz, 1H), 5.47 (t, J = 4.9 Hz, 1H), 4.20 (dt, J = 11.0, 1.0 Hz, 1H), 4.08 - 4.00 (m, 2H), 3.93 (td, J = 8.5, 4.2 Hz, 1H), 2.47 - 2.36 (m, 1H), 2.27 - 2.18 (m, 1H)。

[2106]

I-O-55	363.0	0.67	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.44 (s, 1H), 9.70 (d, J = 1.2 Hz, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 6.7, 1.2 Hz, 1H), 7.59 (d, J = 6.7 Hz, 1H), 4.60 - 4.55 (m, 2H), 3.96 - 3.90 (m, 2H), 3.39 (s, 3H)。
I-O-56	333.0	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.49 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.19 (d, J =5.4 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.77 (s, 2H), 4.25 (q, J = 6.9 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H)。
I-O-57	319.1	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 4.28 (3H, s), 6.81 (2H, br s), 7.68 (1H, d), 8.60 (1H, d), 8.81 (1H, d), 9.47 (1H, d), 9.61 (1H, s)和 10.34 (1H, s) ppm
I-O-58	375.0	0.66	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.31 (s, 1H), 9.62 (s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.39 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 6.6 Hz, 1H), 7.57 (d, J = 6.6 Hz, 1H), 5.51 - 5.45 (m, 1H), 4.20 (d, J = 10.9 Hz, 1H), 4.08 - 4.00 (m, 2H), 3.93 (td, J = 8.5, 4.2 Hz, 1H), 2.47 - 2.36 (m, 1H), 2.29 - 2.18 (m, 1H)。
I-O-59	387.0	0.78	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.41 (s, 1H), 9.79 (d, J = 1.1 Hz, 1H), 8.94 (dd, J = 2.1, 0.4 Hz, 1H), 8.42 (dd, J = 6.6, 1.1 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.61 (d, J = 6.6 Hz, 1H), 5.10 - 5.01 (m, 2H)
I-O-60	418.1	0.63	^{1}H NMR (500 MHz, DMSO-d6) δ 9.91 (s, 1H), 9.47 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 4.35 (t, J = 5.9 Hz, 2H), 3.53 (t, J = 4.6 Hz, 4H), 2.90 (t, J = 5.8 Hz, 2H), 2.52 - 2.50 (掩蔽的信号, 4H)。

[2107]

I-O-61	389.0	0.68	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.28 (s, 1H), 9.75 (d, J = 1.2 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.35 (dd, J = 6.7, 1.3 Hz, 1H), 7.66 (d, J = 6.8 Hz, 1H), 5.15 (dt, J = 7.9, 4.0 Hz, 1H), 4.05 (ddd, J = 10.8, 6.1, 3.9 Hz, 2H), 3.66 (ddd, J = 11.6, 8.2, 3.3 Hz, 2H), 2.22 - 2.14 (m, 2H), 1.92 (ddt, J = 13.2, 8.5, 4.0 Hz, 2H)。
I-O-62	414.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.53 (s, 1H), 9.41 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.80 (s, 2H), 4.75 - 4.66 (m, 1H), 3.38 (d, J = 4.0 Hz, 0H), 2.92 - 2.82 (m, 1H), 2.82 - 2.64 (m, 4H), 2.21 (dd, J = 4.9, 1.8 Hz, 1H), 1.97 (ddd, J = 14.8, 11.1, 3.5 Hz, 1H), 1.76 - 1.66 (m, 1H), 1.66 - 1.55 (m, 1H), 1.48 - 1.39 (m, 1H)。
I-O-63	388.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.51 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.11 - 5.07 (m, 1H), 2.93 (dd, J = 10.7, 6.0 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.45 - 2.40 (m, 2H), 2.32 (s, 3H), 2.02 - 1.96 (m, 1H)。
I-O-64	402.0	0.66	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.52 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 6.79 (s, 2H), 4.66 (dq, J = 8.3, 4.1 Hz, 1H), 2.71 (q, J = 5.5 Hz, 2H), 2.26 (t, J = 10.3 Hz, 2H), 2.20 (s, 3H), 2.12 - 2.01(m, 2H), 1.82 (dtd, J = 12.6, 8.8, 3.6 Hz, 2H)。

[2108]

I-O-65	389.0	0.73	^{1}H NMR (500 MHz, 甲醇-d4) δ 10.47 (s, 1H), 9.74 (d, J = 1.2 Hz, 1H), 8.91 (d, J = 2.2 Hz, 1H), 8.47 (d, J = 2.2 Hz, 1H), 8.37 - 8.32 (m, 1H), 7.59 (dd, J = 6.8, 2.1 Hz, 1H), 4.95 - 4.88 (m, 1H), 4.00 (dd, J = 12.6, 3.8 Hz, 1H), 3.89 (dd, J = 12.5, 2.3 Hz, 1H), 3.82 (dt, J = 11.1, 4.0 Hz, 1H), 3.64 (ddd, J = 11.3, 9.4, 2.8 Hz, 1H), 2.10 (dt, J = 9.1, 4.3 Hz, 2H), 2.06 - 1.99 (m, 1H), 1.59 (dddd, J = 12.8, 7.6, 4.6, 2.7 Hz, 1H)。
I-O-66	349.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.50 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.76 (s, 2H), 4.92 (t, J = 5.1 Hz, 1H), 4.24 (t, J = 4.8 Hz, 2H), 3.94 (q, J = 4.9 Hz, 2H)。
I-O-67	446.2	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.53 (s, 1H), 9.43 (s, 1H), 8.56 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.22 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.71 - 4.56 (m, 1H), 3.44 (dd, J = 6.5, 4.8 Hz, 1H), 3.21 (s, 3H), 3.11 (dd, J = 12.8, 2.5 Hz, 1H), 2.76 - 2.46 (m, 4H), 2.37 (d, J = 5.6 Hz, 1H), 2.30 - 2.20 (m, 1H), 2.13 (d, J = 11.0 Hz, 1H), 1.86 (d, J = 8.5 Hz, 1H), 1.71 - 1.57 (m, 1H), 1.57 - 1.45 (m, 1H)。
I-O-68	410.0	0.76	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.71 (s, 1H), 9.46 (d, J = 2.2 Hz, 1H), 9.30 (s, 1H), 8.76 (d, J = 2.2 Hz, 1H), 7.40 (s, 1H), 6.81 (s, 1H), 4.74 - 4.61 (m, 2H), 3.69 (s, 2H), 2.92 (s, 6H)。

[2109]

I-O-69	388.0	0.69	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.51 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.11 - 5.07 (m, 1H), 2.93 (dd, J = 10.7, 6.0 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.45 - 2.40 (m, 2H), 2.32 (s, 3H), 2.02 - 1.96 (m, 1H)。
I-O-70	382.0	0.67	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.73 (s, 1H), 9.44 (d, J = 2.2 Hz, 1H), 8.71 (dd, J = 2.9, 0.6 Hz, 1H), 8.66 - 8.55 (m, 2H), 8.41 (d, J = 6.0 Hz, 1H), 7.84 (ddd, J = 8.4, 2.9, 1.3 Hz, 1H), 7.61 (ddd, J = 8.4, 4.8, 0.6 Hz, 1H), 7.20 (d, J = 6.0 Hz, 1H), 6.82 (s, 2H)。
I-O-71	444.1	0.84	^{1}H NMR (500 MHz, DMSO-d6) δ 10.01 (s, 1H), 9.70 (br s, 1H), 9.68 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H), 7.72 (s, 1H), 6.85 (s, 2H), 4.84 - 4.69 (m, 2H), 3.71 (s, 2H), 2.92 (s, 6H)。
I-O-72	400.0	0.54	^{1}H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.63 (s, 1H), 9.49 (dt, J = 2.8, 1.4 Hz, 1H), 8.77 (s, 2H), 8.72 (dd, J = 2.1, 0.7 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 7.38 (s, 1H), 6.83 (s, 2H), 5.06 (t, J = 6.3 Hz, 1H), 4.09 (d, J = 3.1 Hz, 4H), 2.99 (dd, J = 13.8, 6.7 Hz, 2H), 2.55 (d, J = 5.6 Hz, 2H)。
I-O-73	360.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.57 (s, 1H), 9.46 (d, J = 2.2 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.4 Hz, 1H), 6.99 (d, J = 5.5 Hz, 1H), 6.80 (s, 2H), 5.32 (tt, J = 6.5, 4.5 Hz, 1H), 4.64 - 4.56 (m, 2H), 4.22 - 4.15 (m, 2H)。

[2110]

I-O-74	388.2	0.62	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.56 (dd, J = 6.7, 1.2 Hz, 1H), 7.84 (d, J = 6.7 Hz, 1H), 5.37 (dt, J = 7.8, 4.0 Hz, 1H), 3.69 (d, J = 4.1 Hz, 2H), 3.44 - 3.36 (m, 2H), 2.49 (ddq, J = 13.6, 8.9, 4.5 Hz, 1H), 2.35 (ddt, J = 25.5, 11.3, 5.0 Hz, 2H), 2.22 - 2.06 (m, 1H)。
I-O-75	388.1	0.65	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.78 (d, J = 1.2 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.42 (dd, J = 6.7, 1.3 Hz, 1H), 7.69 (d, J = 6.7 Hz, 1H), 5.24 (td, J = 5.1, 2.7 Hz, 1H), 3.63 - 3.50 (m, 2H), 3.37 - 3.28 (m, 1H), 3.24 - 3.18 (m, 1H), 2.40 (dd, J = 9.5, 4.7 Hz, 1H), 2.29 - 2.14 (m, 2H), 2.01 (dd, J = 10.3, 4.2 Hz, 1H)。
I-O-76	374.2	0.56	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.57 (dd, J = 6.7, 1.2 Hz, 1H), 7.82 (d, J = 6.8 Hz, 1H), 5.79 (q, J = 4.4, 3.5 Hz, 1H), 3.91 (dd, J = 13.8, 4.7 Hz, 1H), 3.87 - 3.69 (m, 3H), 2.75 - 2.64 (m, 2H)。
I-O-77	374.0	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.01 (s, 1H), 9.51 (s, 1H), 9.43 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.78 (s, 2H), 5.17 - 5.10 (m, 1H), 3.30 - 3.18 (m, 2H), 3.12 - 2.99 (m, 2H), 2.90 (ddd, J = 10.8, 8.0, 4.4 Hz, 1H), 2.16 - 2.05 (m, 1H), 1.99 - 1.90 (m, 1H)。
I-O-78	400.0	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.50 (s, 1H), 9.42 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 5.4 Hz, 1H), 6.99 (d, J = 5.4 Hz, 1H), 6.77 (s, 2H), 4.64 (p, J = 6.9 Hz, 1H), 3.33 (m, 2H), 2.93 (ddd, J = 9.9, 6.7, 3.3 Hz, 2H), 2.32 (t, J = 7.1 Hz, 2H), 2.24 (ddd, J = 10.0, 7.2, 3.5 Hz, 2H)。

[2111]

I-O-79	400.0	0.6	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (s, 1H), 9.45 (dd, J = 2.2, 0.6 Hz, 1H), 9.02 (s, 2H), 8.71 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 5.4 Hz, 1H), 6.92 (d, J = 5.5 Hz, 1H), 6.80 (d, J = 3.6 Hz, 2H), 5.04 (tt, J = 6.7, 4.7 Hz, 1H), 3.83 (t, J = 8.2 Hz, 2H), 3.27 (dd, J = 14.7, 6.8 Hz, 2H), 2.66 - 2.56 (m, 4H)。
I-O-80	388.0	0.56	^{1}H NMR (500 MHz, DMSO-d6) δ 9.98 (s, 1H), 9.52 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 6.78 (s, 2H), 4.77 (tt, J = 7.9, 3.5 Hz, 1H), 3.11 - 3.03 (m, 2H), 2.65 (ddd, J = 12.4, 9.0, 3.1 Hz, 2H), 1.98 (ddt, J = 12.9, 6.5, 3.6 Hz, 2H), 1.65 (dtt, J = 12.4, 9.2, 3.4 Hz, 2H)。
I-O-81	388.2	0.62	^{1}H NMR (500 MHz, 甲醇-d4) δ 9.90 (d, J = 1.2 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.55 (dd, J = 6.7, 1.2 Hz, 1H), 7.83 (d, J = 6.7 Hz, 1H), 5.42 - 5.31 (m, 1H), 3.69 (d, J = 4.1 Hz, 2H), 3.48 - 3.35 (m, 2H), 2.49 (ddq, J = 13.5, 8.8, 4.5 Hz, 1H), 2.43 - 2.25 (m, 2H), 2.21 - 2.08 (m, 1H)。
I-O-82	365.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.66 (s, 1H), 9.33 (s, 1H), 9.20 - 9.01 (m, 2H), 8.76 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 7.31 (d, J = 5.9 Hz, 1H), 6.79 (s, 2H), 5.56 - 5.38 (m, 1H), 4.66 (p, J = 6.5, 6.1 Hz, 2H), 4.25 (dd, J = 13.6, 6.9 Hz, 2H), 4.14 (s, 2H)。
I-O-83	353.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.60 (s, 1H), 9.11 (dd, J = 1.9, 0.9 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 6.1 Hz, 1H), 8.15 (s, 3H), 7.59 (d, J = 6.1 Hz, 1H), 6.77 (s, 2H), 4.61 (t, J = 4.9 Hz, 2H), 4.12 (s, 2H), 3.49 (q, J = 5.2, 4.6 Hz, 2H)。

[2112]

I-O-84	393.1	0.52	^{1}H NMR (500 MHz, DMSO-d6) δ 10.09 (s, 1H), 9.55 (s, 1H), 9.06 (dt, J = 1.5, 0.7 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.74 (s, 2H), 4.77 (tt, J = 7.7, 3.5 Hz, 1H), 4.14 (s, 2H), 3.13 - 3.02 (m, 2H), 2.74 - 2.62 (m, 2H), 2.06 - 1.95 (m, 2H), 1.74 - 1.61 (m, 2H)。
I-O-85	372.2	0.60	----------
I-O-86	377.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 10.08 (s, 1H), 9.52 (s, 1H), 9.04 (dd, J = 2.0, 0.9 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 6.72 (s, 2H), 5.12 (ddt, J = 6.7, 4.6, 2.0 Hz, 1H), 4.14 (s, 2H), 3.20 (dd, J = 12.6, 5.1 Hz, 1H), 3.12 - 3.01 (m, 2H), 2.90 (ddd, J = 10.9, 8.1, 4.5 Hz, 1H), 2.12 (dtd, J = 14.0, 8.0, 6.2 Hz, 1H), 1.97 (dqd, J = 13.4, 4.3, 2.0 Hz, 1H)。
I-O-87	379.1	0.51	^{1}H NMR (500 MHz, DMSO-d6) δ 10.07 (s, 1H), 9.53 (s, 1H), 9.04 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 5.4 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 6.72 (s, 2H), 5.18 - 5.07 (m, 1H), 4.15 (s, 2H), 3.28 - 3.17 (m, 1H), 3.15 - 3.02 (m, 2H), 2.99 - 2.86 (m, 1H), 2.21 - 2.07 (m, 1H), 2.02 - 1.93 (m, 1H)。
I-O-88	345.0	1.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.74 (9H,s), 6.79 (2H, s), 7.82-7.83 (1H, d), 8.45-8.46 (1H, d), 8.74-8.75 (1H, d), 9.53-9.54 (1H, dd), 9.68-9.69 (1H, d), 10.29 (1H, s)。
I-O-89	404.1	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.99-2.15 (2H, m), 2.27-2.37 (2H, m), 2-76-2.79 (3H、m), 3.09-3.30 (2H, m), 3.46-3.57 (2H, m), 4.74 (1H, m), 6.78 (2H, br s), 8.36 (1H, d), 8.83-8.88 (1H, m), 9.45-9.54 (2H, m), 9.77 (1H, m)和 10.09 (1H, s) ppm 观察到旋转异构体

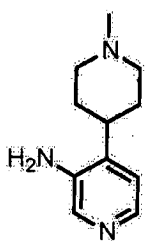
[2113]

I-O-90	332.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.47 (s, 1H), 9.91 (s, 1H), 9.50 (dd, J = 4.8, 2.6 Hz, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.74 (s, 1H), 6.69 (s, 2H), 6.50 (s, 1H), 4.12 (s, 3H), 2.94 (d, J = 4.7 Hz, 3H)。
I-O-91	446.1	2.06*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.85 (2H, m), 1.92-2.08 (4H, m), 2.67 (2H, m), 4.40 (2H, m), 4.49 (2H, m), 4.61 (1H, m), 6.77 (2H, br s), 8.30 (1H, m), 8.82 (1H, m), 9.47 (1H, s), 9.52 (1H, m)和 10.03 (1H, s) ppm 氧杂环丁烷 CH 未观察到
I-O-92	345.0	1.76*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.68 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 8.96 - 8.85 (m, 1H), 8.48 (s, 1H), 7.25 (s, 1H), 6.78 (s, 2H), 5.71 (tt, J = 5.9, 4.5 Hz, 1H), 5.10 (ddd, J = 7.8, 5.9, 1.1 Hz, 2H), 4.79 (ddd, J = 7.9, 4.5, 1.0 Hz, 2H)。

[2114] 将使用实验方法和材料部分中所述的 HPLC 方法 B 测定的保留时间指定为 (*)。对于所有其它化合物，使用 HPLC 方法 A 测定保留时间。

[2115] 制备例 C-1 :4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺

[2116]



[2117] 步骤 1 :4-(1- 甲基 -3,6- 二氢 -2H- 吡啶 -4- 基)-3- 硝基 - 吡啶

[2118] 向 4- 氯 -3- 硝基 - 吡啶 (350mg,2.208mmol) 在甲苯 (7.00mL)、乙醇 (1.75mL) 和碳酸钠溶液 (水溶液) (2.21mL 的 1M,2.21mmol) 中的溶液中加入 1- 甲基 -4-(4,4,5,5- 四甲基 -1,3,2- 二氧杂环戊硼烷 -2- 基)-3,6- 二氢 -2H- 吡啶 (985.3mg,4.416mmol)、$Pd_2(dba)_3$(60.66mg,0.07mmol) 和三苯膦 (115.8mg,102.3μL,0.44mmol)。将该混合物在 75℃ (回流) 搅拌 18 小时。将该反应混合物蒸发至干，使残余物分配在水 (30mL) 与 DCM(2x30mL) 之间。用水 (30mL) 和盐水 (30mL) 洗涤合并的有机层，干燥，蒸发至干，得到深棕色油状物，通过硅胶柱色谱法纯化深棕色油状物，用石油醚 (A) :乙酸乙酯 (B) (20-100% (B),24g,30.0 CV,35mL/min)、然后用乙酸乙酯 (A) :甲醇 (B) (0-10% (B)) 洗脱，得到 4-(1- 甲基 -3,6- 二氢 -2H- 吡啶 -4- 基)-3- 硝基 - 吡啶，为红色油状物 (305mg,63%)。MS(ES+) 220.1.

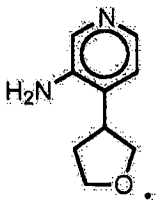
[2119] 步骤 2 :4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺

[2120] 向 4-(1- 甲基 -3,6- 二氢 -2H- 吡啶 -4- 基)-3- 硝基 - 吡啶 (300mg,1.37mmol) 在甲醇 (3.00mL) 中的溶液中加入批 Pd C,(10%,湿的,Degussa)(29.12mg,0.274mmol),将该混合物在环境温度在氢气气氛中搅拌 18 小时。过滤出催化剂,真空浓缩滤液,得到 4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺。MS(ES+)192.1.

[2121] 根据制备例 C-1 合成了如下氨基吡啶 :

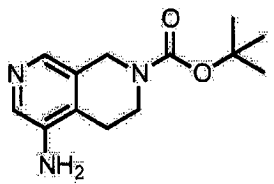
[2122] 4-(四氢呋喃 -3- 基) 吡啶 -3- 胺 :

[2123]



[2124] 制备例 C-2 :5- 氨基 -3,4- 二氢 -2,7- 萘啶 -2(1H)- 甲酸叔丁酯

[2125]



[2126] 步骤 1 :7- 叔丁氧基羰基 -6,8- 二氢 -5H-2,7- 萘啶 -4- 甲酸

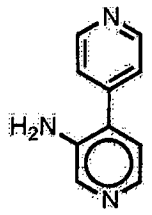
[2127] 向 5,6,7,8- 四氢 -2,7- 萘啶 -4- 甲酸 (盐酸 (2))(1g,3.982mmol) 在 $NaHCO_3$(1.673g,19.91mmol) 在水 (20.00mL) 和二噁烷 (20.00mL) 中的混合物中的溶液中加入 Boc_2O(869.1mg,914.8μL,3.982mmol),将该混合物在 RT 搅拌过夜。真空浓缩该反应混合物。将残余物溶于乙酸乙酯和水混合物,使用硫酸氢钠溶液将水相的 pH 调整至 pH4。分离有机层和水层,用盐水洗涤有机层,用 $MgSO_4$ 干燥,减压浓缩,得到 7- 叔丁氧基羰基 -6,8- 二氢 -5H-2,7- 萘啶 -4- 甲酸 (440mg,40%)。MS(ES+)279.2.

[2128] 步骤 2 :5- 氨基 -3,4- 二氢 -2,7- 萘啶 -2(1H)- 甲酸叔丁酯

[2129] 在室温在氮气气氛中向 7- 叔丁氧基羰基 -6,8- 二氢 -5H-2,7- 萘啶 -4- 甲酸 (440mg,1.581mmol) 在 NMP(6mL) 中的溶液中加入 TEA(207.9mg,286.4μL,2.055mmol),然后加入二苯基磷酰叠氮化物 (478.6mg,374.8μL,1.739mmol)。将该反应体系加热至 90℃ 2 小时。在 RT,使该反应混合物分配在饱和 $NaHCO_3$ 水溶液与 EtOAc 之间。用盐水洗涤合并的有机萃取物,用 $MgSO_4$ 干燥,减压浓缩。通过硅胶色谱法纯化残余物,用 1-15% MeOH : DCM 洗脱,得到 5- 氨基 -3,4- 二氢 -2,7- 萘啶 -2(1H)- 甲酸叔丁酯 (397mg,100.7%)。MS(2ES+)501.2.

[2130] 制备例 C-3 :[4,4'- 联吡啶]-3- 胺

[2131]



[2132] 将在二噁烷 (3mL) 中的 4- 氯 -3- 硝基 - 吡啶 (100mg,0.6307mmol)、4- 吡啶基硼酸 (77.52mg,0.6307mmol)、钯、三苯基正膦 (36.45mg,0.03154mmol)、K_3PO_4(946.0 μL 的 2M,1.892mmol) 在 130℃在微波中加热 30min。使该混合物上 SCX 柱,用 MeOH 洗涤。用 2M NH_3的 MeOH 溶液洗脱产物。真空浓缩滤液。将残余物溶于 MeOH(20mL),加入 Pd/C 10% (42.04mg,0.3950mmol),将该混合物氢化 (H_2气囊) 过夜。过滤出催化剂,真空浓缩滤液,得到 [4,4'- 联吡啶]-3- 胺,将其不肼进一步纯化用于下一步。MS(ES+)172.1.

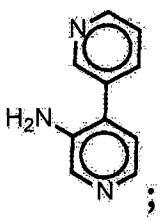
[2133] 制备例 C-4 :3'- 甲基 -[4,4'- 联吡啶]-3- 胺

[2134] 将在噁烷 (4.000mL) 中的 [3-(叔丁氧基羰基氨基)-4- 吡啶基] 硼酸 (100mg, 0.4201mmol)、钯、三苯基正膦 (48.55mg,0.04201mmol、4- 溴 -3- 甲基 - 吡啶 (113.9mg, 0.5461mmol)、K_3PO_4(630.0 μL of 2M,1.260mmol) 在 130℃在 MW 中加热 30min。使该反应混合物分配在水与 DCM 之间。干燥合并的有机萃取物,真空浓缩。将残余物溶于 DCM(10mL), 加入 TFA(2mL)。1H 后,真空浓缩该反应混合物。使残余物上 SCX 柱,用 MeOH 洗涤。用 2M NH_3的 MeOH 溶液洗脱产物,真空浓缩滤液,得到 3'- 甲基 -[4,4'- 联吡啶]-3- 胺,将其不经 (w/o) 进一步纯化用于下一步反应 (90mg)。MS(ES+)172.1.

[2135] 使用与制备例 C-3 或制备例 C-4 类似的方法制备了如下氨基吡啶 :

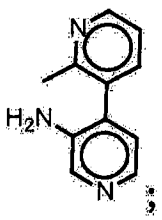
[2136] [3,4'- 联吡啶]-3'- 胺 :

[2137]



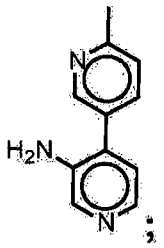
[2138] 2- 甲基 -[3,4'- 联吡啶]-3'- 胺 :

[2139]



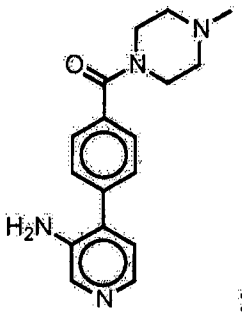
[2140] 6- 甲基 -[3,4'- 联吡啶]-3'- 胺 :

[2141]



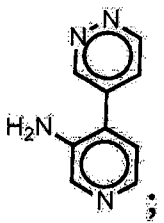
[2142] (4-(3-氨基吡啶-4-基)苯基)(4-甲基哌嗪-1-基)甲酮：

[2143]



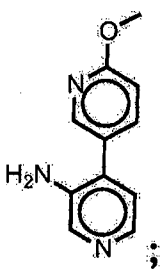
[2144] 4-(哒嗪-4-基)吡啶-3-胺：

[2145]



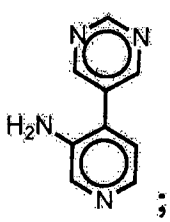
[2146] 6-甲氧基-[3,4'-联吡啶]-3'-胺：

[2147]



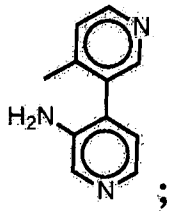
[2148] 4-(嘧啶-5-基)吡啶-3-胺：

[2149]



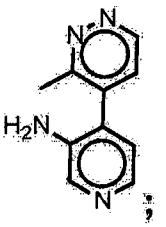
[2150] 4-甲基-[3,4'-联吡啶]-3'-胺：

[2151]



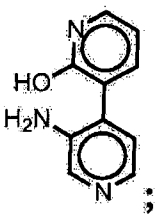
[2152] 4-(3- 甲基哒嗪 -4- 基) 吡啶 -3- 胺 :

[2153]



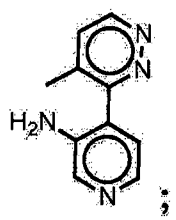
[2154] 3'- 氨基 -[3,4'- 联吡啶]-2- 醇 :

[2155]



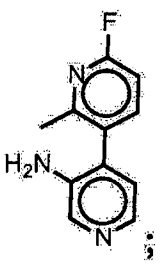
[2156] 4-(4- 甲基哒嗪 -3- 基) 吡啶 -3- 胺 :

[2157]



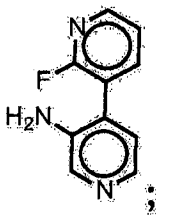
[2158] 6- 氟 -2- 甲基 -[3,4'- 联吡啶]-3'- 胺 :

[2159]



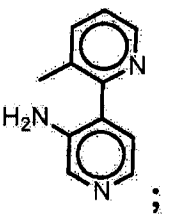
[2160] 2- 氟 -[3,4'- 联吡啶]-3'- 胺 :

[2161]



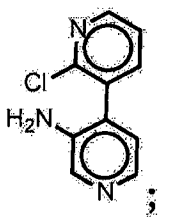
[2162] 3- 甲基 -[2,4'- 联吡啶]-3'- 胺：

[2163]



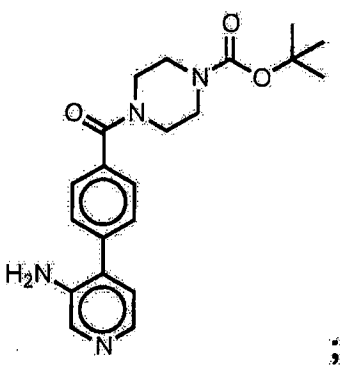
[2164] 2- 氯 -[3,4'- 联吡啶]-3'- 胺：

[2165]



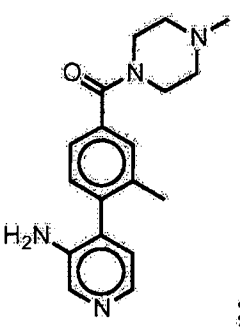
[2166] 4-(4-(3- 氨基吡啶 -4- 基) 苯甲酰基) 哌嗪 -1- 甲酸叔丁酯：

[2167]



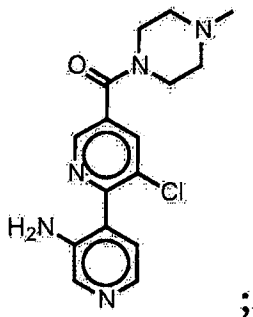
[2168] (4-(3- 氨基吡啶 -4- 基)-3- 甲基苯基)(4- 甲基哌嗪 -1- 基) 甲酮：

[2169]



[2170] (3'-氨基-3-氯-[2,4'-联吡啶]-5-基)(4-甲基哌嗪-1-基)甲酮:

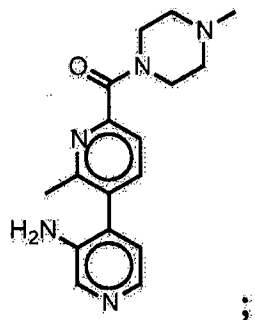
[2171]



;

[2172] (3'-氨基-2-甲基-[3,4'-联吡啶]-6-基)(4-甲基哌嗪-1-基)甲酮:

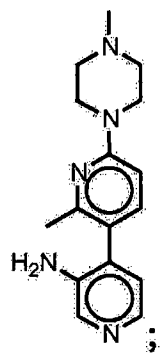
[2173]



;

[2174] 2-甲基-6-(4-甲基哌嗪-1-基)-[3,4'-联吡啶]-3'-胺:

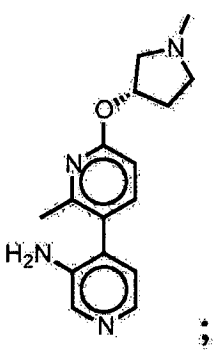
[2175]



;

[2176] (S)-2-甲基-6-((1-甲基吡咯烷-3-基)氧基)-[3,4'-联吡啶]-3'-胺:

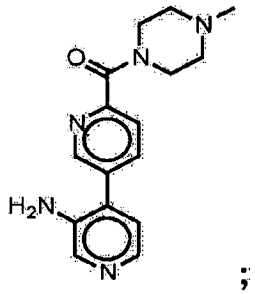
[2177]



;

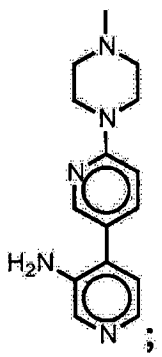
[2178] (3'-氨基-[3,4'-联吡啶]-6-基)(4-甲基哌嗪-1-基)甲酮：

[2179]



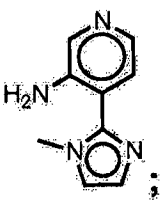
[2180] 6-(4-甲基哌嗪-1-基)-[3,4'-联吡啶]-3'-胺：

[2181]



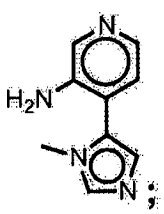
[2182] 4-(1-甲基-1H-咪唑-2-基)吡啶-3-胺：

[2183]



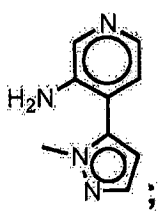
[2184] 4-(1-甲基-1H-咪唑-5-基)吡啶-3-胺：

[2185]



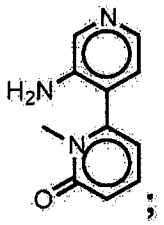
[2186] 4-(1-甲基-1H-吡唑-5-基)吡啶-3-胺：

[2187]



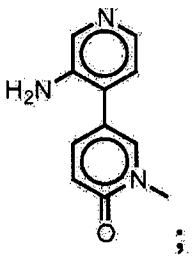
[2188] 3'-氨基-1-甲基-[2,4'-联吡啶]-6(1H)-酮：

[2189]



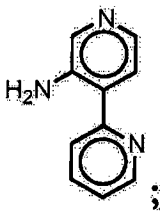
[2190] 3'-氨基-1-甲基-[3,4'-联吡啶]-6(1H)-酮：

[2191]



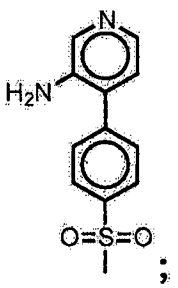
[2192] [2,4'-联吡啶]-3'-胺：

[2193]



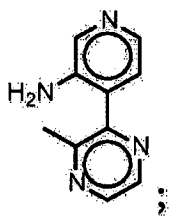
[2194] 4-(4-(甲基磺酰基)苯基)吡啶-3-胺：

[2195]



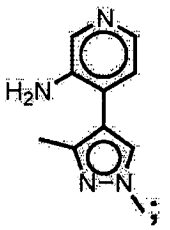
[2196] 4-(3-甲基吡嗪-2-基)吡啶-3-胺：

[2197]



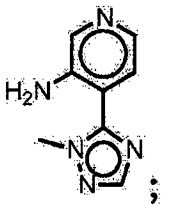
[2198] 4-(1,3-二甲基-1H-吡唑-4-基)吡啶-3-胺：

[2199]



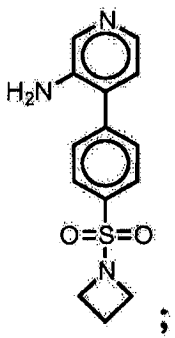
[2200] 4-(1-甲基-1H-1,2,4-三唑-5-基)吡啶-3-胺：

[2201]



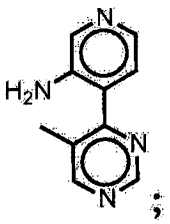
[2202] 4-(4-(氮杂环丁烷-1-基磺酰基)苯基)吡啶-3-胺：

[2203]



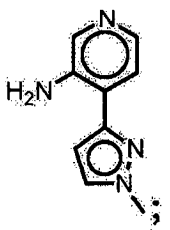
[2204] 4-(5-甲基嘧啶-4-基)吡啶-3-胺：

[2205]



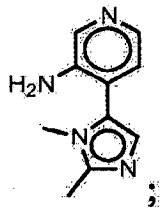
[2206] 4-(1-甲基-1H-吡唑-3-基)吡啶-3-胺：

[2207]



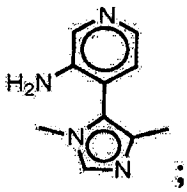
[2208] 4-(1,2-二甲基-1H-咪唑-5-基)吡啶-3-胺：

[2209]



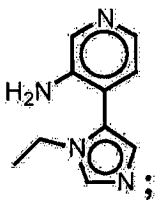
[2210] 4-(1,4-二甲基-1H-咪唑-5-基)吡啶-3-胺：

[2211]



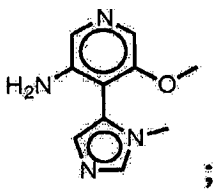
[2212] 4-(1-乙基-1H-咪唑-5-基)吡啶-3-胺：

[2213]



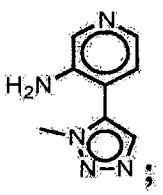
[2214] 5-甲氧基-4-(1-甲基-1H-咪唑-5-基)吡啶-3-胺：

[2215]



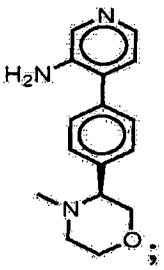
[2216] 4-(1-甲基-1H-1,2,3-三唑-5-基)吡啶-3-胺：

[2217]



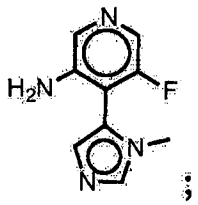
[2218] (S)-4-(4-(4-甲基吗啉-3-基)苯基)吡啶-3-胺：

[2219]



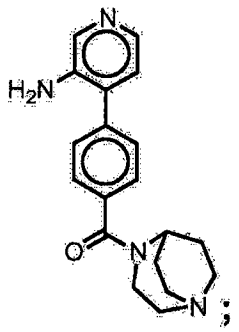
[2220] 5- 氟 -4-(1- 甲基 -1H- 咪唑 -5- 基) 吡啶 -3- 胺 :

[2221]



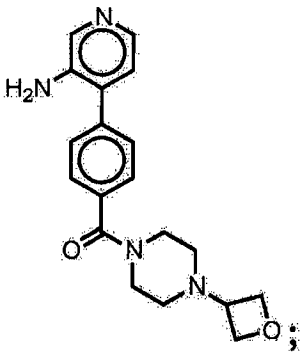
[2222] (4-(3- 氨基吡啶 -4- 基) 苯基)(1,4- 二氮杂双环 [3.2.2] 壬 -4- 基) 甲酮 :

[2223]



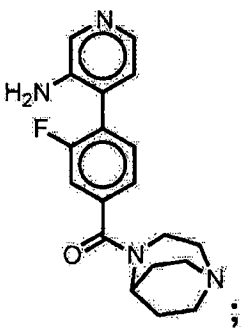
[2224] (4-(3- 氨基吡啶 -4- 基) 苯基)(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 甲酮 :

[2225]



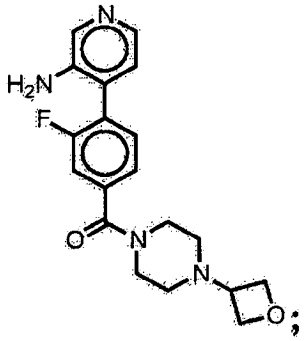
[2226] (4-(3- 氨基吡啶 -4- 基)-3- 氟苯基)(1,4- 二氮杂双环 [3.2.2] 壬 -4- 基) 甲酮 :

[2227]



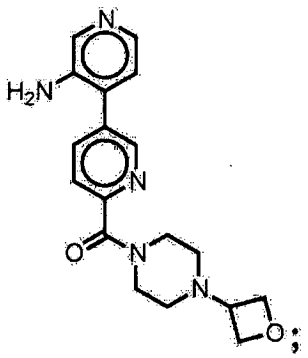
[2228] (4-(3- 氨基吡啶 -4- 基)-3- 氟苯基)(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 基) 甲酮 :

[2229]



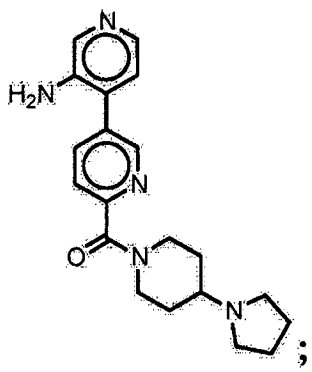
[2230] (3'-氨基-[3,4'-联吡啶]-6-基)(4-(氧杂环丁烷-3-基)哌嗪-1-基)甲酮:

[2231]



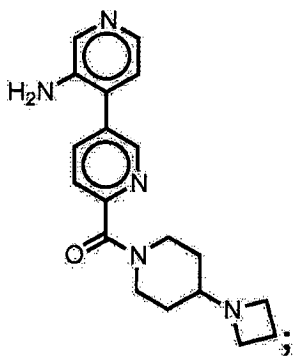
[2232] (3'-氨基-[3,4'-联吡啶]-6-基)(4-(吡咯烷-1-基)哌啶-1-基)甲酮:

[2233]



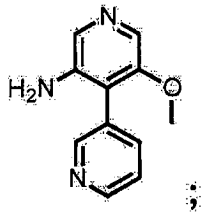
[2234] (3'-氨基-[3,4'-联吡啶]-6-基)(4-(氮杂环丁烷-1-基)哌啶-1-基)甲酮:

[2235]

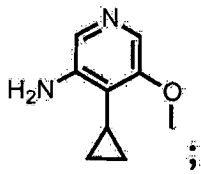


[2236] 5'-甲氧基-[3,4'-联吡啶]-3'-胺：

[2237]

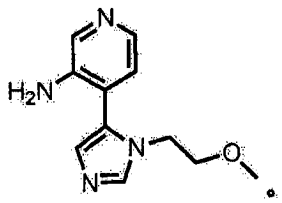


[2238] 4-环丙基-5-甲氧基吡啶-3-胺：

[2239]  以及

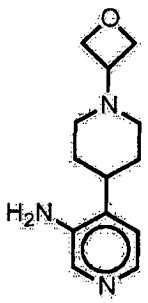
[2240] 4-(1-(2-甲氧基乙基)-1H-咪唑-5-基)吡啶-3-胺：

[2241]



[2242] 制备例C-5：4-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡啶-3-胺

[2243]



[2244] 步骤1：叔丁基3'-硝基-5,6-二氢-[4,4'-联吡啶]-1(2H)-甲酸酯

[2245] 使用3x真空/氮气循环，将DME(20.00mL)中的4-氯-3-硝基-吡啶(1g，6.307mmol)，叔丁基4-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊烷-2-基)-3,6-二氢-2H-吡啶-1-甲酸酯(2.145g,6.938mmol)和$PdCl_2(PPh_3)_2$(221.4mg,0.3154mmol)脱气。添加Na_2CO_3(9.460mL的2M,18.92mmol)，接着再脱气并在80℃将反应加热18小时。将反应冷却至环境温度并用EtOAc/水稀释。分离层并用EtOAc(x 3)萃取水层。将合并的有机萃取物用盐水(x1)洗涤、干燥($MgSO_4$)、过滤并真空浓缩。通过柱色谱法(ISCO Companion,120g柱，用0～70% EtOAc/石油醚洗脱，干的装载)纯化残余物，得到叔丁基3'-硝基-5,6-二氢-[4,4'-联吡啶]-1(2H)-甲酸酯，为淡黄色固体(884mg,46%收率)。MS(ES Na+)328.1.

[2246] 步骤2：3'-硝基-1,2,3,6-四氢-4,4'-联吡啶

[2247] 将TFA(2mL,25.96mmol)加入叔丁基4-(3-硝基-4-吡啶基)-3,6-二氢-2H-吡

啶 -1- 甲酸酯 (883mg,2.892mmol) 在 DCM(10mL) 中搅拌的溶液并在环境温度下将反应搅拌 15 小时。真空除去溶剂并将残余物与 DCM(x 2) 和乙醚 (x 2) 共沸。使残余物通过 25g SCX-2 筒并用 MeOH/DCM 混合物洗涤。洗脱产物通过用 2M NH_3在 MeOH/DCM 中的混合物洗涤所述筒并真空浓缩,得到 3'- 硝基 -1,2,3,6- 四氢 -4,4'- 联吡啶,为橙色油状物 (523mg,88%收率)。MS(ES+)206.1.

[2248] 步骤 3 :3'- 硝基 -1-(氧杂环丁烷 -3- 基)-1,2,3,6- 四氢 -4,4'- 联吡啶

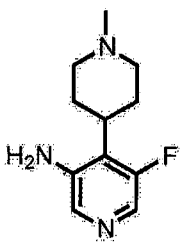
[2249] 在 0℃氮气氛围下,将三乙酰氧基硼氢化钠 (钠离子 (1))(1.189g,5.608mmol) 分批加入 3- 硝基 -4-(1,2,3,6- 四氢吡啶 -4- 基) 吡啶 (523mg,2.549mmol) 和 3- 氧杂环丁酮 (312.2mg,277.8 μL,4.333mmol) 在 THF(10mL) 中搅拌的溶液中。让反应升温至环境温度并搅拌 16 小时。逐滴加入 MeOH(2mL) 并在环境温度下将混合物搅拌 30 分钟。真空浓缩混合物并将残余物分配在水和 EtAOc 之间。通过添加 NH_4OH 将水层的 pH 调节至 pH 7-8 并分离层。用 EtOAc(x 3) 萃取水层并将合并的有机萃取物用水 (x 1) 洗涤、干燥 ($MgSO_4$)、过滤并真空浓缩,得到 3'- 硝基 -1-(氧杂环丁烷 -3- 基)-1,2,3,6- 四氢 -4,4'- 联吡啶,为红色油状物 (615mg,92%收率)。MS(ES+)262.1.

[2250] 步骤 4 :4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 胺

[2251] 将 C 上 Pd, 湿 的, Degussa(240mg,0.2255mmol) 加 入 3- 硝 基 -4-[1-(氧 杂 环 丁 烷 -3- 基)-3,6- 二 氢 -2H- 吡 啶 -4- 基] 吡 啶 (614mg,2.350mmol) 在 EtOAc(20mL)/EtOH(20mL) 中搅拌的溶液中。将反应置于氢气氛围下并在环境温度搅拌 15 小时。通过 C 盐垫过滤除去催化剂并真空浓缩滤液,得到 4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 胺,为淡黄色固体 (518mg,95%收率)。MS(ES+)234.2.

[2252] 制备例 C-6 :5- 氟 -4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺

[2253]



[2254] 步骤 1 :3'- 氯 -5'- 氟 -1- 甲基 -1,2,3,6- 四氢 -4,4'- 联吡啶

[2255] 使用 3x 真空 / 氮气循环将 DME(10.00mL) 中的 3- 氯 -5- 氟 -4- 碘 - 吡啶 (500mg,1.942mmol)、1- 甲基 -4-(4,4,5,5- 四甲基 -1,3,2- 二氧硼杂环戊烷 -2- 基)-3,6- 二氢 -2H- 吡啶 (476.6mg,2.136mmol) 和 $Pd(PPh_3)_2Cl_2$(68.15mg,0.09710mmol) 脱气。加入 Na_2CO_3(2.913mL 的 2M,5.826mmol),接着再脱气并在 80℃将反应加热 18 小时。将反应冷却至环境温度并用 EtOAc/ 水稀释。分离层并用 EtOAc(x 3) 萃取水层。将合并的有机萃取物用盐水 (x1) 洗涤、干燥 ($MgSO_4$)、过滤并真空浓缩。将残余物通过 10g SCX-2 筒并用 MeOH/DCM 混合物洗涤。通过用 MeOH/DCM 混合物中的 2M NH_3洗涤筒来洗脱产物并真空浓缩。通过柱色谱法 (ISCO Companion,40g 柱,用 0 ～ 10% MeOH/DCM+1% NH_4OH 洗脱,载入 DCM) 纯化残余物,得到 3'- 氯 -5'- 氟 -1- 甲基 -1,2,3,6- 四氢 -4,4'- 联吡啶,为红色固体 (378mg,86%收率)。MS(ES+)227.1.

[2256] 步骤 2 :叔丁基 (5- 氟 -1' - 甲基 -1', 2', 3', 6' - 四氢 -[4, 4' - 联吡啶]-3- 基) 氨基甲酸酯

[2257] 将 3- 氯 -5- 氟 -4-(1- 甲基 -3, 6- 二氢 -2H- 吡啶 -4- 基) 吡啶 (377mg, 1.663mmol)、叔丁基氨基甲酸酯 (974.1mg, 8.315mmol)、叔丁醇钠 (815.1mg, 8.481mmol)、BrettPhos 预催化剂 (66.25mg, 0.08315mmol) 和 BrettPhos (44.63mg, 0.08315mmol) 置于可密封管中并用真空 / 氮气循环 (x 5) 脱气。添加无水二噁烷 (10mL) 并将得到的混合物置于在 100℃预加热的模块中并在该温度下搅拌 16 小时。添加另外部分的 BrettPhos 预催化剂 (66.25mg, 0.08315mmol) 和 BrettPhos (44.63mg, 0.08315mmol) 并在 100℃将反应加热 8 小时。将反应混合物冷却至环境温度并用饱和的 NH_4Cl 淬灭。使混合物通过预润湿的 (EtOAc) 硅藻土筒 (2.5g)。用 EtOAc/ 饱和 NH_4Cl 洗涤所述筒并分离滤液的层。用 EtOAc (x 3) 萃取水层并将合并的有机萃取物用盐水 (x 1) 洗涤、干燥 ($MgSO_4$)、过滤并真空浓缩。通过柱色谱法 (ISCO Companion, 40g 柱, 用 0 ～ 10% MeOH/DCM 洗脱, 载入 DCM) 纯化残余物, 得到叔丁基 (5- 氟 -1' - 甲基 -1', 2', 3', 6' - 四氢 -[4, 4' - 联吡啶]-3- 基) 氨基甲酸酯。MS (ES+) 308.2.

[2258] 步骤 3 :5- 氟 -1' - 甲基 -1', 2', 3', 6' - 四氢 -[4, 4' - 联吡啶]-3- 胺

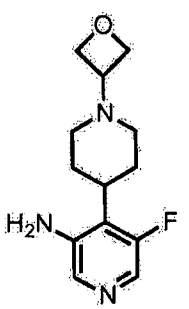
[2259] 将 TFA (2mL, 25.96mmol) 加入叔丁基 N-[5- 氟 -4-(1- 甲基 -3, 6- 二氢 -2H- 吡啶 -4- 基)-3- 吡啶基] 氨基甲酸酯 (483mg, 1.571mmol) 在 DCM (10mL) 中搅拌的溶液中并在环境温度下将反应搅拌 6 小时。真空除去溶剂并将残余物与 DCM (x 2) 和乙醚 (x 2) 共沸。将残余物通过 10g SCX-2 筒并用 MeOH/DCM 混合物洗涤。通过用 MeOH/DCM 混合物中的 2M NH_3 洗涤筒来洗脱产物并真空浓缩。通过柱色谱法 (ISCO Companion, 40g 柱, 用 0 ～ 10% MeOH/DCM+1% NH_4OH 洗脱, 载入 DCM) 纯化残余物, 得到 5- 氟 -1' - 甲基 -1', 2', 3', 6' - 四氢 -[4, 4' - 联吡啶]-3- 胺, 为灰白色固体 (61mg, 19% 收率, 2 步)。MS (ES+) 208.1.

[2260] 步骤 4 :5- 氟 -4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺

[2261] 将 C 上 Pd, 湿的, Degussa (25mg, 0.1175mmol) 加入 5- 氟 -4-(1- 甲基 -3, 6- 二氢 -2H- 吡啶 -4- 基) 吡啶 -3- 胺 (61mg, 0.2943mmol) 在 EtOAc (5mL)/EtOH (5mL) 中搅拌的溶液中。将反应置于氢气氛围下并在环境温度搅拌 15 小时。添加另外部分的 C 上 Pd, 湿的, Degussa (25mg, 0.1175mmol) 并将反应置于氢气氛围下并在环境温度搅拌 24 小时。通过 C 盐垫过滤除去催化剂并真空浓缩滤液, 得到 5- 氟 -4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 胺, 为灰白色固体 (58mg, 95% 收率)。MS (ES+) 210.1.

[2262] 制备 C-7 :5- 氟 -4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 胺

[2263]



[2264] 步骤 1 :叔丁基 3' - 氯 -5' - 氟 -5, 6- 二氢 -[4, 4' - 联吡啶]-1 (2H)- 甲酸酯

[2265] 使用 3x 真空 / 氮气循环，将 DME(15mL) 中的 3- 氯 -5- 氟 -4- 碘 - 吡啶 (750mg, 2.913mmol)、叔丁基 4-(4,4,5,5- 四甲基 -1,3,2- 二氧硼杂环戊烷 -2- 基)-3,6- 二氢 -2H- 吡啶 -1- 甲酸酯 (990.7mg,3.204mmol) 和 $Pd(PPh_3)_2Cl_2$(102.2mg,0.1456mmol) 脱气。Na_2CO_3(4.370mL 的 2M,8.739mmol) 加入，接着再脱气并在 90℃将反应加热 2 小时。将反应冷却至环境温度并用 EtOAc/ 水稀释。分离层并用 EtOAc(x 3) 萃取水层。将合并的有机萃取物用盐水 (x1) 洗涤、干燥 ($MgSO_4$)、过滤并真空浓缩。通过柱色谱法 (ISCO Companion,80g 柱，用 0 ～ 20％ EtOAc/ 石油醚洗脱，载入 DCM) 纯化残余物，得到叔丁基 3'- 氯 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 甲酸酯，为灰白色固体 (708mg,78％收率)。MS(ES+)313.1.

[2266] 步骤 2 :3'- 氯 -5'- 氟 -1,2,3,6- 四氢 -4,4'- 联吡啶

[2267] 将 TFA(2mL,25.96mmol) 加入叔丁基 4-(3- 氯 -5- 氟 -4- 吡啶基)-3,6- 二氢 -2H- 吡啶 -1- 甲酸酯 (708mg,2.264mmol) 在 DCM(10mL) 中搅拌的溶液中并在环境温度下将反应搅拌 2 小时。真空除去溶剂并将残余物于 DCM(x 2) 和乙醚 (x 2) 共沸。将残余物通过 10g SCX-2 筒并用 MeOH/DCM 混合物洗涤。通过用 MeOH/DCM 混合物中的 2M NH_3洗涤筒来洗脱产物并真空浓缩，得到 3'- 氯 -5'- 氟 -1,2,3,6- 四氢 -4,4'- 联吡啶，为灰白色固体 (468mg,97％收率)。MS(ES+)213.1.

[2268] 步骤 3 :3'- 氯 -5'- 氟 -1-(氧杂环丁烷 -3- 基)-1,2,3,6- 四氢 -4,4'- 联吡啶

[2269] 在 0℃氮气氛围下，将三乙酰氧基硼氢化钠 (钠离子 (1)) (1.026g,4.842mmol) 分批加入 3- 氯 -5- 氟 -4-(1,2,3,6- 四氢吡啶 -4- 基) 吡啶 (468mg,2.201mmol) 和 3- 氧杂环丁酮 (269.7mg,239.9μL,3.742mmol) 在 THF(10mL) 中搅拌的溶液中。用 16 小时让反应升温至环境温度。逐滴加入 MeOH(2mL) 中的混悬液中并在环境温度下将混合物搅拌 30 分钟。真空浓缩混合物并分配在水和 EtAOc 之间。通过添加 NH_4OH 将水层的 pH 调节至 p H 7-8 并分离层。用 EtOAc(x 3) 萃取水层并将合并的有机萃取物用盐水 (x 1) 洗涤、干燥 ($MgSO_4$)、过滤并真空浓缩，得到 3'- 氯 -5'- 氟 -1-(氧杂环丁烷 -3- 基)-1,2,3,6- 四氢 -4,4'- 联吡啶，为白色固体 (573mg,97％收率)。MS(ES+)269.1.

[2270] 步骤 4 :叔丁基 (5- 氟 -1'-(氧杂环丁烷 -3- 基)-1',2',3',6'- 四氢 -[4,4'- 联吡啶]-3- 基) 氨基甲酸酯

[2271] 将 3- 氯 -5- 氟 -4-[1-(氧杂环丁烷 -3- 基)-3,6- 二氢 -2H- 吡啶 -4- 基] 吡啶 (572mg,2.129mmol)、叔丁基氨基甲酸酯 (1.246g,10.64mmol)、叔丁醇钠 (1.044g, 10.86mmol)、BrettPhos 预催化剂 (84.78mg,0.1064mmol) 和 BrettPhos(57.11mg, 0.1064mmol) 置于可密封管中并通过真空 / 氮气循环 (x5) 脱气。添加无水二噁烷 (10mL) 并将得到的混合物置于在 100℃预加热的模块中并在该温度下搅拌 16 小时。将反应混合物冷却至环境温度并用饱和 NH_4Cl 淬灭。使混合物通过预润湿的 (EtOAc) 硅藻土筒 (2.5g)。用 EtOAc/ 饱和 NH_4Cl 洗涤所述筒并分离滤液的层。用 EtOAc(x 3) 萃取水层并将合并的有机萃取物干燥 (Na_2SO_4)、过滤并真空浓缩。通过柱色谱法 (ISCO Companion,80g 柱，用 0 ～ 100％ EtOAc/ 石油醚洗脱，载入 DCM) 纯化残余物，得到叔丁基 (5- 氟 -1'-(氧杂环丁烷 -3- 基)-1',2',3',6'- 四氢 -[4,4'- 联吡啶]-3- 基) 氨基甲酸酯，为淡黄色固体 (180mg,24％收率)。同时分离了 197mg 的 SM 和产物的混合物。MS(ES+)350.2.

[2272] 步骤 5 :叔丁基 (5- 氟 -4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 基) 氨

基甲酸酯

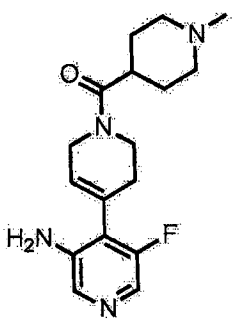
[2273] 将 C 上 Pd，湿的，Degussa(70mg，0.06578mmol) 加入叔丁基 N-[5- 氟 -4-[1-(氧杂环丁烷 -3- 基)-3,6- 二氢 -2H- 吡啶 -4- 基]-3- 吡啶基] 氨基甲酸酯 (180mg，0.5152mmol) 在 EtOH(5mL)/EtOAc(5mL) 中搅拌的溶液中。将反应置于氢气氛围下并在环境温度搅拌 46 小时。通过 C 盐垫过滤除去催化剂并真空浓缩滤液，得到叔丁基 (5- 氟 -4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 基) 氨基甲酸酯，为灰白色固体 (175mg，97％收率)。MS(ES+)352.2.

[2274] 步骤 6 :5- 氟 -4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 胺

[2275] 将 TFA(1mL，12.98mmol) 加入叔丁基 N-[5- 氟 -4-[1-(氧杂环丁烷 -3- 基)-4- 哌啶基]-3- 吡啶基] 氨基甲酸酯 (174mg，0.4951mmol) 在 DCM(5mL) 中搅拌的溶液中并在环境温度下将反应搅拌 4 小时。真空除去溶剂并将残余物于 DCM(x 2) 和乙醚 (x 2) 共沸。将残余物通过 5g SCX-2 筒并用 MeOH/DCM 混合物洗涤。通过用 MeOH/DCM 混合物中的 2M NH_3 洗涤筒来洗脱产物并真空浓缩，得到 5- 氟 -4-(1-(氧杂环丁烷 -3- 基) 哌啶 -4- 基) 吡啶 -3- 胺，为黄色油状物 (109mg，88％收率)。MS(ES+)252.1.

[2276] 制备例 C-8 :(3'- 氨基 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮

[2277]



[2278] 步骤 1 :(3'- 氯 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮

[2279] 向 3- 氯 -5- 氟 -4-(1,2,3,6- 四氢吡啶 -4- 基) 吡啶 (540mg，2.539mmol)(根据与制备例 C-7 的步骤 1 和步骤 2 中所述方法类似的方法制备) 在 NMP(5mL) 中的溶液中加入 TBTU(1.223g，3.809mmol)、1- 甲基哌啶 -4- 甲酸 (盐酸 (1))(547.4mg，3.047mmol) 和 DIPEA(656.3mg，884.5μL，5.078mmol) 并在环境温度搅拌反应 2 小时。将反应混合物吸附在预润湿的 (甲醇，20mL)SCX-2 筒 (10g) 上并用 DCM/ 甲醇 (1 :1，2x 20mL) 冲洗，然后用甲醇 (2x20mL) 中的 2M 氨洗脱碱性组分。将碱性洗脱液蒸发至干，得到浅橙色油状物 (744mg)。将残余物在 DCM(2mL) 中研磨并滤出白色固体。通过硅胶柱色谱法纯化滤液，用 DCM(A) :DCM/ 甲醇 /NH_4OH(90 :10 :1，(B))(0-100％ (B)，40g，20.0 CV，40mL/min) 洗脱，得到 (3'- 氯 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮，为浅橙色油状物 (410mg，48％)。MS(ES+)338.5.

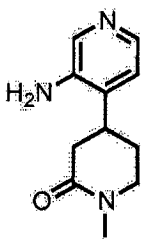
[2280] 步骤 2 :(3'- 氨基 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮

[2281] 在氮气氛围下，将 [4-(3- 氯 -5- 氟 -4- 吡啶基)-3,6- 二氢 -2H- 吡

啶 -1- 基]-(1- 甲 基 -4- 哌 啶 基) 甲 酮 (400mg,1.184mmol)、叔 丁 基 氨 基 甲 酸 酯 (693.5mg,5.920mmol)、BrettPhos(63.55mg,0.1184mmol)、BrettPhos 预催化剂 (94.34mg, 0.1184mmol) 和叔丁醇钠 (580.3mg,6.038mmol) 加入 Schlenk 管。通过真空 / 氮气循环 (x5) 将固体混合物脱气,然后添加无水甲苯 (8.000mL),将得到的混合物置于在 100℃预加热的模块中并搅拌 4 小时。将反应混合物冷却至环境温度,用饱和 NH_4Cl 溶液淬灭并分配在 DCM/MeOH(9 :1,2x50mL) 和水 (50mL) 之间。将合并的有机物用盐水 (50mL) 洗涤、干燥并真空浓缩,得到浅橙色油状物 (456mg)。通过硅胶柱色谱法纯化残余物,用 DCM(A) : DCM/MeOH/NH_4OH(90 :10 :1, (B)) (0-100% (B),40g,20.0 CV,40mL/min) 洗脱,得到 (3'- 氨基 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮 (200mg)。将其溶于 DCM(2.000mL),添加 TFA(1.0mL) 并在环境温度将混合物搅拌过夜。真空浓缩反应混合物,将残余装载至预润湿 (DCM/ 甲醇 (1 :1)10mL) 的 SCX-2 筒 (5g) 上,并用 DCM/ 甲醇 (1 : 1,25mL) 冲洗,然后用甲醇 (20mL) 中的 2M 氨洗脱碱性组分。将碱性洗脱液蒸发至干,得到浅黄色油状物 (325mg),通过硅胶柱色谱法纯化所述油状物,用 DCM(A) :DCM/ 甲醇 /NH_4OH(90 : 10 :1, (B)) (50-100% (B),24g,20.0 CV,35mL/min) 洗脱,得到 (3'- 氨基 -5'- 氟 -5,6- 二氢 -[4,4'- 联吡啶]-1(2H)- 基)(1- 甲基哌啶 -4- 基) 甲酮,为无色油状物 (55mg,12%)。MS(ES+)319.2.

[2282] 制备例 C-9 :4-(3- 氨基吡啶 -4- 基)-1- 甲基哌啶 -2- 酮

[2283]



[2284] 步骤 1 :(1'- 甲基 -2'- 氧代 -1',2'- 二氢 -[4,4'- 联吡啶]-3- 基) 氨基甲酸叔丁酯

[2285] 向 [3-(叔丁氧基羰基氨基)-4- 吡啶基] 硼酸 (200mg,0.8402mmol)、4- 溴 -1- 甲基 - 吡啶 -2- 酮 (158.0mg,0.8402mmol) 和 $Pd(PPh_3)_4$(48.55mg,0.04201mmol) 在二噁烷 (2mL) 中的混悬液中加入 Na_2CO_3(840.0 μL 的 2M,1.680mmol),在 80℃加热过夜。将该反应混合物冷却至环境温度,通过预湿的 (甲醇,5mL)C 盐柱 (2.5g) 过滤,用甲醇 (35mL) 洗涤。真空浓缩滤液,得到浅棕色油状物 (500mg)。使残余物分配在 DCM(2x30mL) 与饱和碳酸氢钠溶液 (30mL) 之间。干燥合并的有机层 (相分离柱),真空浓缩,得到橙色油状物 (280mg)。通过 ISCO Companion 柱色谱法纯化残余物,用 DCM(A) :DCM/ 甲醇 /NH_4OH(90 :10 :1, (B)) (0-100% (B),12g,16.0 CV,30mL/min),得到 (1'- 甲基 -2'- 氧代 -1',2'- 二氢 -[4,4'- 联吡啶]-3- 基) 氨基甲酸叔丁酯,为淡黄色油状物 (121mg,48%)。MS(ES+)302.1.

[2286] 步骤 2 :(4-(1- 甲基 -2- 氧代哌啶 -4- 基) 吡啶 -3- 基) 氨基甲酸叔丁酯

[2287] 在 50 C和 50 巴使 0.05M N-[4-(1- 甲基 -2- 氧代 -4- 吡啶基)-3- 吡啶基] 氨基甲酸叔丁酯 (120mg,0.3982mmol) 在乙醇 (8mL) 中溶液在 H- 立方体中以 0.5mL/min 的流速通过 Pd/C CatCart。将该过程重复 3 次以上。真空浓缩产物溶液,得到 (4-(1- 甲基 -2- 氧代

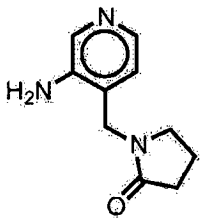
哌啶 -4- 基) 吡啶 -3- 基) 氨基甲酸叔丁酯，为无色油状物 (74mg，61％)。MS(ES+)306.1.

[2288] 步骤 3 :4-(3- 氨基吡啶 -4- 基)-1- 甲基哌啶 -2- 酮

[2289] 将 TFA(0.75mL，9.735mmol) 加入到 N-[4-(1- 甲基 -2- 氧代 -4- 哌啶基)-3- 吡啶基] 氨基甲酸叔丁酯 (74mg，0.2423mmol) 在 DCM(2mL) 中的溶液中，在环境温度搅拌 2 小时。使该反应混合物吸附在预润湿的 (甲醇 /DCM(1 :1)，2mL)SCX-2 柱 (2g) 上，用 DCM/ 甲醇 (1 :1，20mL) 冲洗，然后用 2M 氨的甲醇溶液 (20mL) 洗脱碱性组分。将碱性洗脱液蒸发至干，得到 4-(3- 氨基吡啶 -4- 基)-1- 甲基哌啶 -2- 酮，为淡黄色油状物 (50mg，97％)。MS(ES+)206.1.

[2290] 制备例 C-10 :1-((3- 氨基吡啶 -4- 基) 甲基) 吡咯烷 -2- 酮

[2291]



[2292] 步骤 1 :1-((3- 溴吡啶 -4- 基) 甲基) 吡咯烷 -2- 酮

[2293] 溶液 A :将氢化钠 (141.5mg，3.537mmol) 加入到吡咯烷 -2- 酮 (316.1mg，282.2μL，3.714mmol) 在 THF(5mL) 中的溶液中，将该溶液搅拌 30mins。

[2294] 溶液 B :在 0℃向 (3- 溴 -4- 吡啶基) 甲醇 (665mg，3.537mmol) 在 DCM(20mL) 中的溶液中加入三乙胺 (0.467mL，3.351mmol) 和甲磺酰氯 (0.287mL，3.708mmol)，将该溶液温至室温，搅拌 1h。

[2295] 将溶液 B 加入到溶液 A 中，将该混合物搅拌 2h。使该反应混合物分配在水与 EtOAc 之间。用盐水洗涤合并的有机萃取物，干燥 ($MgSO_4$)，真空浓缩 (在 RT)，得到油状物，通过硅胶色谱法纯化 (用 2-4％ MeOH 的 EtOAc 溶液洗脱)，得到 1-((3- 溴吡啶 -4- 基) 甲基) 吡咯烷 -2- 酮，为黄色油状物。MS(ES+)211.0.

[2296] 步骤 2 :1-((3- 氨基吡啶 -4- 基) 甲基) 吡咯烷 -2- 酮

[2297] 根据与制备例 N-14 步骤 3 类似的方法制备。MS(ES+)192.0.

[2298] 使用与实施例 1 或实施例 3a 类似的方法形成了如下酰胺类 :

[2299] 2- 氨基 -6- 氟 -N-(4-(1- 甲基哌啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-1) ;

[2300] 2- 氨基 -6- 氯 -N-(4- 甲基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-2) ;

[2301] 2- 氨基 -6-(氰基甲基)-N-(4- 甲基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-3) ;

[2302] 2- 氨基 -6- 氟 -N-(4- 甲基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-4) ;

[2303] 2- 氨基 -6- 氟 -N-(4- 苯基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-5) ;

[2304] 2- 氨基 -6-(氰基甲基)-N-(4- 苯基吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰

胺（化合物 I-C-6）；

[2305] 2-氨基-6-氟-N-(5,6,7,8-四氢-2,7-萘啶-4-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-7）；

[2306] 2-氨基-6-氟-N-(4-(1-(氧杂环丁烷-3-基）哌啶-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-10）；

[2307] 2-氨基-6-氯-N-(4-(1-(氧杂环丁烷-3-基）哌啶-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-11）；

[2308] 2-氨基-6-氟-N-(5-氟-1'-(氧杂环丁烷-3-基)-1',2',3',6'-四氢-[4,4'-联吡啶]-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-12）；

[2309] 2-氨基-6-氟-N-(5-氟-4-(1-(氧杂环丁烷-3-基）哌啶-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-13）；

[2310] 2-氨基-6-氟-N-(5-氟-4-(1-甲基哌啶-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-14）；

[2311] N-([3,4'-联吡啶]-3'-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-15）；

[2312] 2-氨基-6-氟-N-(6-(4-甲基哌嗪-1-羰基)-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-19）；

[2313] 2-氨基-6-氟-N-(2-甲基-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-20）

[2314] 2-氨基-6-氟-N-(6-(4-甲基哌嗪-1-基)-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-21）；

[2315] 2-氨基-6-氟-N-(6-甲基-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-22）；

[2316] 2-氨基-6-(2-氰基丙-2-基)-N-(4-(1-甲基哌啶-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-23）；

[2317] N-([4,4'-联吡啶]-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-24）；

[2318] 2-氨基-6-氟-N-(4-(4-(4-甲基哌嗪-1-羰基）苯基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-25）；

[2319] 2-氨基-6-氟-N-(4-(哒嗪-4-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-26）；

[2320] 2-氨基-6-氟-N-(6-甲氧基-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-27）；

[2321] 2-氨基-6-氟-N-(4-(嘧啶-5-基）吡啶-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-28）；

[2322] 2-氨基-6-氟-N-(3'-甲基-[4,4'-联吡啶]-3-基）吡唑并[1,5-a]嘧啶-3-甲酰胺 I-C-29）；

[2323] 2-氨基-6-氟-N-(4-甲基-[3,4'-联吡啶]-3'-基）吡唑并[1,5-a]嘧啶-3-甲酰胺（化合物 I-C-30）；

[2324] 2-氨基-6-氟-N-(4-(3-甲基哒嗪-4-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-31);

[2325] 2-氨基-6-氟-N-(2-羟基-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-32);

[2326] 2-氨基-6-氟-N-(4-(4-甲基哒嗪-3-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-33);

[2327] 2-氨基-6-氟-N-(6-氟-2-甲基-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-34);

[2328] 2-氨基-6-氟-N-(2-氟-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-35);

[2329] 2-氨基-6-氟-N-(3-甲基-[2,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-36);

[2330] 2-氨基-N-(2-氯-[3,4'-联吡啶]-3'-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-37);

[2331] 2-氨基-6-氟-N-(5-氟-1'-(1-甲基哌啶-4-羰基)-1',2',3',6'-四氢-[4,4'-联吡啶]-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-38);

[2332] 2-氨基-6-氟-N-(2-甲基-6-(4-甲基哌嗪-1-羰基)-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-39);

[2333] 2-氨基-6-氟-N-(2-甲基-6-(4-甲基哌嗪-1-基)-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-40);

[2334] (R)-2-氨基-6-氟-N-(2-甲基-6-((1-甲基吡咯烷-3-基)氧基)-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-41);

[2335] 2-氨基-N-(4-环丙基吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-42);

[2336] 2-氨基-6-氟-N-(5-氟-4-(4-(4-甲基哌嗪-1-羰基)苯基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-43);

[2337] 2-氨基-6-氟-N-(4-(4-(哌嗪-1-羰基)苯基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-44);

[2338] 2-氨基-6-氟-N-(4-(2-甲基-4-(4-甲基哌嗪-1-羰基)苯基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-45);

[2339] 2-氨基-N-(3-氯-5-(4-甲基哌嗪-1-羰基)-[2,4'-联吡啶]-3'-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-46);以及

[2340] 2-氨基-N-(4-(1-(环丙基磺酰基)哌啶-4-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-47);

[2341] N-(4-(4-(1,4-二氮杂双环[3.2.2]壬烷-4-羰基)苯基)吡啶-3-基)-2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-48);

[2342] 2-氨基-6-氟-N-(4-(4-(4-(氧杂环丁烷-3-基)哌嗪-1-羰基)苯基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-49);

[2343] N-(4-(4-(1,4-二氮杂双环[3.2.2]壬烷-4-羰基)-2-氟苯基)吡

啶 -3- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-50) ;

[2344] 2- 氨基 -6- 氟 -N-(4-(2- 氟 -4-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 羰基) 苯基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-51) ;

[2345] 2- 氨基 -6- 氟 -N-(6-(4-(氧杂环丁烷 -3- 基) 哌嗪 -1- 羰基)-[3,4'- 联吡啶]-3'- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-52) ;

[2346] 2- 氨基 -6- 氟 -N-(6-(4-(吡咯烷 -1- 基) 哌啶 -1- 羰基)-[3,4'- 联吡啶]-3'- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-53) ;

[2347] 2- 氨基 -N-(6-(4-(氮杂环丁烷 -1- 基) 哌啶 -1- 羰基)-[3,4'- 联吡啶]-3'- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-54) ;

[2348] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H- 咪唑 -2- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-55) ;

[2349] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H- 咪唑 -5- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-56) ;

[2350] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H- 吡唑 -5- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-57) ;

[2351] 2- 氨基 -6- 氟 -N-(1- 甲基 -6- 氧代 -1,6- 二氢 -[2,4'- 联吡啶]-3'- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-58) ;

[2352] 2- 氨基 -6- 氟 -N-(1- 甲基 -6- 氧代 -1,6- 二氢 -[3,4'- 联吡啶]-3'- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-59) ;

[2353] N-([2,4'- 联吡啶]-3'- 基)-2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-60) ;

[2354] 2- 氨基 -6- 氟 -N-(4-(4-(甲基磺酰基) 苯基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-61) ;

[2355] 2- 氨基 -6- 氟 -N-(4-(3- 甲基吡嗪 -2- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-62) ;

[2356] 2- 氨基 -N-(4-(1,3- 二甲基 -1H- 吡唑 -4- 基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-63) ;

[2357] 2- 氨基 -N-(4-(4-(氮杂环丁烷 -1- 基磺酰基) 苯基) 吡啶 -3- 基)-6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-64) ;

[2358] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H-1,2,4- 三唑 -5- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-65) ;

[2359] (S)-2- 氨基 -6- 氟 -N-(4-(4-(4- 甲基吗啉 -3- 基) 苯基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-66) ;

[2360] 2- 氨基 -6- 氟 -N-(4-(5- 甲基嘧啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-67) ;

[2361] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H- 吡唑 -3- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-68) ;

[2362] 2- 氨基 -6- 氟 -N-(4-(1- 甲基 -1H-1,2,3- 三唑 -5- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-72) ;

[2363] 2-氨基-6-氟-N-(4-(1-甲基-2-氧代哌啶-4-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-73);

[2364] 2-氨基-6-氟-N-(4-(四氢呋喃-3-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-75);

[2365] 2-氨基-6-氟-N-(4-((2-氧代吡咯烷-1-基)甲基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-76);

[2366] 2-氨基-N-(4-(1,2-二甲基-1H-咪唑-5-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-77);

[2367] 2-氨基-N-(4-(1,4-二甲基-1H-咪唑-5-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-78);

[2368] 2-氨基-6-氟-N-(5-氟-4-(1-甲基-1H-咪唑-5-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-79);

[2369] 2-氨基-N-(4-(1-乙基-1H-咪唑-5-基)吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-80);

[2370] 2-氨基-6-氟-N-(5-甲氧基-4-(1-甲基-1H-咪唑-5-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-81);

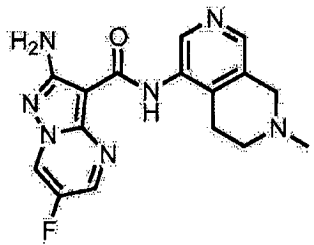
[2371] 2-氨基-6-氟-N-(5'-甲氧基-[3,4'-联吡啶]-3'-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-82);

[2372] 2-氨基-6-氟-N-(4-(1-(2-甲氧基乙基)-1H-咪唑-5-基)吡啶-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-83);以及

[2373] 2-氨基-N-(4-环丙基-5-甲氧基吡啶-3-基)-6-氟吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-84)。

[2374] 实施例15:2-氨基-6-氟-N-(7-甲基-5,6,7,8-四氢-2,7-萘啶-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(化合物I-C-8)

[2375]

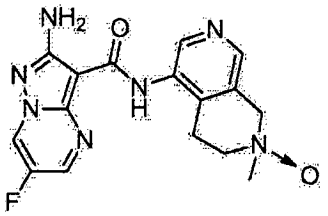


[2376] 将5-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-3,4-二氢-2,7-萘啶-2(1H)-甲酸叔丁酯溶于MeOH(8mL)。依次加入乙酸(91.88mg,87.01μL,1.530mmol)、甲醛(37%的水溶液,99.33mg,91.13μL,1.224mmol)和$NaBH(OAc)_3$(324.3mg,1.530mmol),将该混合物在RT搅拌1小时。使该反应混合物分配在饱和$NaHCO_3$溶液DCM与之间。过滤出不溶物,干燥合并的有机萃取物,真空浓缩。合并不溶物和残余物,通过fractionlynx纯化,得到2-氨基-6-氟-N-(7-甲基-5,6,7,8-四氢-2,7-萘啶-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。MS(ES+)342.2.

[2377] 实施例16:5-(2-氨基-6-氟吡唑并[1,5-a]嘧啶-3-甲酰氨基)-2-甲

基 -1,2,3,4- 四氢 -2,7- 萘啶 2- 氧化物 (化合物 I-C-9)

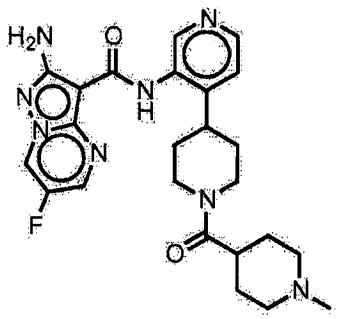
[2378]



[2379] 向在 DCM(2mL) 中的 2- 氨基 -6- 氟 -N-(7- 甲基 -5,6,7,8- 四氢 -2,7- 萘啶 -4- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (12mg,0.03516mmol) 中加入 mCPBA(5.764mg,0.03340mmol),将该混合物在 RT 搅拌 2h,然后真空除去溶剂。通过 FractionLynx 纯化残余物,得到 5-(2- 氨基 -6- 氟吡唑并 [1,5-a] 嘧啶 -3- 甲酰氨基)-2- 甲基 -1,2,3,4- 四氢 -2,7- 萘啶 2- 氧化物。MS(ES+)358.2.

[2380] 实施例 17 :2- 氨基 -6- 氟 -N-(4-(1-(1- 甲基哌啶 -4- 羰基) 哌啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (化合物 I-C-16)

[2381]



[2382] 步骤 1 :2- 氨基 -6- 氟 -N-(4-(哌啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺

[2383] 向 4-[3-[(2- 氨基 -6- 氟 - 吡唑并 [1,5-a] 嘧啶 -3- 羰基) 氨基]-4- 吡啶基] 哌啶 -1- 甲酸叔丁酯 (555mg,1.218mmol)(使用与实施例 2 类似的方法制备) 在 MeOH(2.135mL) 和 DCM(2.135mL) 中的溶液中加入 TFA(6.2g,4.2mL,54mmol),将得到的溶液在 rt 搅拌 96h。真空浓缩该反应混合物,溶于甲醇和 DCM,使器通过 25g SCX 柱,用甲醇 (3 个柱体积) 冲洗,然后用 2M 氨的甲醇溶液 (3 个柱体积) 冲洗,以洗脱产物。真空浓缩滤液,得到 2- 氨基 -6- 氟 -N-(4-(哌啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺,为黄色固体,将其不经进一步纯化直接用于下一步。MS(ES+)356.1.

[2384] 步骤 2 :2- 氨基 -6- 氟 -N-(4-(1-(1- 甲基哌啶 -4- 羰基) 哌啶 -4- 基) 吡啶 -3- 基) 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺

[2385] 将 TBTU(154.5mg,0.4812mmol) 和 DIPEA(82.92mg,111.8μL,0.6416mmol) 加入到 2- 氨基 -6- 氟 -N-[4-(4- 哌啶基)-3- 吡啶基] 吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (114mg,0.3208mmol) 和 1- 甲基哌啶 -4- 甲酸 (盐酸 (1))(69.16mg,0.3850mmol) 在 NMP(2.280mL) 中的溶液中,将得到的溶液在 RT 搅拌 2h。使其通过 SCX 柱,用 2M 氨的甲醇溶液冲洗期望的产物,真空浓缩滤液。通过 fractionlynx HPLC 纯化残余物,合并产物级,冷冻干燥,得到 2- 氨基 -6- 氟 -N-(4-(1-(1- 甲基哌啶 -4- 羰基) 哌啶 -4- 基) 吡啶 -3- 基) 吡唑并

[1,5-a] 嘧啶 -3- 甲酰胺，为黄色结晶固体。MS(ES+)481.3.

[2386] 使用与实施例 17 类似的方法形成了如下化合物：

[2387] 2- 氨基 -6- 氟 -N-(4-(1-(4- 甲基哌嗪 -1- 羰基）哌啶 -4- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-C-17）；以及

[2388] 2- 氨基 -6- 氟 -N-(4-(1-(奎宁环 -4- 羰基）哌啶 -4- 基）吡啶 -3- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-C-18）。

[2389] 实施例 18：2- 氨基 -6- 氟 -N-(1- 甲基 -1H- 吡咯并 [2,3-c] 吡啶 -4- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺（化合物 I-C-74）

[2390] 在 N_2 气氛中将 NaH(3.958mg,0.09894mmol) 加入到 2- 氨基 -6- 氟 -N-(1H- 吡咯并 [2,3-c] 吡啶 -4- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (28mg,0.08995mmol)（根据与实施例 1 或实施例 3a 类似的方法合成）和 MeI(11.49mg,5.039μL,0.08096mmol) 在 DMF(3mL) 中的混悬液中。将该混悬液在 RT 搅拌 5h，然后加入水 (2 滴）。通过 fractionlynx HPLC 纯化粗混合物。冻干澄清级分，得到 2- 氨基 -6- 氟 -N-(1- 甲基 -1H- 吡咯并 [2,3-c] 吡啶 -4- 基）吡唑并 [1,5-a] 嘧啶 -3- 甲酰胺 (5mg,16％）。MS(ES+)326.1.

[2391] 化合物分析数据

[2392]

化合物编号	LCMS ES+	LCMS (Rt分)	HNMR
I-C-1	370.2	0.57	^{1}H NMR (500 MHz, DMSO-d6) δ 9.55 (s, 1H), 9.49 (dd, J = 4.7, 2.5 Hz, 1H), 9.24 (s, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.29 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 5.1 Hz, 1H), 6.71 (s, 2H), 2.93 (dt, J = 12.0, 2.9 Hz, 2H), 2.81 (tq, J = 7.4, 3.8, 3.4 Hz, 1H), 2.23 (s, 3H), 2.04 (td, J = 11.7, 2.6 Hz, 2H), 1.82 - 1.66 (m, 4H)。
I-C-2	303.1	0.94	^{1}H NMR (500 MHz, DMSO-d6) δ 9.81 (s, 1H), 9.51 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H), 7.74 (d, J = 5.3 Hz, 1H), 6.80 (s, 2H), 2.57 (s, 3H)。
I-C-3	308.1	0.58	----------
I-C-4	287.1	0.62	^{1}H NMR (500 MHz, DMSO-d6) δ 9.89 (s, 1H), 9.57 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 8.91 (dd, J = 2.6, 0.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 7.91 - 7.73 (m, 1H), 6.77 (s, 2H), 2.61 (s, 3H)。
I-C-5	349.0	2.48*	^{1}H NMR (500 MHz, CDCl3) δ7.53-7.55 (2H, m), 7.67-7.73 (3H, m), 7.87 (1H, s), 8.45-8.46 (1H, d), 7.61-8.62 (1H, d), 9.96 91H, s), 10.28 (1H, s)。
I-C-6	370.0	0.74	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.64 (s, 1H), 8.97 - 8.93 (m, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.62 - 7.55 (m, 3H), 7.54 - 7.50 (m, 2H), 7.33 (dd, J = 4.8, 0.7 Hz, 1H), 6.68 (s, 2H), 4.06 (s, 2H)。
I-C-7	328.1	0.49	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 (s, 1H), 9.53 (dd, J = 4.8, 2.6 Hz, 1H), 9.24 (s, 1H), 9.16 (s, 2H), 8.85 (dd, J = 2.6, 0.5 Hz, 1H), 8.30 (s, 1H), 6.73 (s, 2H), 4.49 - 4.34 (m, 2H), 3.57 - 3.49 (m, 2H), 3.04 (t, J = 6.2 Hz, 2H)。

[2393]

I-C-8	342.2	0.58	^{1}H NMR (500 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.59 - 9.47 (m, 2H), 9.24 (s, 1H), 8.83 (dd, J = 2.6, 0.5 Hz, 1H), 8.26 (s, 1H), 6.73 (s, 2H), 4.74 - 4.58 (m, 1H), 4.45 - 4.32 (m, 1H), 3.91 - 3.71 (m, 1H), 3.51 - 3.37 (m, 1H), 3.24 - 3.12 (m, 1H), 3.12 - 3.03 (m, 1H), 3.00 (s, 3H)。
I-C-9	358.2	0.38	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 (s, 1H), 9.50 (dd, J = 4.8, 2.5 Hz, 1H), 9.24 (s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.10 (s, 1H), 6.75 - 6.67 (m, 3H), 4.77 (d, J = 14.9 Hz, 1H), 4.36 (d, J = 14.9 Hz, 1H), 3.73 (td, J = 11.5, 5.1 Hz, 1H), 3.61 - 3.49 (m, 1H), 3.25 - 3.15 (m, 1H), 3.02 - 2.90 (m, 1H)。隐藏在水峰下面的甲基单峰。
I-C-10	412.2	1.78*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.62 (s, 1H), 9.55 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 8.94 (d, J = 2.5 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.44 (d, J = 5.1 Hz, 1H), 6.75 (s, 2H), 4.89 - 4.71 (m, 4H), 4.51 (s, 1H), 3.59 (d, J = 11.8 Hz, 2H), 3.37 - 3.09 (m, 1H), 3.08 - 2.84 (m, 2H), 2.17 (d, J = 14.0 Hz, 2H), 1.97 (q, J = 13.2 Hz, 2H)。
I-C-11	428.1	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.37 (s, 1H), 9.53 (s, 1H), 9.48 (d, J = 2.2 Hz, 1H), 9.27 (s, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 6.1 Hz, 1H), 6.78 (s, 2H), 4.79 (p, J = 8.0 Hz, 4H), 4.51 (s, 1H), 3.59 (s, 2H), 3.27 - 3.15 (m, 1H), 2.98 (d, J = 15.4 Hz, 2H), 2.16 (d, J = 14.0 Hz, 2H), 1.95 (q, J = 10.6, 8.2 Hz, 2H)。
I-C-12	428.2	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.56 - 9.52 (m, 2H), 9.45 (s, 1H), 8.93 (d, J = 2.5 Hz, 1H), 8.39 (s, 1H), 6.78 (s, 1H), 6.16 (s, 2H), 4.79 (s, 4H), 4.40 - 3.35 (极宽 m, 7H)。

[2394]

I-C-13	430.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.51 (dd, J = 4.8, 2.5 Hz, 1H), 9.03 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 6.71 (s, 2H), 4.55 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.52 - 3.43 (m, 1H), 3.09 - 2.91 (m, 1H), 2.86 (d, J = 10.9 Hz, 2H), 2.11 (q, J = 13.0, 12.4 Hz, 2H), 1.85 (t, J = 11.5 Hz, 2H), 1.77 (d, J = 12.3 Hz, 2H)。
I-C-14	388.2	1.82*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 9.53 (dd, J = 4.7, 2.5 Hz, 1H), 9.41 (s, 1H), 8.91 (d, J = 2.6 Hz, 1H), 8.86 (s, 1H), 8.40 (d, J = 2.3 Hz, 1H), 6.71 (s, 2H), 3.56 (d, J = 13.0 Hz, 2H), 3.16 (t, J = 12.2 Hz, 1H), 3.03 (q, J = 12.0, 11.5 Hz, 2H), 2.82 (d, J = 4.6 Hz, 3H), 2.26 (q, J = 13.8, 12.8 Hz, 2H), 2.08 (d, J = 13.7 Hz, 2H)。
I-C-15	350.0	1.84*	^{1}H NMR (500 MHz, DMSO-d6) δ 6.8 (2H, br s), 7.68-7.69 (1H, d), 7.75-7.77 (1H, dd), 8.14-8.16 (1H, dd), 8.21-8.22 (1H, d), 8.56-8.57 (1H, dd), 8.82-8.83 (1H, d), 8.87-8.88 1H, d), 9.41-9.42 (1H, d), 9.67 (1H, s), 9.77 (1H, s)。
I-C-16	481.3	1.80*	^{1}H NMR (DMSO-d6, 500 MHz) δ 1.42-1.65 (6H, m), 1.91 (2H, m), 2.10 (1H, m), 2.29 (3H, br s), 2.64-2.71 (2H, m), 2.89 (2H, m), 3.12-3.21 (3H, m), 4.09 (1H, m), 4.63 (1H, m), 6.72 (2H, br s), 7.34 (1H, d, J = 5 Hz), 8.29 (1H, d, J = 5 Hz), 8.93 (1H, m), 9.28 (1H, s), 9.51 (1H, dd)和 9.62 (1H, s) ppm.
I-C-17	482.2	1.85*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.67-1.75 (2H, m), 1.87 (2H, m), 2.85 (3H, s), 3.01-3.22 (7H, m), 3.41 (2H, m), 3.69 (2H, m), 3.86 (2H, m), 6.77 (2H, br s), 7.65 (1H, d, J = 5 Hz), 8.47 (1H, d), 8.95 (1H, d), 9.49 (1H, s), 9.55 (1H, m), 9.83 (1H, s)和 9.95 (1H, br s) ppm.

[2395]

I-C-18	493.2	1.69*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.50-1.59 (2H, m), 1.73 (6H、m), 1.87 (2H, m), 2.76 (6H、m), 2.93 (2H, m), 3.15 (1H, m), 4.61 (2H, m), 6.72 (2H, br s), 7.34 (1H, d), 8.29 (1H, d), 8.93 (1H, d), 9.26 (1H, s), 9.50 (1H, dd)和 9.62 (1H, s) ppm.
I-C-19	476.0	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.70 (s, 1H), 9.53 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.75 (dd, J = 2.2, 0.9 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.36 - 8.32 (m, 1H), 8.22 (dd, J = 8.0, 2.2 Hz, 1H), 7.90 (dd, J = 8.0, 0.9 Hz, 1H), 7.48 (dd, J = 4.9, 0.7 Hz, 1H), 6.70 (m, 2H), 4.68 (m, 1H), 4.07 (m, 1H), 3.59 (m, 1H), 3.44 (m, 2H), 3.16 (m, 3H), 2.87 (s, 3H)。
I-C-20	364.0	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (s, 0H), 9.42 (dd, J = 4.8, 2.5 Hz, 0H), 9.35 (s, 0H), 8.86 (dd, J = 5.2, 1.6 Hz, 0H), 8.57 (d, J = 5.1 Hz, 0H), 8.07 (d, J = 2.5 Hz, 0H), 7.99 (d, J = 7.5 Hz, 0H), 7.68 (dd, J = 7.7, 5.2 Hz, 0H), 7.63 (d, J = 5.1 Hz, 0H), 2.35 (s, 1H)。
I-C-21	448.0	1.94*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.90 (s, 1H), 9.67 (s, 1H), 9.47 (dd, *J* = 4.8, 2.5 Hz, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 8.42 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.30 (d, *J* = 2.5 Hz, 1H), 7.94 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.69 (d, *J* = 5.4 Hz, 1H), 7.21 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.60 (s, 2H), 3.59 (s, 2H), 3.28 (s, 2H), 3.13 (s, 2H), 2.89 (s, 3H)。
I-C-22	364.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.68 (s, 1H), 9.44 (dd, J = 4.8, 2.5 Hz, 1H), 8.81 (dd, J = 2.4, 0.9 Hz, 1H), 8.58 (d, J = 5.2 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 8.21 (dd, J = 8.1, 2.3 Hz, 1H), 7.76 - 7.72 (m, 1H), 7.69 (dd, J = 5.2, 0.6 Hz, 1H), 2.72 (s, 3H)。

[2396]

I-C-23	419.1	2.01*	^{1}H NMR (500 MHz, DMSO-d6) δ 1.86 (6H, s), 1.90 - 2.00 (2H, br m), 2.07 (2H, d), 2.79 (3H,s), 3.0-3.1 (1H,m), 3.52 (2H,br s), 6.63 (2H,s), 7.32 (1H,s), 8.40 (1H,d), 8.81 (1H,d), 9.09 (2H,d), 9.51 (1H,s)。
I-C-24	350.0	1.80*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.62 (s, 1H), 9.58 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.91 - 8.86 (m, 2H), 8.54 (d, J = 5.1 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.77 - 7.72 (m, 2H), 7.59 (d, J = 5.0 Hz, 1H)。
I-C-25	475.0	1.99*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.80 (s, 1H), 9.66 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.75 - 7.69 (m, 2H), 7.68 - 7.63 (m, 2H), 7.56 (d, J = 5.0 Hz, 1H), 6.72 (s, 2H), 4.65 (s, 2H), 3.0 to 4.0 (m, 6H), 2.86 (s, 3H)。
I-C-26	351.0	1.47*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.49 (s, 1H), 9.49 (s, 1H), 9.48 (dd, J = 5.3, 1.3 Hz, 1H), 9.44 (dd, J = 2.4, 1.2 Hz, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 8.50 (d, J = 4.9 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 5.3, 2.4 Hz, 1H), 7.52 (dd, J = 5.0, 0.7 Hz, 1H), 6.66 (s, 1H)。
I-C-27	380.0	2.23*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (s, 1H), 9.69 (s, 1H), 9.45 (dd, J = 4.8, 2.5 Hz, 1H), 8.55 (d, J = 5.3 Hz, 1H), 8.41 (dd, J = 2.6, 0.8 Hz, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 8.6, 2.5 Hz, 1H), 7.69 (dd, J = 5.2, 0.6 Hz, 1H), 7.12 (dd, J = 8.6, 0.8 Hz, 1H), 3.99 (s, 3H)。
I-C-28	351.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.54 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 9.40 (s, 1H), 9.05 (s, 2H), 8.26 (d, J = 2.5 Hz, 1H), 7.53 (d, J = 4.7 Hz, 1H), 6.68 (s, 2H)。

[2397]

I-C-29	364.0	1.95*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.22 (s, 1H), 8.80 (s, 1H), 8.71 (d, J = 5.0 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.50 - 7.44 (m, 2H), 6.70 (bs, 1h), 2.12 (s, 3H)。
I-C-30	364.0	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.80 (d, J = 0.7 Hz, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.29 (s, 1H), 8.79 (d, J = 5.3 Hz, 1H), 8.59 (s, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.11 (d, J = 2.5 Hz, 1H), 7.75 - 7.68 (m, 1H), 7.54 (dd, J = 5.1, 0.7 Hz, 1H), 6.71 (s, 2H), 2.19 (d, J = 0.7 Hz, 3H)。
I-C-31	365.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (d, J = 0.6 Hz, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.38 (d, J = 5.0 Hz, 1H), 9.21 (s, 1H), 8.53 (d, J = 5.0 Hz, 1H), 2.45 (s, 3H)。
I-C-32	366.0	1.53*	^{1}H NMR (500 MHz, DMSO-d6) δ 12.15 (s, 1H), 9.61 (s, 1H), 9.52 (s, 1H), 9.43 (dd, J = 4.8, 2.6 Hz, 1H), 8.46 (s, 1H), 8.42 (d, J = 5.0 Hz, 1H), 7.78 - 7.60 (m, 2H), 7.45 (d, J = 5.1 Hz, 1H), 6.70 (s, 2H), 6.43 (t, J = 6.6 Hz, 1H)。
I-C-33	365.0	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.59 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 9.37 (d, J = 5.3 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.87 (dd, J = 5.1, 1.0 Hz, 1H), 7.71 - 7.62 (m, 1H), 2.21 (d, J = 0.8 Hz, 3H)。
I-C-34	382.0	2.24*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.44 (dd, J = 4.8, 2.5 Hz, 1H), 9.35 (s, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 7.98 (t, J = 8.2 Hz, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.33 - 7.26 (m, 1H), 2.23 (s, 3H)。

[2398]

I-C-35	368.0	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 9.47 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.55 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.19 (ddd, J = 9.6, 7.4, 2.0 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.65 (ddd, J = 7.1, 4.9, 1.9 Hz, 1H), 7.59 (d, J = 5.0 Hz, 1H)。
I-C-36	364.0	2.03*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 9.78 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.77 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.95 (ddd, J = 7.8, 1.6, 0.8 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.60 (dd, J = 7.8, 4.8 Hz, 1H), 2.22 (s, 3H)。
I-C-37	384.0	2.08*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.42 (dd, J = 4.8, 2.5 Hz, 1H), 9.34 (s, 1H), 8.74 (dd, J = 4.8, 1.9 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.07 - 8.00 (m, 2H), 7.72 (dd, J = 7.5, 4.8 Hz, 1H), 7.55 (d, J = 5.0 Hz, 1H)。
I-C-38	497.2	2.02*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.58 (s, 1H), 9.46 (s, 1H), 9.32 (dd, J = 4.7, 2.5 Hz, 1H), 8.61 (s, 1H), 8.31 (s, 1H), 6.08 (dt, J = 3.3, 1.9 Hz, 1H), 4.29 (q, J = 2.9 Hz, 2H), 3.82 (t, J = 5.6 Hz, 2H), 3.49 (s, 1H), 3.01 (s, 3H), 2.80 (s, 3H), 2.44 (d, J = 6.3 Hz, 3H), 1.90 (s, 4H)。
I-C-39	490.0	1.89*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.86 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 9.31 (s, 1H), 8.51 (s, 1H), 8.29 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 6.72 (s, 2H), 4.70 (s, 1H), 4.02 (s, 1H), 3.33 (d, J = 118.2 Hz, 5H), 2.87 (s, 3H), 2.28 (s, 3H)。

[2399]

I-C-40	462.0	2.33*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.47 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.27 (dd, J = 4.8, 0.7 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.70 (s, 2H), 3.63 (d, J = 33.6 Hz, 4H), 2.47 (s, 4H), 2.28 (s, 3H), 2.08 (s, 3H)。
I-C-41	463.0	2.35*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 9.32 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 4.8, 0.7 Hz, 1H), 6.85 (dd, J = 8.4, 0.8 Hz, 1H), 6.71 (s, 2H), 2.86 (dd, J = 10.5, 6.1 Hz, 1H), 2.73 (td, J = 8.2, 5.7 Hz, 1H), 2.69 - 2.62 (m, 1H), 2.41 (td, J = 7.9, 6.1 Hz, 1H), 2.37 - 2.31 (m, 0H), 2.29 (s, 3H), 2.15 (s, 3H), 1.93 - 1.83 (m, 1H)。
I-C-42	313.0	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.61 (s, 1H), 9.52 (dd, J = 4.7, 2.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.51 - 8.40 (m, 1H), 7.58 (d, J = 5.6 Hz, 1H), 6.77 (s, 2H), 2.18 (tt, J = 8.4, 5.2 Hz, 1H), 1.39 - 1.33 (m, 2H), 1.01 - 0.94 (m, 2H)。
I-C-43	493.0	2.22*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.39 (s, 1H), 9.22 (dd, J = 4.7, 2.5 Hz, 1H), 8.42 (s, 1H), 8.35 (dd, J = 2.5, 0.6 Hz, 1H), 7.69 - 7.54 (m, 4H), 6.49 (s, 2H), 3.66 (s, 4H), 2.74 (s, 4H), 2.48 (s, 3H)。
I-C-44	461.0	1.79*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.70 (s, 1H), 9.54 (s, 1H), 9.37 (dd, J = 4.8, 2.5 Hz, 1H), 8.41 - 8.38 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.57 - 7.53 (m, 2H), 7.37 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 3.62 (s, 2H), 2.73 (d, J = 55.4 Hz, 4H)。

[2400]

I-C-45	489.0	2.16*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, 1H), 9.34 (dd, J = 4.8, 2.5 Hz, 1H), 9.27 (s, 1H), 8.39 (s, 1H), 8.39 (d, J = 1.9 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.41 (dd, J = 7.7, 1.6 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.30 (dd, J = 4.7, 0.7 Hz, 1H), 6.68 (s, 2H), 3.73 (bs, 2H), 3.42 (bs, 2H), 2.45 - 2.30 (m, 4H), 2.08 (s, 3H)。
I-C-46	510.0	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.78 (d, J = 0.7 Hz, 1H), 9.61 (s, 1H), 9.41 (dd, J = 4.8, 2.5 Hz, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.53 (dd, J = 2.6, 0.6 Hz, 1H), 8.50 (d, J = 4.9 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 7.53 (dd, J = 5.0, 0.7 Hz, 1H), 6.71 (s, 2H), 2.86 (s, 3H)。
I-C-47	460.1	2.13*	^{1}H NMR (500 MHz, 甲醇-d4) δ 1.09-1.15 (4H, m), 1.99 (2H, m), 2.15-2.17 (2H, m), 2.64-2.69 (1H, m), 3.17-3.19 (2H, m), 3.31-3.34 (1H, 被掩蔽), 4.03-4.06 (2H, m), 7.94-7.95 (1H, d), 8.50-8.51 (1H, d), 8.78 (1H, dd), 9.13-9.14 (1H, dd), 9.74 (1H, s)。
I-C-48	501.0	2.01*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.77 (s, 1H), 9.61 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 (d, J = 4.9 Hz, 1H), 8.41 (s, 1H), 7.71 (d, J = 7.7 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 5.0 Hz, 1H), 6.72 (bs, 2H), 4.85 (s, 1H), 4.09 (s, 1H), 3.77 (t, J = 5.6 Hz, 1H), 3.58 (s, 1H), 3.45 (s, 2H), 3.33 (s, 1H), 2.20 (d, J = 69.6 Hz, 4H), 1.96 (s, 1H)。
I-C-49	517.0	1.93*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.69 (s, 1H), 9.53 (s, 1H), 9.38 (dd, J = 4.8, 2.5 Hz, 1H), 8.44 - 8.32 (m, 2H), 7.64 - 7.59 (m, 2H), 7.59 - 7.53 (m, 2H), 7.37 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 4.56 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.73 (s, 2H), 3.47 (t, J = 6.2 Hz, 1H), 3.40 (d, J = 5.8 Hz, 2H), 2.38 (d, J = 6.0 Hz, 2H), 2.27 (s, 2H)。

[2401]

I-C-50	519.0	2.08*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.42 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 – 8.38 (m, 2H), 7.63 – 7.54 (m, 2H), 7.45 (dd, J = 7.8, 1.5 Hz, 1H), 7.42 (dd, J = 4.8, 0.7 Hz, 1H), 6.70 (s, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 3.73 (s, 2H), 3.49 (m, 2H), 3.39 (m, 2H), 2.46 – 2.35 (m, 3H), 2.29 (m, 2H)。
I-C-51	535.0	2.00*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.42 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.46 - 8.39 (m, 2H), 7.62 - 7.55 (m, 2H), 7.48 - 7.40 (m, 2H), 6.70 (s, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.73 (s, 2H), 3.49 (s, 1H), 3.39 (s, 2H), 2.40 (s, 2H), 2.29 (s, 2H)。
I-C-52	518.0	1.7*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 1H), 9.49 (s, 1H), 9.39 (dd, J = 4.8, 2.5 Hz, 1H), 8.71 (dd, J = 2.1, 0.8 Hz, 1H), 8.44 (d, J = 4.9 Hz, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.13 (dd, J = 8.0, 2.2 Hz, 1H), 7.80 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (d, J = 4.9 Hz, 1H), 6.69 (s, 2H), 4.56 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.1 Hz, 2H), 3.76 (s, 2H), 3.58 - 3.40 (m, 3H), 2.42 (s, 2H), 2.29 (s, 2H)。
I-C-53	530.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 9.50 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.70 (dd, J = 2.2, 0.9 Hz, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.41 - 8.40 (m, 1H), 8.12 (dd, J = 8.0, 2.2 Hz, 1H), 7.78 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (dd, J = 4.8, 0.7 Hz, 1H), 6.69 (s, 2H), 4.37 (d, J = 12.1 Hz, 1H), 3.64 (d, J = 12.6 Hz, 1H), 3.18 - 3.03 (m, 2H), 2.56 (s, 4H), 2.37 (s, 1H), 1.98 (d, J = 12.1 Hz, 1H), 1.80 (d, J = 10.1 Hz, 1H), 1.71 (d, J = 6.2 Hz, 4H), 1.47 (td, J = 20.6, 17.0, 10.5 Hz, 2H)。

[2402]

I-C-54	516.2	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 11.57 (s, 1H), 10.33 (s, 1H), 9.68 (s, 1H), 9.43 (dd, J = 4.8, 2.6 Hz, 1H), 8.96 (dd, J = 2.2, 0.9 Hz, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.09 (dd, J = 8.1, 2.2 Hz, 1H), 8.04 (dd, J = 8.1, 0.9 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 6.73 (s, 2H), 4.60 (s, 1H), 4.16 (s, 2H), 4.06 (s, 2H), 3.69 (s, 1H), 3.55 - 3.38 (m, 1H), 3.17 (d, J = 7.9 Hz, 1H), 2.90 (s, 1H), 2.45 (dt, J = 11.6, 9.3 Hz, 1H), 2.24 (ddd, J = 12.4, 7.8, 4.6 Hz, 1H), 2.07 (d, J = 11.5 Hz, 1H), 1.89 (s, 1H), 1.37 (s, 2H)。
I-C-55	353.0	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.72 (d, J = 0.6 Hz, 1H), 9.40 (dd, J = 4.9, 2.6 Hz, 1H), 8.67 (d, J = 2.6 Hz, 1H), 8.42 (d, J = 4.9 Hz, 1H), 7.59 (dd, J = 5.0, 0.7 Hz, 1H), 7.48 (d, J = 1.2 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 6.71 (s, 2H), 3.72 (s, 3H)。
I-C-56	353.0	1.66*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 - 9.70 (m, 1H), 9.35 - 9.28 (m, 1H), 8.52 (d, J = 4.9 Hz, 1H), 8.50 (dd, J = 2.5, 0.5 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 7.60 (dd, J = 5.0, 0.7 Hz, 1H), 3.69 (d, J = 0.6 Hz, 3H)。
I-C-57	353.1	1.88*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.65 (3H, s), 6.55 (1H, d), 6.71 (2H, br s), 7.44 (1H, m), 7.75 (1H, m), 8.35 (1H, m), 8.42 (1H, m), 9.41 (1H, m), 9.56 (1H, s)和 9.77 (1H, s) ppm.
I-C-58	380.0	1.67*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.16 (3H, s), 6.34 (1H, m), 6.70 (1H, m), 7.53 (1H, m), 7.59-7.62 (1H, m), 8.24 (1H, m), 8.49 (1H, d), 9.39 (1H, s), 9.45 (1H, m)和 9.79 (1H, s) ppm.
I-C-59	380.1	1.52*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.47 (3H, s), 6.57 (1H, m), 6.72 (2H, br s), 7.36 (1H, m), 7.58 (1H, m), 8.06 (1H, m), 8.26 (1H, m), 8.36 (1H, m), 9.44 (1H, m)和 9.52 (1H, s) ppm.

[2403]

I-C-60	350.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 6.73 (2H, br s), 7.54 (1H, m), 7.72 (1H, m), 7.96 (1H, m), 8.04 (1H, m), 8.42 (1H, m), 8.89 (1H, m), 9.40 (1H, m), 9.58 (1H, s)和 11.85 (1H, s) ppm.
I-C-61	427.0	1.98*	^{1}H NMR (500 MHz, DMSO-d6) δ 3.37 (3H, s), 6.70 (2H, br s), 7.40 (1H, m), 7.81 (2H, m), 8.14-8.17 (2H, m), 8.43 (1H, m), 9.39 (1H, m), 9.47 (1H, s)和 9.64 (1H, s) ppm.
I-C-62	365.0	1.74*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.92 (s, 1H), 9.83 (s, 1H), 9.43 (dd, J = 4.8, 2.5 Hz, 1H), 8.88 (dd, J = 2.5, 0.8 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 5.4 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 5.3 Hz, 1H), 6.67 (s, 2H), 2.46 (d, J = 0.7 Hz, 3H).
I-C-63	367.8	1.83*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.06 (3H, s), 3.88 (3H, s), 6.72 (2H, br s), 7.27 (1H, m), 7.91 (1H, s), 8.30 (1H, m), 8.37 (1H, m), 9.42 (1H, m)和 9.59 (2H, m) ppm.
I-C-64	468.0	2.29*	^{1}H NMR (500 MHz, DMSO-d6) δ 2.02-2.08 (2H, m), 3.78 (4H, m), 6.69 (2H, br s),7.44 (1H, m), 7.82 (2H, m), 8.01 (2H, m), 8.21 (1H, m), 8.44 (1H, m), 9.40 (1H, m), 9.48 (1H, s)和 9.57 (1H, s) ppm.
I-C-65	354.0	1.51*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.82 (d, J = 0.7 Hz, 1H), 9.43 (dd, J = 4.9, 2.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H), 7.84 - 7.79 (m, 1H), 6.75 (s, 1H), 3.91 (s, 3H).

[2404]

I-C-66	448.1	2.26*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.59 (s, 1H), 9.52 (s, 1H), 9.40 (dd, J = 4.8, 2.5 Hz, 1H), 8.37 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 2.5 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 4.8, 0.7 Hz, 1H), 6.70 (s, 2H), 3.90 - 3.80 (m, 1H), 3.72 - 3.62 (m, 2H), 3.17 (dd, J = 10.2, 3.3 Hz, 1H), 2.85 (dt, J = 11.8, 1.9 Hz, 1H), 2.32 (td, J = 11.7, 3.4 Hz, 1H), 1.98 (d, J = 11.0 Hz, 3H)。
I-C-67	365.1	1.69*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.76 (s, 1H), 9.46 - 9.39 (m, 2H), 9.00 (d, J = 0.9 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.41 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 5.2 Hz, 1H), 6.68 (s, 2H), 2.23 (t, J = 0.7 Hz, 3H)。
I-C-68	353.1	1.93*	1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 9.49 - 9.36 (m, 2H), 8.86 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 5.1 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.74 (s, 2H), 3.92 (s, 3H)。
I-C-69	398.0	1.76*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.88 (s,1H), 9.53-9.55 (m, 2H), 8.99 (dd, 1H), 8.50 (d, 1H), 7.71-7.73 (d, 1H), 6.80 3(s, 2H), 4.63-4.66 (m, 1H),4.03-4.05 (m, 1H), 3.25-3.28 (m, 2H), 2.70-2.75 (m, 1H), 2.06 (s, 3H), 1.85-1.95 (m, 2H), 1.75-1.80 (m, 1H), 1.55-1.60 (m, 1H)。
I-C-70	424.0	2.04*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.90 (s,1H), 9.53-9.55 (m, 2H), 9.00 (dd, 1H), 8.50 (dd, 1H), 7.73-7.74 (d, 1H), 6.80 3(s, 2H), 4.65-4.70 (m, 1H), 4.50-4.55 (m, 1H), 3.25-3.33 (m, 2H), 2.85-2.88 (m, 1H), 1.85- 2.06 (m, 3H), 1.55-1.80 (m, 2H), 0.71-0.77 (m, 4H)。
I-C-71	449.0	2.07*	----------

[2405]

I-C-72	354.1	1.61*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (d, J = 0.7 Hz, 1H), 9.48 (s, 1H), 9.45 (dd, J = 4.8, 2.6 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.06 (s, 1H), 7.56 (dd, J = 4.9, 0.7 Hz, 1H), 6.71 (s, 2H), 3.91 (s, 3H)。
I-C-73	384.1	1.58*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.72 (s, 1H), 9.53 (dd, J = 4.8, 2.5 Hz, 1H), 9.34 (s, 1H), 8.69 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 5.4 Hz, 1H), 7.58 (d, J = 5.2 Hz, 1H), 6.73 (s, 2H), 3.38 (dt, J = 12.4, 4.5 Hz, 2H), 2.91 (s, 3H), 2.70 - 2.62 (m, 1H), 2.49 - 2.45 (m, 1H), 2.15 - 2.08 (m, 2H)。
I-C-74	326.1	1.97*	^{1}H NMR (500 MHz, DMSO-d6) δ 10.02 (s, 1H), 9.51-9.52 (dd, 1H), 9.11 (s, 1H), 9.00 (dd, 1H), 8.70 (s, 1H), 7.70 (s, 1H), 6.74-6.75 (m, 3H), 3.97 (s, 3H)。
I-C-75	343.1	1.81*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.87 (s, 1H), 9.53 (dd, 1H), 9.39 (s, 1H), 8.91 (dd, 1H), 8.48 (d, 1H), 7.68 (d, 1H), 6.74 (s, 2H), 4.09 (dd, 1H), 3.97 - 3.88 (m, 3H), 3.81 -3.76 (m, 1H), 2.61 - 2.53 (m, 1H), 2.04 - 1.97 (m, 1H)。
I-C-76	370.0	1.53*	在 D6-DMSO 中运行
I-C-77	367.1	1.68*	^{1}H NMR (500 MHz, DMSO) δ 15.03 (s, 1H), 9.76 (d, J = 0.7 Hz, 1H), 9.52 - 9.46 (m, 2H), 8.55 (d, J = 2.5 Hz, 1H), 8.51 (d, J = 4.8 Hz, 1H), 8.02 (s, 1H), 7.52 (dd, J = 4.9, 0.7 Hz, 1H), 6.75 (s, 2H), 3.49 (s, 3H), 2.72 (s, 3H)。
I-C-78	367.1	1.71*	^{1}H NMR (500 MHz, DMSO) δ? 9.80 (d, J = 0.7 Hz, 1H), 9.56 (s, 1H), 9.42 (dd, J = 4.8, 2.6 Hz, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.91 (s, 1H), 7.39 (dd, J = 4.8, 0.7 Hz, 1H), 6.71 (s, 2H), 3.40 (s, 3H), 1.97 (s, 3H)。

[2406]

I-C-79	371.0	1.84*	^{1}H NMR (500 MHz, DMSO-d6) 9.70 (s, 2H), 09.44 (dd, 1H), 8.47 (s, 1H), 8.32 (d, 1H), 8.08 (dd, 1H), 7.26 (d, 1H), 6.79 - 6.64 (m, 2H), 3.47 (s, 3H)。
I-C-80	367.1	1.76*	^{1}H NMR (500 MHz, DMSO-d6) 9.76 (s, 1H), 9.59 (s, 1H), 9.41-9.43 (m, 1H), 8.40 (d, 1H), 8.33 (d, 1H), 8.07 (d, 1H), 7.40 (m, 1H), 7.13 (d, 1H), 6.71 (s, 2H), 3.79-3.83 (qd, 2H), 1.09-1.12 (t, 3H)。
I-C-81	383.1	1.7*	^{1}H NMR (500 MHz, 甲醇-d4) 3.90 (d, 1H), 9.08 (s, 1H), 8.91 (d, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.78 (s, 1H), 3.91 (s, 3H), 3.65 (s, 3H)。
I-C-82	380.1	1.92*	^{1}H NMR (500 MHz, DMSO-d6) δ 9.49 (s, 1H0, 9.39-9.40 (d, 1H), 9.32 (s, 1H), 8.87-8.89 (d, 1H), 8.69 (dd, 1H), 8.41 (s, 1H), 8.08 (d, 1H0, 8.02-8.05 (m, 1H0, 7.78-7.80 (m, 1H0, 6.80 (br s, 2H), 3.89 (s, 3H)。
I-C-83	397.1	1.69*	^{1}H NMR (500 MHz, CDCl3) δ 9.95 (s, 1H), 9.60 (s, 1H), 8.53 (m, 1H0, 8.47-8.48 (m, 1H), 8.43-8.44 (m, 1H), 8.38 (m, 1H), 7.93 (s, 1H), 7.20-7.30 (掩蔽的, 2H),5.73 (s, 2H), 3.91-3.93 (t, 2H), 3.40-3.42 (t, 2H), 3.14 (s, 3H)。
I-C-84	343.1	2.3*	----------

[2407] 将使用上述实验方法和材料部分中所述的 HPLC 方法 B 测定的保留时间指定为(*)。对于所有其它化合物,使用 HPLC 方法 A 测定保留时间。

[2408] 实施例 19 :细胞 ATR 抑制试验 :

[2409] 使用免疫荧光显微镜测试筛选化合物抑制胞内 ATR 的能力,以检测羟基脲处理的细胞中 ATR 底物组蛋白 H2AX 的磷酸化。以 14,000 个细胞 / 孔将 HT29 细胞在 96- 孔黑色成像板 (BD 353219) 中的 McCoy′ s 5A 培养基 (Sigma M8403) 中铺平板,该培养基补充了 10%胎牛血清 (JRHBiosciences 12003)、1:100 稀释的青霉素 / 链霉素溶液 (Sigma P7539) 和 2mM L- 谷氨酰胺 (Sigma G7513),且允许其在 37℃在 5% CO_2中粘附过夜。然后将化合物加入到从 25 μM 的终浓度开始 3- 倍连续稀释的细胞培养基中,并且将细胞在 37℃在 5% CO_2中温育。15min 后,添加羟基脲 (Sigma H8627) 至终浓度为 2mM。

[2410] 在用羟基脲处理 45min 后,在 PBS 中洗涤细胞,在 4 % 用 PBS 稀释的甲醛 (Polysciences Inc 18814) 中固定 10min、用 0.2% Tween-20 的 PBS 溶液 (洗涤缓冲液) 洗涤、并且在 0.5% Triton X-100 的 PBS 溶液中进行渗透化处理 10min,全部在室温下进行。然后用洗涤缓冲液将细胞洗涤一次,在室温在用洗涤缓冲液稀释的 10% 山羊血清 (Sigma

G9023)(封闭缓冲液)中封闭 30min。为了检测 H2AX 磷酸化水平,然后将细胞在室温在用封闭缓冲液按照 1:250 稀释的一次抗体(小鼠单克隆抗磷酸化组蛋白 H2AX Ser139 抗体;Upstate 05-636)中温育 1h。然后用洗涤缓冲液将细胞洗涤 5 次,然后在室温在黑暗中、在分别用洗涤缓冲液按照 1:500 和 1:5000 稀释的二次抗体(山羊抗小鼠 Alexa Fluor488 缀合抗体;Invitrogen A11029)和 Hoechst 染料(Invitrogen H3570)的混合物中温育 1h。然后用洗涤缓冲液将细胞洗涤 5 次,最终在成像前将 100ul PBS 加入到各孔中。

[2411] 使用 BD Pathway 855Bioimager 和 Attovision 软件(BD Biosciences,1.6/855 版本)使细胞进行 Alexa Fluor 488 和 Hoechst 强度成像,以分别对磷酸化 H2AX Ser139 和 DNA 染色定量。然后使用 BD Image Data Explorer 软件(BD Biosciences 2.2.15 版本)对各孔计算 20x 放大倍数下 9 个图像的剪辑画面中的磷酸化 H2AX- 阳性细胞核的百分比。将磷酸化 H2AX- 阳性细胞核定义为所关注的 Hoechst- 阳性区,其包含的 Alexa Fluor 488 强度是未用羟基脲处理的细胞中平均 Alexa Fluor 488 强度的 1.75- 倍。最终将 H2AX 阳性核百分比对各化合物的浓度作图并且使用 Prism 软件(Macintosh 的 GraphPad Prism 3.0cx 版本,GraphPad Software,San DiegoCalifornia,USA)测定胞内 ATR 抑制的 I C50。

[2412] 还可以根据本领域公知的其它方法测试本申请中所述的化合物(参见 Sarkaria 等 人,"Inhibition of ATM and ATR Kinase Activities by the Radiosensitizing Agent,Caffeine:Cancer Research 59:4375-5382(1999);Hickson 等人,"Identification and Characterization of a Nove and Specific Inhibitor of the Ataxia-Telangiectasia Mutated Kinase ATM"Cancer Research 64:9152-9159(2004);Kim 等人,"Substrate Specificities and Identification of Putative Substrates of ATM Kinase Family Members"The Journal of Biological Chemistry,274(53):37538-37543(1999);以及 Chiang 等人,"Determination of the catalytic activities of mTOR and other members of the phosphoinositide-3-kinase-related kinase family"Methods Mol.Biol.281:125-41(2004))。

[2413] 实施例 20:ATR 抑制试验:

[2414] 使用放射性磷酸盐掺入试验筛选化合物抑制 ATR 激酶的能力。在 50mM Tris/HCl(pH 7.5)、10mM $MgCl_2$和 1mM DTT 的混合物中进行试验。最终底物浓度为 10μM[γ-33P]ATP(3mCi 33P ATP/mmol ATP,PerkinElmer)和 800μM 靶肽(ASELPASQPQPFSAKKK)。

[2415] 在 25℃、在 5nM 全长 ATR 的存在下进行试验。制备包含除 ATP 和所关注待测化合物之外的全部上述举出的试剂的试验储备缓冲溶液。将 13.5μL 储备溶液放入 96 孔培养板,然后添加包含顺序稀释的测试化合物的 2μL DMSO 储备溶液(典型地使用 3- 倍顺序稀释液,从 15μM 终浓度开始),一式两份(DMSO 终浓度为 7%)。将培养板在 25℃预温育 10 分钟,通过添加 15μL[γ-33P]ATP(终浓度 10μM)启动反应。

[2416] 24 小时后通过添加 30μL 包含 2mM ATP 的 0.1M 磷酸终止反应。用 100μL 0.2M 磷酸预处理多筛选磷酸纤维素滤膜 96- 孔培养板(Millipore,目录号 MAPHN0B50),然后添加 45μL 终止后的试验混合物。用 5x 200μL 0.2M 磷酸洗涤培养板。干燥后,将 100μL Optiphase 'SuperMix' 液体闪烁混合物(Perkin Elmer)加入到该孔中,然后进行闪烁计数(1450Microbeta Liquid Scintillation Counter,Wallac)。

[2417] 在除去全部数据点的平均背景值后,使用 Prism 软件包(Macintosh 的 GraphPad

Prism 3.0cx 版本，GraphPad Software, SanDiego California, USA) 由初始比率数据的非线性回归分析来计算 Ki(app) 数据。

[2418] 下表 5 显示了本申请中公开的化合物的 ATR 抑制 Ki 值。用“+++”标记具有 <0.01 μM 的 Ki 值的化合物。用“++”标记具有 >0.01 μM 但 <1 μM 的 Ki 值的化合物。用“+”标记具有 >1 μM 但 <5 μM 的 Ki 值的化合物。

[2419] 表 5

[2420]

化合物编号	ATR Ki
I-N-1	++
I-N-2	++
I-N-3	++
I-N-4	++
I-N-5	++
I-N-6	-----
I-N-7	++
I-N-22	++
I-N-23	++
I-N-24	++
I-N-25	++
I-N-26	++
I-N-27	++
I-N-28	++
I-N-29	++
I-N-30	++
I-N-31	+
I-N-32	++
I-N-33	++
I-N-34	+
I-N-35	+
I-N-36	+
I-N-37	+
I-N-38	++
I-N-39	++
I-N-40	++

化合物编号	ATR Ki
I-N-8	+
I-N-9	+
I-N-10	++
I-N-11	++
I-N-12	++
I-N-13	++
I-N-14	++
I-N-54	++
I-N-55	++
I-N-56	++
I-N-57	++
I-N-58	++
I-N-59	++
I-N-60	++
I-N-61	++
I-N-62	++
I-N-63	++
I-N-64	++
I-N-65	++
I-N-66	++
I-N-67	++
I-N-68	++
I-N-69	++
I-N-70	++
I-N-71	++
I-N-72	++

化合物编号	ATR Ki
I-N-15	++
I-N-16	++
I-N-17	++
I-N-18	++
I-N-19	++
I-N-20	++
I-N-21	++
I-N-86	++
I-N-87	++
I-N-88	++
I-N-89	++
I-N-90	++
I-N-91	+++
I-N-92	+
I-N-93	++
I-N-94	++
I-N-95	++
I-N-96	-----
I-N-97	++
I-N-98	++
I-N-99	++
I-N-100	++
I-N-101	++
I-N-102	++
I-N-103	++
I-N-104	++

[2421]

I-N-41	++
I-N-42	++
I-N-43	++
I-N-44	++
I-N-45	++
I-N-46	++
I-N-47	++
I-N-48	++
I-N-49	++
I-N-50	++
I-N-51	++
I-N-52	+
I-N-53	++
I-N-118	++
I-N-119	++
I-N-120	++
I-N-121	++
I-N-122	++
I-N-123	++
I-N-124	++
I-N-125	++
I-N-126	++
I-N-127	++
I-N-128	++
I-N-129	++
I-N-130	++
I-N-131	++
I-N-132	++
I-N-133	++
I-N-134	++
I-N-135	++
I-N-136	++
I-N-137	++
I-N-138	+
I-N-139	++
I-N-140	++
I-N-141	++

I-N-73	++
I-N-74	++
I-N-75	++
I-N-76	+
I-N-77	++
I-N-78	++
I-N-79	++
I-N-80	++
I-N-81	++
I-N-82	+++
I-N-83	+++
I-N-84	+++
I-N-85	++
I-N-150	++
I-N-151	+
I-N-152	++
I-N-153	----
I-N-154	++
I-N-155	++
I-N-156	++
I-N-157	++
I-N-158	++
I-N-159	++
I-N-160	++
I-N-161	++
I-N-162	++
I-N-163	++
I-N-164	++
I-N-165	++
I-N-166	++
I-N-167	++
I-N-168	++
I-N-169	++
I-N-170	++
I-N-171	++
I-N-172	++
I-N-173	++

I-N-105	++
I-N-106	++
I-N-107	++
I-N-108	++
I-N-109	++
I-N-110	-----
I-N-111	+
I-N-112	+
I-N-113	+
I-N-114	-----
I-N-115	++
I-N-116	++
I-N-117	++
I-N-182	++
I-N-183	++
I-N-184	++
I-N-185	++
I-N-186	++
I-N-187	++
I-N-188	++
I-N-189	++
I-N-190	++
I-N-191	+
I-N-192	++
I-N-193	++
I-N-194	++
I-N-195	++
I-N-196	++
I-N-197	++
I-N-198	++
I-N-199	++
I-N-200	++
I-N-201	++
I-N-202	++
I-N-203	++
I-N-204	++
I-N-205	++

[2422]

I-N-142	+
I-N-143	++
I-N-144	+
I-N-145	++
I-N-146	++
I-N-147	++
I-N-148	++
I-N-149	++
I-N-214	++
I-N-215	++
I-N-216	++
I-N-217	++
I-N-218	++
I-N-219	++
I-N-220	++
I-N-221	++
I-N-222	++
I-N-223	++
I-N-224	++
I-N-225	++
I-N-226	++
I-N-227	++
I-N-228	++
I-N-229	++
I-N-230	++
I-N-231	++
I-N-232	++
I-N-233	++
I-N-234	++
I-N-235	++
I-N-236	++
I-N-237	++
I-N-238	++
I-N-239	++
I-N-240	++

I-N-174	++
I-N-175	++
I-N-176	++
I-N-177	++
I-N-178	++
I-N-179	++
I-N-180	++
I-N-181	++
I-N-245	-----
I-N-246	++
I-N-247	++
I-N-248	++
I-N-249	++
I-N-250	++
I-N-251	++
I-N-252	++
I-N-253	++
I-N-254	++
I-N-255	++
I-N-256	++
I-N-257	++
I-N-258	++
I-N-259	+
I-N-260	++
I-N-261	++
I-N-262	++
I-N-263	++
I-N-264	+
I-N-265	++
I-N-266	++
I-N-267	++
I-N-268	++
I-N-269	++
I-N-270	++
I-N-271	++

I-N-206	++
I-N-207	++
I-N-208	++
I-N-209	++
I-N-210	++
I-N-211	++
I-N-212	++
I-N-213	++
I-N-276	++
I-N-277	++
I-N-278	++
I-N-279	++
I-N-280	++
I-N-281	++
I-N-282	++
I-N-283	++
I-N-284	++
I-N-285	++
I-N-286	++
I-N-287	++
I-N-288	++
I-N-289	+
I-N-290	++
I-O-1	++
I-O-2	+++
I-O-3	++
I-O-4	++
I-O-5	++
I-O-6	++
I-O-7	++
I-O-8	++
I-O-9	++
I-O-10	++
I-O-11	++
I-O-12	++

[2423]

化合物编号	ATR Ki
I-N-241	++
I-N-242	-----
I-N-243	++
I-N-244	++
I-O-17	++
I-O-18	++
I-O-19	++
I-O-20	++
I-O-21	++
I-O-22	++
I-O-23	++
I-O-24	+++
I-O-25	+++
I-O-26	+++
I-O-27	+++
I-O-28	+++
I-O-29	+++
I-O-30	+++
I-O-31	+++
I-O-32	+++
I-O-33	+++
I-O-34	+++
I-O-35	+++
I-O-36	+++
I-O-37	+++
I-O-38	+++
I-O-39	+++
I-O-40	+++

化合物编号	ATR Ki
I-N-272	++
I-N-273	++
I-N-274	++
I-N-275	++
I-O-46	+
I-O-47	++
I-O-48	++
I-O-49	++
I-O-50	++
I-O-51	++
I-O-52	+
I-O-53	++
I-O-54	++
I-O-55	++
I-O-56	++
I-O-57	++
I-O-58	++
I-O-59	++
I-O-60	++
I-O-61	++
I-O-62	++
I-O-63	++
I-O-64	++
I-O-65	++
I-O-66	++
I-O-67	++
I-O-68	++
I-O-69	++

化合物编号	ATR Ki
I-O-13	++
I-O-14	++
I-O-15	++
I-O-16	++
I-O-75	++
I-O-76	++
I-O-77	++
I-O-78	++
I-O-79	-----
I-O-80	++
I-O-81	++
I-O-82	+++
I-O-83	+++
I-O-84	+++
I-O-85	++
I-O-86	+++
I-O-87	++
I-O-88	++
I-O-89	++
I-O-90	++
I-O-91	++
I-O-92	++
I-C-1	+
I-C-2	+
I-C-3	++
I-C-4	++
I-C-5	++
I-C-6	++

[2424]

化合物编号	ATR Ki
I-O-41	+++
I-O-42	+++
I-O-43	+++
I-O-44	++
I-O-45	++
I-C-12	++
I-C-13	+
I-C-14	+
I-C-15	++
I-C-16	++
I-C-17	++
I-C-18	++
I-C-19	++
I-C-20	++
I-C-21	++
I-C-22	++
I-C-23	+
I-C-24	++
I-C-25	++
I-C-26	++
I-C-27	++
I-C-28	++
I-C-29	++
I-C-30	++
I-C-31	++
I-C-32	++
I-C-33	++
I-C-34	++

化合物编号	ATR Ki
I-O-70	++
I-O-71	++
I-O-72	++
I-O-73	++
I-O-74	++
I-C-41	++
I-C-42	++
I-C-43	++
I-C-44	++
I-C-45	++
I-C-46	++
I-C-47	++
I-C-48	++
I-C-49	++
I-C-50	++
I-C-51	++
I-C-52	++
I-C-53	++
I-C-54	++
I-C-55	++
I-C-56	++
I-C-57	++
I-C-58	++
I-C-59	++
I-C-60	++
I-C-61	++
I-C-62	++
I-C-63	++

化合物编号	ATR Ki
I-C-7	++
I-C-8	++
I-C-9	++
I-C-10	++
I-C-11	++
I-C-70	++
I-C-71	++
I-C-72	++
I-C-73	++
I-C-74	++
I-C-75	++
I-C-76	+
I-C-77	++
I-C-78	++
I-C-79	++
I-C-80	++
I-C-81	+++
I-C-82	++
I-C-83	++
I-C-84	++
I-G-1	++
I-G-2	++
I-G-3	++
I-G-4	++
I-G-5	++
I-G-6	++
I-G-7	++
I-G-8	++

[2425]

化合物编号	ATR Ki
I-C-35	++
I-C-36	++
I-C-37	+
I-C-38	++
I-C-39	++
I-C-40	++
I-G-15	++
I-G-16	++
I-G-17	+
I-G-18	++
I-G-19	++
I-G-20	++
I-G-21	++
I-G-22	++
I-G-23	++
I-G-24	++
I-G-25	++
I-G-26	++
I-G-27	++
I-C-28	++
I-G-29	++
I-G-30	++
I-G-31	++
I-G-32	++
I-G-33	++
I-G-34	++
I-G-35	++
I-G-36	++

化合物编号	ATR Ki
I-C-64	++
I-C-65	++
I-C-66	++
I-C-67	++
I-C-68	++
I-C-69	++
I-G-45	++
I-G-46	+
I-G-47	++
I-G-48	++
I-G-49	++
I-G-50	++
I-G-51	++
I-G-52	++
I-G-53	++
I-G-54	++
I-G-55	++
I-G-56	++
I-G-57	++
I-G-58	++
I-G-59	++
I-G-60	++
I-G-61	++
I-G-62	++
I-G-63	++
I-G-64	++
I-G-65	++
I-G-66	++

化合物编号	ATR Ki
I-G-9	++
I-G-10	++
I-G-11	++
I-G-12	++
I-G-13	++
I-G-14	+++
I-G-74	++
I-G-75	++
I-G-76	++
I-G-77	++
I-G-78	++
I-G-79	++
I-G-80	++
I-G-81	++
I-G-82	++
I-G-83	++
I-G-84	++
I-G-85	++
I-G-86	++
I-G-87	++
I-G-88	++
I-G-89	++
I-G-90	++
I-G-91	++
I-G-92	++
I-G-93	++
I-G-94	++
I-G-95	++

[2426]

化合物编号	ATR Ki
I-G-37	++
I-G-38	++
I-G-40	++
I-G-41	+
I-G-42	++
I-G-43	++
I-G-44	++

化合物编号	ATR Ki
I-G-67	+++
I-G-68	+++
I-G-69	++
I-G-70	++
I-G-71	++
I-G-72	++
I-G-73	++

化合物编号	ATR Ki
I-G-96	++
I-G-98	++
I-G-99	++

[2427] 实施例 21 :顺铂增敏试验

[2428] 使用 96h 细胞存活 (MTS) 试验筛选化合物使 HCT116 结肠直肠癌细胞对顺铂敏感的能力。以 470 个细胞 / 孔将在对顺铂的 ATM 信号传导方面存在缺陷的 HCT116 细胞 (参见 Kim 等人 ;Oncogene 21:3864(2002) ;另外参见 Takemura 等人 ;JBC281:30814(2006)) 在 96- 孔聚苯乙烯培养板 (Costar 3596) 中的 150 μ l McCoy′ s 5A 培养基 (Sigma M8403) 中铺平板,该培养基补充了 10% 胎牛血清 (JRH Biosciences 12003)、1:100 稀释的青霉素 / 链霉素溶液 (Sigma P7539) 和 2mM L- 谷氨酰胺 (Sigma G7513),且允许其在 37℃在 5% CO_2 中粘附过夜。然后将化合物和顺铂同时加入到细胞培养基中 (从作为在 200 μ l 最终细胞体积中的完整基质浓度的 10 μ M 的最高终浓度开始 2- 倍连续稀释),然后将细胞在 37℃在 5% CO_2 中温育。96h 之后,将 40 μ l MTS 试剂 (Promega G358a) 加入到每一孔,并将细胞在 37℃在 5% CO_2 中温育 1h。最后,使用 SpectraMax Plus 384 读数器 (Molecular Devices) 在 490nm 测定吸光度,并且报告将仅有顺铂的样品的 IC_{50} 降低到至多三分之一 (到小数第 1 位) 所需的化合物浓度。

[2429] 下表 6 显示本申请中公开的化合物的顺铂增敏值。用“+++”标记具有 <0.02 μ M 的顺铂增敏值的化合物。用“++”标记具有 >0.02 μ M 但 <0.2 μ M 的顺铂增敏值的化合物。用“+”标记具有 >0.2 μ M 但 <5 μ M 的顺铂增敏值的化合物。

[2430] 表 6

[2431]

化合物编号	顺铂增敏试验
I-N-1	++
I-N-2	+++
I-N-3	+++
I-N-4	+++
I-N-5	++
I-N-6	-----
I-N-7	++
I-N-22	-----
I-N-23	+++
I-N-24	+++
I-N-25	-----
I-N-26	+
I-N-27	++
I-N-28	+++
I-N-29	++
I-N-30	++
I-N-31	+
I-N-32	++
I-N-33	+
I-N-34	++
I-N-35	+
I-N-36	++
I-N-37	++
I-N-38	++
I-N-39	++
I-N-40	++
I-N-41	+++
I-N-42	-----
I-N-43	++
I-N-44	++
I-N-45	++
I-N-46	+++
I-N-47	++

化合物编号	顺铂增敏试验
I-N-8	+
I-N-9	+
I-N-10	++
I-N-11	++
I-N-12	+++
I-N-13	+++
I-N-14	+++
I-N-54	+++
I-N-55	++
I-N-56	++
I-N-57	+++
I-N-58	++
I-N-59	++
I-N-60	+++
I-N-61	+++
I-N-62	++
I-N-63	++
I-N-64	+++
I-N-65	+
I-N-66	+++
I-N-67	+++
I-N-68	+++
I-N-69	+++
I-N-70	++
I-N-71	+++
I-N-72	+++
I-N-73	+++
I-N-74	+++
I-N-75	+++
I-N-76	+++
I-N-77	+
I-N-78	-----
I-N-79	++

化合物编号	顺铂增敏试验
I-N-15	+++
I-N-16	+++
I-N-17	+++
I-N-18	++
I-N-19	+++
I-N-20	+++
I-N-21	+++
I-N-86	+++
I-N-87	++
I-N-88	++
I-N-89	++
I-N-90	+
I-N-91	++
I-N-92	+
I-N-93	-----
I-N-94	+++
I-N-95	++
I-N-96	-----
I-N-97	+++
I-N-98	+++
I-N-99	+++
I-N-100	++
I-N-101	++
I-N-102	++
I-N-103	+++
I-N-104	+++
I-N-105	+++
I-N-106	+++
I-N-107	+++
I-N-108	+++
I-N-109	+++
I-N-110	-----
I-N-111	++

[2432]

I-N-48	++
I-N-49	+++
I-N-50	+
I-N-51	-----
I-N-52	++
I-N-53	++
I-N-118	+++
I-N-119	++
I-N-120	+++
I-N-121	+++
I-N-122	++
I-N-123	++
I-N-124	+++
I-N-125	+++
I-N-126	+++
I-N-127	+++
I-N-128	+++
I-N-129	-----
I-N-130	++
I-N-131	+++
I-N-132	+++
I-N-133	++
I-N-134	+
I-N-135	+++
I-N-136	++
I-N-137	++
I-N-138	++
I-N-139	+++
I-N-140	+++
I-N-141	+++
I-N-142	++
I-N-143	++
I-N-144	+++
I-N-145	-----
I-N-146	+++
I-N-147	+++
I-N-148	+++

I-N-80	++
I-N-81	+++
I-N-82	++
I-N-83	++
I-N-84	+++
I-N-85	++
I-N-150	+++
I-N-151	+
I-N-152	+++
I-N-153	++
I-N-154	+++
I-N-155	+++
I-N-156	+++
I-N-157	++
I-N-158	+++
I-N-159	+++
I-N-160	+++
I-N-161	+
I-N-162	++
I-N-163	+++
I-N-164	+++
I-N-165	+++
I-N-166	+++
I-N-167	+++
I-N-168	+
I-N-169	+++
I-N-170	+++
I-N-171	+++
I-N-172	+++
I-N-173	+++
I-N-174	+++
I-N-175	+++
I-N-176	+++
I-N-177	+++
I-N-178	+++
I-N-179	+++
I-N-180	-----

I-N-112	+
I-N-113	+
I-N-114	-----
I-N-115	+++
I-N-116	++
I-N-117	+++
I-N-182	++
I-N-183	+++
I-N-184	++
I-N-185	++
I-N-186	+++
I-N-187	+++
I-N-188	+++
I-N-189	+++
I-N-190	+++
I-N-191	+
I-N-192	+++
I-N-193	+++
I-N-194	+++
I-N-195	+++
I-N-196	+++
I-N-197	+++
I-N-198	++
I-N-199	+++
I-N-200	+++
I-N-201	+++
I-N-202	+++
I-N-203	+++
I-N-204	-----
I-N-205	++
I-N-206	+++
I-N-207	-----
I-N-208	+++
I-N-209	+++
I-N-210	+++
I-N-211	++
I-N-212	+++

[2433]

I-N-149	+++
I-N-214	++
I-N-215	+++
I-N-216	+++
I-N-217	++
I-N-218	+
I-N-219	+++
I-N-220	++
I-N-221	++
I-N-222	++
I-N-223	++
I-N-224	+
I-N-225	++
I-N-226	+++
I-N-227	+++
I-N-228	+++
I-N-229	+++
I-N-230	+++
I-N-231	+++
I-N-232	++
I-N-233	++
I-N-234	+
I-N-235	++
I-N-236	+++
I-N-237	+
I-N-238	++
I-N-239	+++
I-N-240	++
I-N-241	+++
I-N-242	+
I-N-243	+++
I-N-244	+++
I-N-245	++
I-O-20	++
I-O-21	++

I-N-181	+++
I-N-246	++
I-N-247	+++
I-N-248	++
I-N-249	+++
I-N-250	++
I-N-251	+++
I-N-252	+++
I-N-253	+++
I-N-254	+++
I-N-255	++
I-N-256	++
I-N-257	+++
I-N-258	++
I-N-259	+
I-N-260	+++
I-N-261	+++
I-N-262	+++
I-N-263	+
I-N-264	+
I-N-265	++
I-N-266	+++
I-N-267	+++
I-N-268	+++
I-N-269	++
I-N-270	+++
I-N-271	+++
I-N-272	+++
I-N-273	+++
I-N-274	+++
I-N-275	+++
I-N-276	+++
I-N-277	+++
I-O-47	+
I-O-48	++

I-N-213	+++
I-N-278	+++
I-N-279	+++
I-N-280	+++
I-N-281	+++
I-N-282	+++
I-N-283	++
I-N-284	+++
I-N-285	++
I-N-286	++
I-N-287	+++
I-N-288	+++
I-N-289	++
I-N-290	++
I-O-1	+++
I-O-2	++
I-O-3	++
I-O-4	++
I-O-5	+++
I-O-6	+++
I-O-7	++
I-O-8	+
I-O-9	++
I-O-10	+++
I-O-11	+++
I-O-12	+++
I-O-13	+++
I-O-14	+++
I-O-15	+++
I-O-16	+++
I-O-17	+++
I-O-18	----
I-O-19	+++
I-O-74	++
I-O-75	++

[2434]

化合物编号	顺铂增敏试验
I-O-22	-----
I-O-23	+++
I-O-24	++
I-O-25	+++
I-O-26	++
I-O-27	++
I-O-28	+++
I-O-29	+++
I-O-30	+++
I-O-31	+++
I-O-32	+++
I-O-33	++
I-O-34	++
I-O-35	+++
I-O-36	+++
I-O-37	+++
I-O-38	+++
I-O-39	+++
I-O-40	++
I-O-41	+++
I-O-42	+++
I-O-43	+++
I-O-44	++
I-O-45	+++
I-O-46	+
I-C-9	+
I-C-10	+++
I-C-11	+++

化合物编号	顺铂增敏试验
I-O-49	+
I-O-50	+
I-O-51	-----
I-O-52	+
I-O-53	+++
I-O-54	+++
I-O-55	++
I-O-56	+++
I-O-57	+++
I-O-58	+++
I-O-59	+++
I-O-60	++
I-O-61	+++
I-O-62	+++
I-O-63	++
I-O-64	+++
I-O-65	+++
I-O-66	+
I-O-67	++
I-O-68	++
I-O-69	++
I-O-70	+++
I-O-71	+
I-O-72	+
I-O-73	+
I-C-36	+++
I-C-37	+++
I-C-38	++

化合物编号	顺铂增敏试验
I-O-76	++
I-O-77	++
I-O-78	+
I-O-79	++
I-O-80	+++
I-O-81	++
I-O-82	++
I-O-83	+++
I-O-84	++
I-O-85	+++
I-O-86	++
I-O-87	++
I-O-88	+++
I-O-89	++
I-O-90	+
I-O-91	++
I-O-92	+++
I-C-1	++
I-C-2	++
I-C-3	----
I-C-4	++
I-C-5	+++
I-C-6	+++
I-C-7	++
I-C-8	+
I-C-63	+++
I-C-64	+++
I-C-65	++

[2435]

化合物编号	顺铂增敏试验
I-C-12	+++
I-C-13	++
I-C-14	+
I-C-15	++
I-C-16	+
I-C-17	++
I-C-18	+
I-C-19	++
I-C-20	+++
I-C-21	+++
I-C-22	++
I-C-23	+
I-C-24	+++
I-C-25	+++
I-C-26	++
I-C-27	++
I-C-28	-----
I-C-29	+++
I-C-30	+++
I-C-31	+++
I-C-32	-----
I-C-33	+
I-C-34	+++
I-C-35	+++
I-G-6	+++
I-G-7	+++
I-G-8	+++
I-G-9	+++

化合物编号	顺铂增敏试验
I-C-39	+++
I-C-40	+++
I-C-41	+++
I-C-42	++
I-C-43	+++
I-C-44	+++
I-C-45	+++
I-C-46	+
I-C-47	+++
I-C-48	+++
I-C-49	+++
I-C-50	+++
I-C-51	++
I-C-52	++
I-C-53	+++
I-C-54	+++
I-C-55	+
I-C-56	+++
I-C-57	+++
I-C-58	+++
I-C-59	++
I-C-60	++
I-C-61	+++
I-C-62	++
I-G-33	+++
I-G-34	+++
I-G-35	+++
I-G-36	+++

化合物编号	顺铂增敏试验
I-C-66	+++
I-C-67	++
I-C-68	+
I-C-69	+++
I-C-70	+++
I-C-71	+++
I-C-72	+++
I-C-73	++
I-C-74	+
I-C-75	++
I-C-76	+
I-C-77	+++
I-C-78	++
I-C-79	+++
I-C-80	+++
I-C-81	+++
I-C-82	+++
I-C-83	++
I-C-84	++
I-G-1	+++
I-G-2	+++
I-G-3	+++
I-G-4	+++
I-G-5	+++
I-G-61	+++
I-G-62	+++
I-G-63	+++
I-G-64	+++

[2436]

化合物编号	顺铂增敏试验
I-G-10	+++
I-G-11	+++
I-G-12	+++
I-G-13	+++
I-G-14	+++
I-G-15	+++
I-G-16	+++
I-G-17	+
I-G-18	+++
I-G-19	++
I-G-20	+
I-G-21	+++
I-G-22	+++
I-G-23	+++
I-G-24	+++
I-G-25	+++
I-G-26	++
I-G-27	++
I-G-28	+++
I-G-29	+++
I-G-30	+++
I-G-31	+++
I-G-32	+++
I-G-88	+++
I-G-89	+
I-G-90	+++
I-G-91	+++
I-G-92	+++

化合物编号	顺铂增敏试验
I-G-37	++
I-G-38	+++
I-G-40	+++
I-G-41	+++
I-G-42	+++
I-G-43	+++
I-G-44	+++
I-G-45	+++
I-G-46	+++
I-G-47	+++
I-G-48	+++
I-G-49	+++
I-G-50	+++
I-G-51	+++
I-G-52	+++
I-G-53	+++
I-G-54	+++
I-G-55	+++
I-G-56	+++
I-G-57	+++
I-G-58	+++
I-G-59	+++
I-G-60	+++
I-G-96	+++
I-G-98	+++
I-G-99	+++

化合物编号	顺铂增敏试验
I-G-65	+++
I-G-66	+++
I-G-67	+++
I-G-68	+++
I-G-69	+++
I-G-70	-----
I-G-71	-----
I-G-72	+++
I-G-73	+++
I-G-74	+++
I-G-75	+++
I-G-76	+++
I-G-77	+++
I-G-78	+++
I-G-79	+++
I-G-80	+++
I-G-81	+++
I-G-82	+++
I-G-83	+++
I-G-84	+++
I-G-85	+++
I-G-86	+++
I-G-87	+++

[2437]

化合物编号	顺铂增敏试验
I-G-93	+++
I-G-94	+++
I-G-95	+++

化合物编号	顺铂增敏试验

化合物编号	顺铂增敏试验

[2438] 实施例 22 :单一活性剂 HCT116 活性

[2439] 使用 96h 细胞存活 (MTS) 试验筛选化合物对 HCT116 结肠直肠癌细胞的单一活性剂活性。以 470 个细胞 / 孔将 HCT116 在 96- 孔聚苯乙烯培养板 (Costar 3596) 中的 150 μ l McCoy′ s 5A培养基 (Sigma M8403) 中铺平板,该培养基补充了 10% 胎牛血清 (JRH Biosciences 12003)、1:100 稀释的青霉素 / 链霉素溶液 (Sigma P7539) 和 2mM L- 谷氨酰胺 (Sigma G7513),且允许其在 37℃在 5% CO_2中粘附过夜。然后将化合物加入到细胞培养基中 (从作为在 200 μ l 最终细胞体积中的完整基质浓度的 10 μ M 的最高终浓度开始 2- 倍连续稀释),然后将细胞在 37℃在 5% CO_2中温育。96h 之后,将 40 μ l MTS 试剂 (Promega G358a) 加入到每一孔,并将细胞在 37℃在 5% CO_2中温育 1h。最后,使用 SpectraMax Plus 384 读数器 (Molecular Devices) 在 490nm 测定吸光度,并且计算 IC50 值。

[2440] 实施例 23 :ATR 复合物抑制试验

[2441] 使用放射性磷酸盐掺入试验在配偶体蛋白 ATRIP、CLK2 和 TopBP1 的存在下筛选化合物抑制 ATR 激酶的能力。在 50mM Tris/HCl(pH 7.5)、10mM $MgCl_2$和 1mM DTT 的混合物中进行试验。最终底物浓度为 10 μ M[g-33P]ATP(3.5 μ Ci 33P ATP/nmol ATP, Perkin Elmer, Massachusetts, USA) 和 800 μ M 靶肽 (ASELPASQPQPFSAKKK, Isca Biochemicals, Cambridgeshire, UK)。

[2442] 在 25 ℃、在 4nM 全长 ATR、40nM 全长 ATRIP、40nM 全长 CLK2 和 600nM TopBP1(A891-S1105) 的存在下进行试验。制备包含除靶肽、ATP 和所关注待测化合物之外的全部上述举出的试剂的酶储备缓冲溶液。将这种酶储备溶液在 25℃预温育 30 分钟。将 8.5 μ L 该酶储备溶液放入 96 孔培养板,然后添加 5 μ l 靶肽和包含顺序稀释的测试化合物的 2 μ L DMSO 储备溶液 (典型地使用 2.5- 倍顺序稀释液,从 1.5 μ M 终浓度开始),一式两份 (DMSO 终浓度为 7%)。将培养板在 25℃预温育 10 分钟,通过添加 15 μ L[g-33P]ATP(终浓度 10 μ M) 启动反应。

[2443] 20 小时后通过添加 30 μ L 包含 2mM ATP 的 0.3M 磷酸终止反应。用 100 μ L 0.1M 磷酸预处理多磷酸纤维素滤膜 96- 孔培养板 (Multiscreen HTS MAPHNOB50, Merck-Millipore, Massachusetts, USA),然后添加 45 μ L 终止后的试验混合物。用 5x 200 μ L 0.1M 磷酸洗涤培养板。干燥后,将 50 μ L Optiphase ‘SuperMix’ 液体闪烁混合物 (Perkin Elmer, Massachusetts, USA)) 加入到该孔中,然后进行闪烁计数 (Wallac 1450Microbeta Liquid Scintillation Counter, Perkin Elmer, Massachusetts, USA)。

[2444] 在除去全部数据点的平均背景值后,使用 Prism 软件包 (Macintosh 的 GraphPad Prism 6.0c 版本,GraphPad Software, SanDiego California, USA) 由初始比率数据的非线性回归分析来计算 Ki(app) 数据。

[2445] 下表 7 是显示本公开文本的化合物的顺铂增敏值。用“+++”标记具有 <0.02 μM 的顺铂增敏值的化合物。用“++”标记具有 >0.02 μM、但 <0.2 μM 的 Ki 值的化合物。用“+”标记具有 >0.2 μM、但 <5 μM 的 Ki 值的化合物。

[2446] 表 7

[2447]

化合物编号	ATR Ki
I-N-1	+++
I-N-13	+++
I-N-58	+++
I-N-118	+++
I-N-166	+++

[2448]

化合物编号	ATR Ki
I-N-186	+++
I-N-275	+++
I-C-25	+++
I-C-31	+++
I-C-43	+++
I-C-79	+++
I-G-4	+++
I-G-7	+++
I-G-12	+++
I-G-21	+++
I-G-32	+++

[2449] 尽管我们已经描述了本发明的许多实施方案，但显而易见，可以改变我们的基础实例以提供使用本发明化合物、方法和工艺的其它实施方案。因此，应当理解本发明的范围由随附权利要求而非本文已借助实施例来体现的具体实施方案限定。