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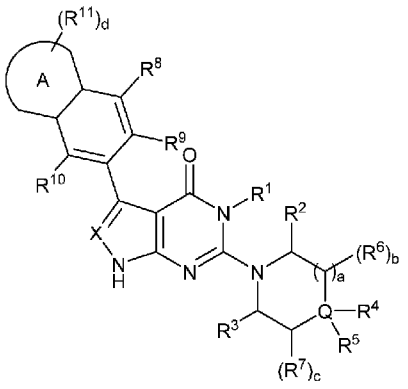
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(54) **Title:** HETEROBICYCLIC COMPOUNDS FOR INHIBITING THE ACTIVITY OF SHP2



(I)

(57) **Abstract:** A compound of formula (I):wherein Ring A, Q, R^1,R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11},X, a,b, c and d are as defined in the specification.

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Description

Title of Invention: HETEROBICYCLIC COMPOUNDS FOR INHIBITING THE ACTIVITY OF SHP2

Technical Field

[0001] The present invention relates to novel heterobicyclic compounds for inhibiting the activity of SHP2, pharmaceutical compositions comprising the compound and uses of the compounds.

Background Art

[0002] Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) is a ubiquitously expressed protein tyrosine phosphatase encoded by the PTPN11 gene. SHP2 contains two N-terminal tandem SH2 domains (N-SH2, C-SH2), a catalytic phosphatase (PTP) domain and a C-terminal tail with 2 tyrosine phosphorylation sites.

[0003] SHP2 switches between "open" active and "closed" inactive forms due to autoinhibitory interactions between the N-SH2 and the PTP domain. This naturally occurring autoinhibition is released when bis-tyrosylphosphorylated peptides bind to the N-SH2 domains and SHP2 adopts an "open" conformation, resulting in activation of the enzyme and exposure of the PTP domain for substrate recognition and catalysis.

[0004] PTPN11 mutations have been linked to several human diseases including cancer. Germline PTPN11 mutations are associated with developmental disorders such as Noonan Syndrome and Leopard Syndrome, whilst somatic mutations occur in several types of hematologic malignancies, such as JMML and more rarely in solid tumours.

[0005] SHP2 is required for signalling downstream of receptor tyrosine kinases (e.g. EGFR, ALK, PDGFR) and plays a positive role in regulating many cellular processes such as proliferation in response to growth factor and cytokine stimulation. Previous studies have shown that SHP2 acts upstream of Ras and is required for full, sustained activation of the MAPK pathway. RTK deregulation often leads to a wide range of cancers, making SHP2 a valuable target in RTK-activated cancers. SHP2 is also reported to play a role in regulating immune responses by mediating immune checkpoint pathways (e.g. PD-1) as immunoreceptor tyrosine-based inhibitory motifs (ITIMs) bind to the SH2 domains of SHP2 to mediate a negative signal.

[0006] It has been reported that some SHP2 inhibitor compound show inhibitory effect on proliferation of in vitro cancer cells and on increase in tumour volume in a mouse xenograft model (Nature (2016) 535: 148-152).

Citation List

Non Patent Literature

[0007] NPL 1: Nature (2016) 535: 148-152

Summary of Invention

Technical Problem

[0008] An object of the present invention is to provide a novel series of compounds which selectively inhibit SHP2 and which can be used to treat a disease or condition mediated by SHP2.

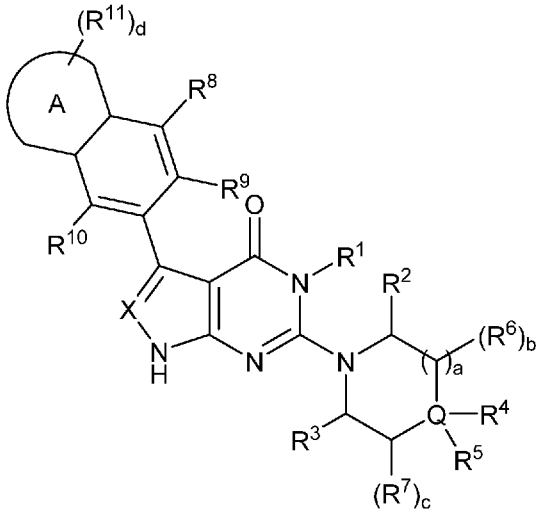
Solution to Problem

[0009] The present inventors conducted extensive research to achieve the above object, and consequently found that a compound group represented by Formulas (I) below showed excellent inhibitory activity against SHP2, and was useful as a pharmaceutical preparation for treating SHP2 mediated diseases such as cancer. Thus, the present invention has been completed.

[0010] The present invention comprises the following items.

[0011] Item 1. A compound of formula (I):

[0012] [Chem.1]



(I)

[0013] or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is $-CH_3$;

R^2 and R^3 are independently selected from hydrogen and C_{1-4}alkyl;

Q is C or N;

wherein when Q is C then either:

(i) R^4 is amino, aminoC_{1-4}alkyl or monoC_{1-4}alkylamino;

R^5 is hydrogen, C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl or C_{1-4} alkoxyC_{1-4}alkyl;

; or

(ii) R^4 and R^5 together with Q form a four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, S, NH, C(O)

and $S(O)_m$, and said ring formed by R^4 and R^5 can be unsubstituted or substituted with 1 to 4 groups independently selected from amino, halogen, haloC_{1-4}alkyl, hydroxyl, methoxy, methylamino, and C_{1-4}alkyl, and m is selected from 1 and 2; and

wherein when Q is N then:

R^4 is absent; and

R^5 is hydrogen;

R^6 and R^7 are independently selected from halogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl and hydroxyl provided that when Q is N then R^6 or R^7 are not halogen or hydroxyl;

Or, any two groups selected from R^2, R^3, R^6 and R^7 together form a one- to three-membered bridge group selected from C_{1-3}alkylene, C_{2-3}alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen and C_{1-4}alkyl;

Or, R^4 and R^7 form a four- to six-membered ring containing a N atom;

Or, R^5 and R^7 form a three- to six-membered ring;

Or, R^6 and R^7 form a direct bond;

a is selected from 0, 1 and 2;

b is selected from 0, 1 and 2;

c is selected from 0, 1 and 2;

Or, Q is C, c is 2, R^4 is hydrogen and the two R^7 join to form a 4 to 6 membered nitrogen containing ring;

Ring A is either:

(i) a five-membered nitrogen-containing heterocyclic ring wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S, or

(ii) a six-membered aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S; or

(iii) a six-membered non-aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N and S;

R^8 is selected from hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl and halogen;

R^9 is selected from hydrogen and halogen;

R^{10} is selected from haloC_{1-4}alkyl, C_{1-4}alkyl, halogen, hydrogen or C_{1-4}alkoxy;

R^{11} are independently selected from halogen, cyano, cyanoC_{1-4}alkyl, hydroxyl, oxo (=O), C_{1-4}alkyl optionally substituted with five- or six-membered heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxylC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulfone, amino, monoC_{1-4}alkylamino,

diC_{1-4}alkylamino, aminoC_{1-4}alkyl, -C_{1-4}alkylene-C(=O)$NH_{(2-q)}(C_{1-6}alkyl)_q$), -$C_{1-4}$ alkylene-NHC(=O)C_{1-6}alkyl, sulfonamide, sulfonamideC_{1-4}alkyl, 3 to 6 membered cycloalkyl, C_{1-4}alkyl substituted with 3 to 6 membered cycloalkyl, five- or six-membered unsaturated heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, N, or S, and optionally substituted four- to six-membered saturated heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S where the optional substituent is selected from C_{1-4}alkyl;

q is selected from 0, 1 or 2; and

d is selected from 0, 1 and 2.

[0014] Item 2. A compound according to item 1 or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a five-membered or six-membered nitrogen-containing heteroaromatic ring wherein the ring optionally contains one or two additional heteroatoms selected from N, O and S.

[0015] Item 3. A compound according to item 1 or 2, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein any two groups selected from R^2, R^3, R^6 and R^7 together form a one- to three-membered bridge group selected from C_{1-3}alkylene, C_{2-3}alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen and C_{1-4}alkyl.

[0016] Item 4. A compound according to any one of items 1 to 3, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein

Q is C.

[0017] Item 5. A compound according to any one of items 1 to 4, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein

R^4 is amino, aminoC_{1-4}alkyl or monoC_{1-4}alkylamino;

R^5 is hydrogen, C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl or C_{1-4} alkoxyC_{1-4}alkyl

[0018] Item 6. A compound according to any one of items 1 to 4, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein

R^4 and R^5 together with Q form a four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, S, NH, C(O) and $S(O)_m$, and said ring formed by R^4 and R^5 can be unsubstituted or substituted with 1 to 4 groups independently selected from amino, halogen, haloC_{1-4}alkyl, hydroxyl, methoxy, methylamino, and C_{1-4}alkyl, and m is selected from 1 and 2

[0019] Item 7. A compound according to any one of items 1 to 5, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein Q is N.

[0020] Item 8. A compound according to any one of items 1 to 7, or a tautomer or a solvate

or a pharmaceutically acceptable salt thereof, wherein X is CH.

[0021] Item 9. A compound according to any one of items 1 to 7, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein X is N.

[0022] Item 10. A compound according to item 1, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-amino-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-Amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(2-(tert-butyl)-4-chloro-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

(R)-2-(1-amino-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

(S)-2-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-

3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(hydroxymethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(2-hydroxyethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(2,5-diazabicyclo[2.2.2]octan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl

)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,8-diazaspiro[4.5]decan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(piperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,7-diazabicyclo[4.2.0]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,9-diazaspiro[5.5]undecan-9-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,7-diazaspiro[3.5]nonan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,4R)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-amino-3,3-difluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-met

hyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4R)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4S)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-amino-3-(hydroxymethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(1-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-methoxypiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-methyl-5-(2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6,7-difluoro-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-methoxy-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-1-methyl-1H-benzo[d][1,

2,3]triazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-(2-hydroxy-2-methylpropyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2,7-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(1H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
3-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(6-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-7-chlorobenzo[d]thiazol-2-yl)-N,N-dimethylacetamide,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-i

ndazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2,3-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-methoxy-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-(fluoromethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-3-(difluoromethyl)-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-(hydroxymethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(4-chloro-2-ethyl-2H-indaz

ol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-met

hyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,4S,7S)-7-(methylamino)-2-azabicyclo[2.2.1]heptan-2-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
endo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{3,8-diazabicyclo[3.2.1]octan-8-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R,3S)-1-amino-3-hydroxy-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
exo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{2,7-diazaspiro[3.5]nonan-7-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R)-1-amino-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R,3R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2

H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-(1,4-diazepan-1-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-[(1R,2R,5R)-2-amino-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-(4-aminoazepan-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2-ethyl-2H-indazole-3-carbonitrile,
6-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((3R,4S)-4-amino-3-fluoropiperidin-1-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(rac-(1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,2S,4R)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-5-(3,4,7-trichloro-2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-methoxyquinox

alin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-(dimethylamino)quinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
6-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-6-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(5-chloroquinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(ethylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-(2-methoxyethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(isopropylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-4-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(7-chloro-2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(endo)-3-amino-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(3R,4S)-4-amino-3-fluoropiperidin-1-yl]-5-(7-chloro-1,3-benzothiazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1S,6R)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-

3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1R,5R)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1S,5S)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1S,5R)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1R,5S)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one
,
2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-7-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(endo)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
Rac-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{2,6-diazaspiro[3.4]octan-6-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one, and
2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one.

[0023] Item 11. A pharmaceutical composition comprising a compound according to any one of items 1 to 10 and a pharmaceutically acceptable carrier.

[0024] Item 12. A pharmaceutical composition according to item 11 for the prophylaxis or treatment of a disease or condition mediated by SHP2.

[0025] Item 13. A compound according to any one of items 1 to 10 for use in therapy.

[0026] Item 14. A compound according to any one of items 1 to 10 for use in the prophylaxis or treatment of a disease or condition mediated by SHP2.

[0027] Item 15. A use of a compound according to any one of items 1 to 10 for the manufacture of a medicament for use in the prophylaxis or treatment of a disease or condition mediated by SHP2.

[0028] Item 16. A method for the prophylaxis or treatment of a disease or condition mediated by SHP2 comprising administering to a patient a compound according to any one of items 1 to10.

[0029] Item 17. A pharmaceutical composition of items 11 and 12, a compound of items 13

and 14, a use of item 15 or a method of item 16, wherein the subject of therapy or the disease or condition mediated by SHP2 is cancer.

[0030] It is understood that "a compound" in a pharmaceutical composition, a compound, a use or a method of items 11 to 17 encomapsses a tautomer or a solvate or a pharmaceutically acceptable salt of the corresponding compound.

[0031] rac-2-[(1R,2R,5R)-2-amino-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one, herein referred as Compound 152, which is outside the scope of Item 1, can be independently claimed as a compound or a tautomer or a solvate or a pharmaceutically acceptable salt thereof. A pharmaceutical composition, a compound, a use or a method wherein Compound 152 is comprised, used or administered can be claimed similarly as Items 11 to 17.

Advantageous Effects of Invention

[0032] It has been revealed that the compound of the formula (I) or a tautomer or a solvate or a pharmaceutically acceptable salt thereof has excellent SHP2 inhibitory activity. Therefore, the compound of the present invention or a derivative thereof is useful as an agent for preventing and/or treating SHP2 mediated diseases such as cancer.

[0033] The compound of the formula (I) or a tautomer or a solvate or a pharmaceutically acceptable salt thereof have superior properties in some aspects, for example, potency, selectivity, pharmacokinetics e.g., ADME properties, oral bioavailability, ability to cross the blood brain barrier, duration of action, physicochemical properties, hERG activity, QT prolongation, etc.

Description of Embodiments

[0034] The compound represented by Formula (I) of the present invention is a novel pyrrolopyrimidone or pyrazolopyrimidone compound comprising (i) a monocyclic, bicyclic, bridged cyclic or spirocyclic nitrogen-containing saturated five to seven-membered heterocyclic group and (ii) an aromatic or non-aromatic fused ring containing a benzo- ring, and a five or six-membered nitrogen containing heterocyclic ring.

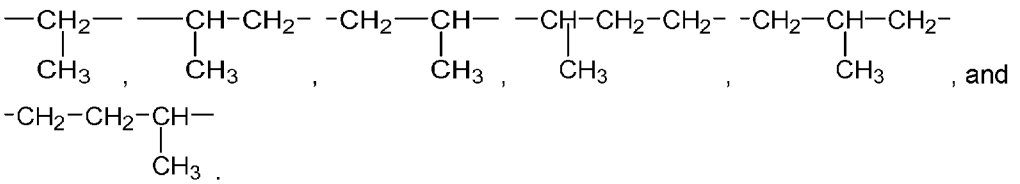
[0035] In the present specification, * represents a bonding position, unless otherwise specified.

[0036] In the present specification, examples of the "halogen" include fluorine, chlorine, bromine, iodine, and the like, with fluorine, chlorine, bromine, or iodine being preferable, and fluorine or chlorine being more preferable.

[0037] In the present specification, the "alkyl" may be straight or branched. Examples of C_{1-6} alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, tert-pentyl, and n-hexyl. Examples of C_{1-4}alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

[0038] In the present specification, "alkylene" is a divalent group where one hydrogen is removed from above-listed alkyl groups. Examples of C_{1-4}alkylene include straight C_{1-4} alkylene such as methylene, ethylene, propylene, butylene, and branched C_{1-4}alkylene such as

[0039] [Chem.2]



[0040] In the present specification, "heterocyclic ring" includes any monocyclic or polycyclic, saturated or unsaturated ring system comprising carbon atoms and at least one hetero atom. "heterocyclic ring" covers aromatic and non-aromatic groups.

[0041] In the present specification, examples of "C_{2-3}alkenylene" include vinylene and allylene.

[0042] In the present specification, the "3 to 6 membered cycloalkyl"includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0043] In the present specification, "aminoC_{1-4}alkyl" is the above-listed straight or branched C_{1-4} alkyl having one amino group and refers to a group represented by -C_{1-4} alkylene-NH_2. Examples include -methylene-amino, -ethylene-amino, -propylene-amino, -butylene-amino, and the like.

[0044] Examples of "monoC_{1-4}alkylamino" include amino monosubstituted with straight or branched C_{1-4}alkyl, such as methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert-butylamino, and the like.

[0045] Examples of "diC_{1-4}alkylamino" include amino disubstituted with the same or different straight or branched C_{1-4}alkyl groups, such as dimethylamino, diethylamino, di(n-propyl)amino, diisopropylamino, di(n-butyl)amino, diisobutylamino, di(tert-butyl)amino, and the like.

[0046] In the present specification, examples of the "hydroxyC_{1-4}alkyl" include the above-listed straight or branched alkyl groups that have at least one hydroxy group (e.g., one or two hydroxy groups). Specific examples include hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-methyl-2-hydroxyethyl, 4-hydroxybutyl, 2,2-dimethyl-2-hydroxyethyl, and the like, with hydroxyalkyl having one hydroxy group being preferable.

[0047] In the present specification, the "C_{1-4}alkoxy" refers to oxy(-O-) to which the above-listed straight or branched C_{1-4}alkyl is bonded. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy etc.

[0048] In the present specification, examples of the "cyanoC_{1-4}alkyl" include the above-

listed straight or branched C_{1-4}alkyl groups that have at least one cyano group (e.g., one or two cyano groups). Specific examples include cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl, 2-cyanopropyl, 1-methyl-2-cyanoethyl, 4-cyanobutyl, 2,2-dimethyl-2-cyanoethyl, and the like, with cyanoalkyl having one cyano group being preferable.

[0049] In the present specification, the "haloC_{1-4}alkyl" is the above-listed straight or branched C_{1-4} alkyl having 1 to 7 halogen atoms (halogeno C_{1-4}alkyl). Examples include fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, fluoroethyl, 1,1,1-trifluoroethyl, monofluoro-n-propyl, perfluoro-n-propyl, and perfluoroisopropyl.

[0050] In the present specification, "C_{1-4}alkoxyC_{1-4}alkyl" is the above-listed straight or branched C_{1-4} having one of the above listed C_{1-4}alkoxy and refers to a group represented by -C_{1-4}alkylene-C_{1-4}alkoxy (-C_{1-4}alkylene-O-C_{1-4}alkyl). Examples of C_{1-4} alkylene, C_{1-4}alkoxy and C_{1-4}alkyl are above listed.

[0051] In the present specification, "C_{1-4}alkylsulfone" refers to a group represented by -SO_2 -C_{1-4}alkyl. Examples include methylsulfone, ethylsulfone, propylsulfone, butylsulfone, and the like.

[0052] In the present specification, examples of "-C_{1-4}alkylene-C(=O)$NH_{(2-q)}$(C_{1-6}alkyl)$_q$)" wherein q is an integer of 0, 1 or 2, include -C_{1-4}alkylene-C(=O)NH_2, -C_{1-4} alkylene-C(=O)NH(C_{1-6}alkyl), and -C_{1-4}alkylene-C(=O)N(C_{1-6}alkyl)$_2$. Examples of C_{1-4}alkylene and C_{1-6}alkyl are above listed.

[0053] In the present specification, "-C_{1-4}alkylene-NHC(=O)C_{1-6}alkyl," refers to a group where the above-mentioned C_{1-4}alkylene and C_{1-6}alkyl, are joined by an amide bond (-NHC(=O)-). Examples of C_{1-4}alkylene and C_{1-6}alkyl are above listed.

[0054] In the present specification,"sulfonamideC_{1-4}alkyl" refers to a group represented by -C_{1-4}alkylene-SO_2-NH_2. Examples include -SO_2-NH_2, -methylene-SO_2-NH_2, -ethylene-SO_2-NH_2, -propylene-SO_2-NH_2, -butylene-SO_2-NH_2, and the like.

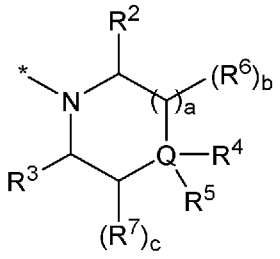
[0055] In the compound represented by formula (I) of the present invention, X represents CH or N. When X represents CH, the compound represented by formula (I) is a pyrrolopyrimidone compound, and when X represents N, the compound represented by formula (I) is a pyrazolopyrimidone compound.

[0056] In the compound represented by formula (I) of the present invention, R^1 represents methyl (-CH_3).

[0057] In the compound represented by formula (I) of the present invention, the following portion (hereafter refered to as portion Z):

[0058]

[Chem.3]



(Z)

[0059] wherein Q, R^2, R^3, R^4, R^5, R^6 and R^7, a, b and c are as defined above;

is a monocyclic, bicyclic, bridged cyclic or spirocyclic nitrogen-containing saturated heterocyclic group.

[0060] In the compound represented by formula (I) of the present invention, R^2 and R^3 independently represent any one selected from hydrogen and C_{1-4}alkyl.

[0061] In the compound represented by formula (I) of the present invention, R^6 and R^7 independently represent any one selected from halogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, and hydroxyl. When Q is N, then R^6 or R^7 do not represent halogen or hydroxyl, thus represents C_{1-4}alkyl.

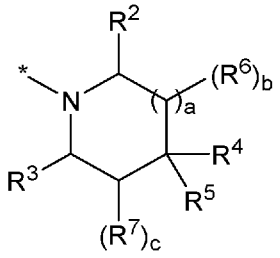
[0062] In the compound represented by formula (I) of the present invention, Q represents C or N.

[0063] In one embodiment when Q represents C, R^4 is amino, aminoC_{1-4}alkyl or monoC_{1-4} alkylamino;

R^5 is hydrogen, C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl or C_{1-4} alkoxyC_{1-4}alkyl. In one embodiment when R^4 is amino then R^5 is selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4} alkyl.

[0064] In such embodiment, the portion Z is a monocyclic nitrogen-containing saturated five to seven-membered heterocyclic group containing one nitrogen, represented by the formula below:

[0065] [Chem.4]



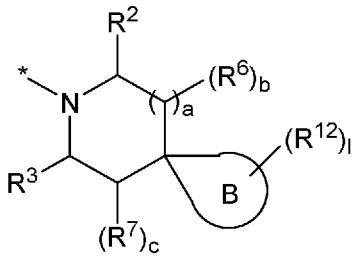
[0066] wherein R^2, R^3, R^4, R^5, R^6 and R^7, a, b and c are as defined above;

[0067] In another embodiment when Q represents C, R^4 and R^5 together with Q form a four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups inde-

pendently selected from N, O, S, NH, C(O) and $S(O)_m$, and said ring formed by R^4 and R^5 can be unsubstituted or substituted with 1 to 4 groups independently selected from amino, halogen, haloC_{1-4}alkyl, hydroxyl, methoxy, methylamino, C_{1-4}alkyl, and m is selected from 1 and 2.

[0068] In such embodiment, the portion Z is a spirocyclic nitrogen-containing saturated heterocyclic group containing eight to twelve members including Q, one to four among the members being nitrogen, and one to four among the members optionally being identical or different heteroatoms selected from oxygen, and sulfur. In such embodiment, the portion Z is represented by the formula below:

[0069] [Chem.5]



[0070] wherein R^2, R^3, R^6, R^7, a, b and c are as defined above;

wherein Ring B is a saturated four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, S, NH, C(O) and $S(O)_m$,

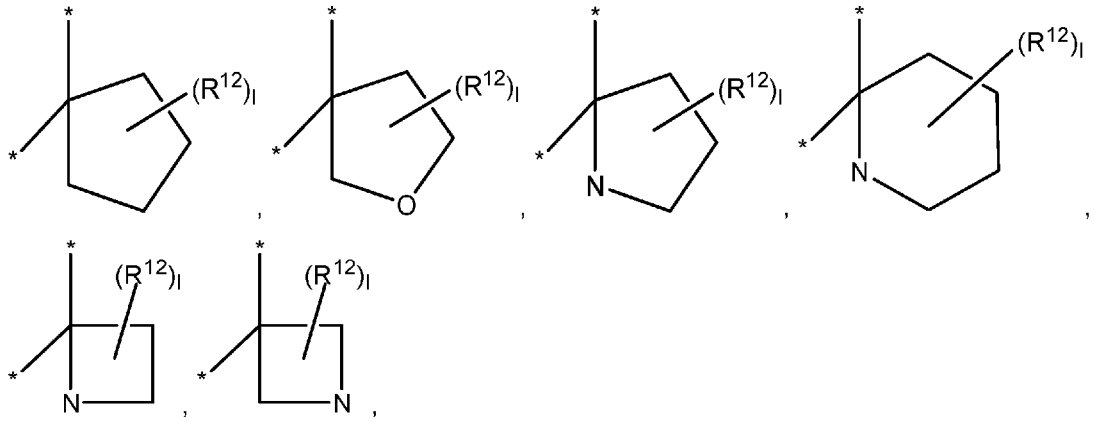
R^{12} is independently selected from amino, halogen, haloC_{1-4}alkyl, hydroxyl, methoxy, methylamino, C_{1-4}alkyl,

l is a integer selected from 0, 1, 2, 3 and 4,

m is a integer selected from 1 and 2.

[0071] Examples of the four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, C(O) and $S(O)_m$ include

[0072] [Chem.6]

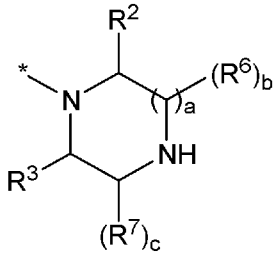


[0073] wherein R^{12} and l are as defined above.

[0074] In one embodiment when Q represents N, then R^4 is absent and R^5 is hydrogen.

In such embodiment, the portion Z may be represented by the formula below:

[0075] [Chem.7]



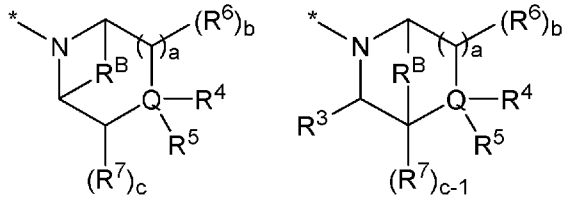
[0076] wherein R^2, R^3, a, b and c are as defined above; R^6 and R^7 independently selected from hydroxyC_{1-4}alkyl and C_{1-4}alkyl, provided a is not zero;

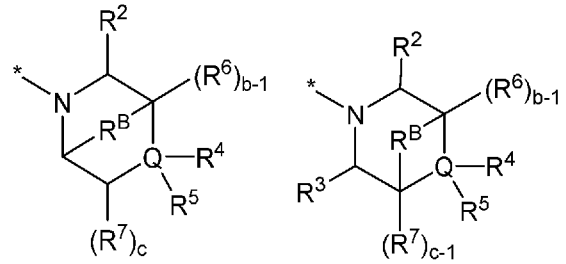
and is a monocyclic nitrogen-containing saturated five to seven-membered hetero-rocyclic group containing two nitrogen.

[0077] In the compound represented by formula (I) of the present invention, R^2, R^3, R^6 and R^7 may alternatively have the following structure wherein any two groups selected from R^2, R^3, R^6 and R^7 together form a one- to three-membered bridge group selected from C_{1-3}alkylene, C_{2-3}alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen, and C_{1-4}alkyl.

[0078] Examples of such embodiment includes the portion Z being represented by any one of the formulas below:

[0079] [Chem.8]





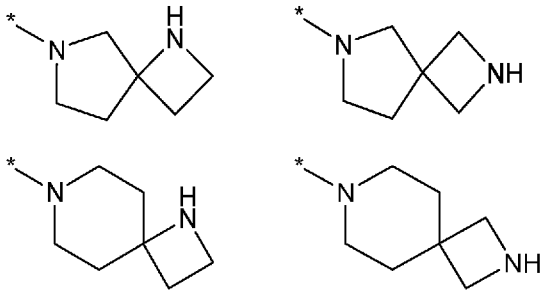
[0080] wherein Q, R^2, R^3, R^4, R^5, R^6 and R^7, a, b and c are as defined above, , with the provisio that in the formulas containing "b-1" and/or "c-1", "b-1" (can be refered to as b') and "c-1" (can be refered to as c') are independently selected from 0 and 1.

[0081] R^B represents a one- to three-membered bridge group selected from straight C_{1-3}

alkylene, C_{2-3}alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen and C_{1-4}alkyl.

[0082] In another embodiment of the compound represented by formula (I) of the present invention, Q is C, c is 2, R^4 is hydrogen and the two R^7 join to form a 4 to 6 membered nitrogen containing ring. Examples of such embodiment includes the portion Z being represented by any one of the formulas below:

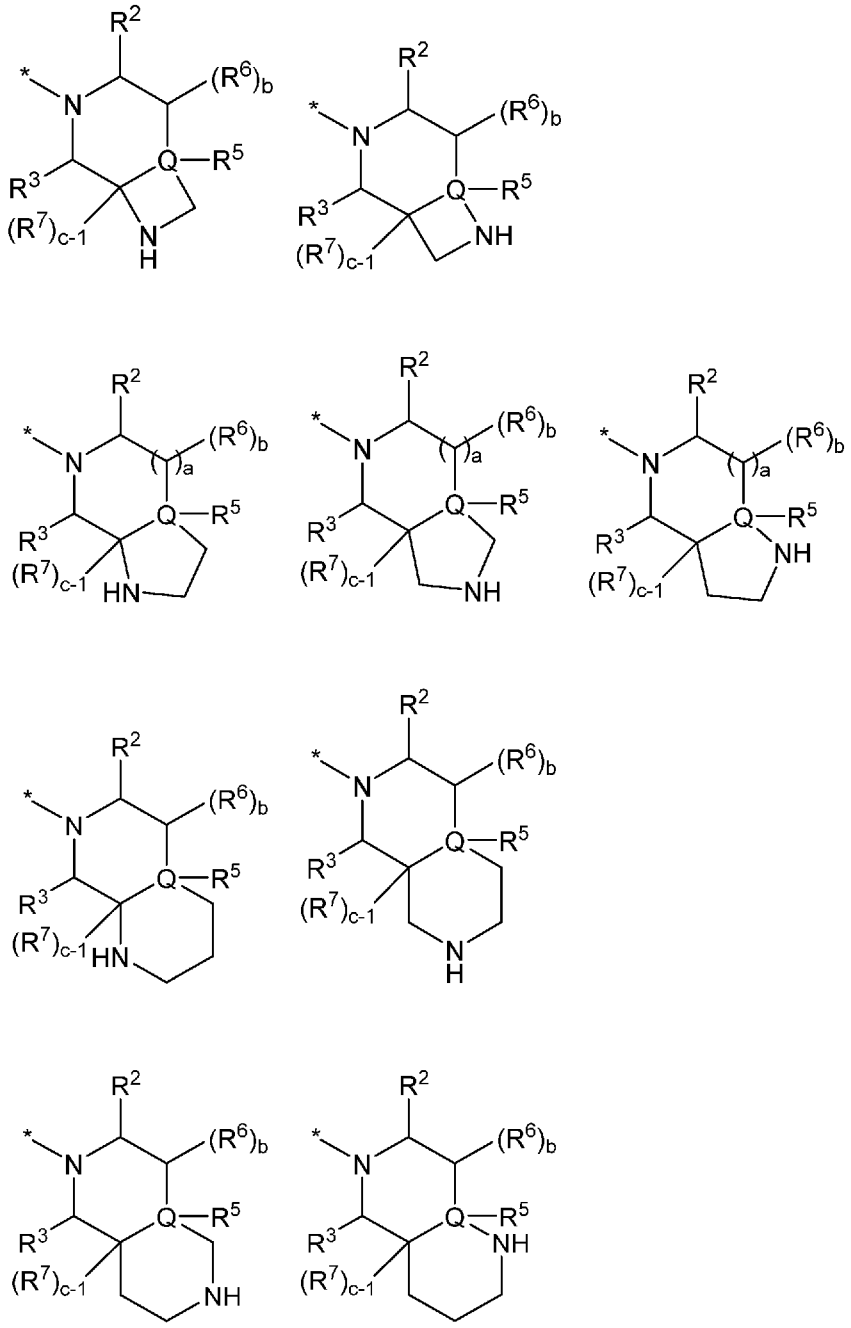
[0083] [Chem.9]



[0084] In the compound represented by formula (I) of the present invention, R^4 and R^7 may alternatively form a four- to six-membered ring containing one N atom. Examples of such embodiment where includes the portion Z being represented by any one of the formulas below:

[0085]

[Chem.10]

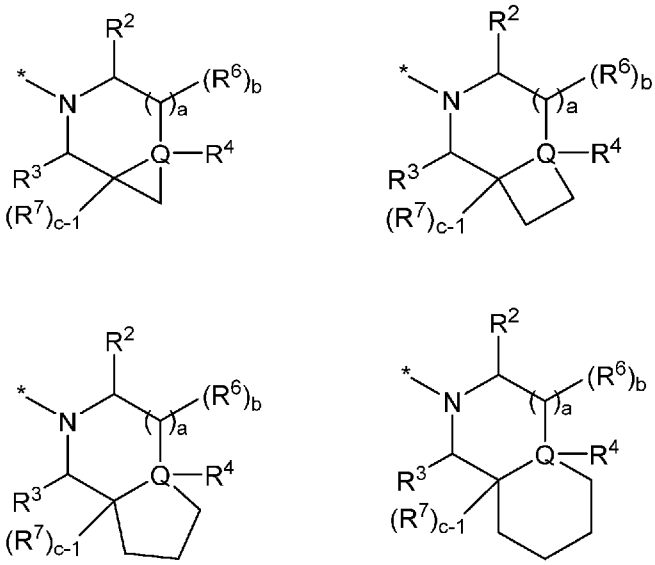


[0086] wherein Q, R^2, R^3, R^5, R^6 and R^7, a, b and c are as defined above, with the provisio that "c-1" (can be refered to as c') is selected from 0 and 1.

[0087] In the compound represented by formula (I) of the present invention, R^5 and R^7 may alternatively form a three- to six-membered ring. Examples of such embodiment includes the portion Z being represented by any one of the formulas below:

[0088]

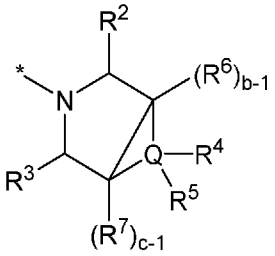
[Chem.11]



[0089] wherein Q, R^2, R^3, R^4, R^6 and R^7, a, b and c are as defined above, with the provisio that "c-1" (can be refered to as c') is selected from 0 and 1.

[0090] In one alternative embodiment, R^6 and R^7 alternatively form a direct bond. Examples of such embodiment includes the portion Z being represented by formula below:

[0091] [Chem.12]



[0092] wherein Q, R^2, R^3, R^4, R^5, R^6, R^7, b and c are as defined above, with the provisio that "b-1" (can be refered to as b') and "c-1" (can be refered to as c') are independently selected from 0 and 1.

[0093] In the compound represented by formula (I), a is an integer selected from 0, 1 and 2.

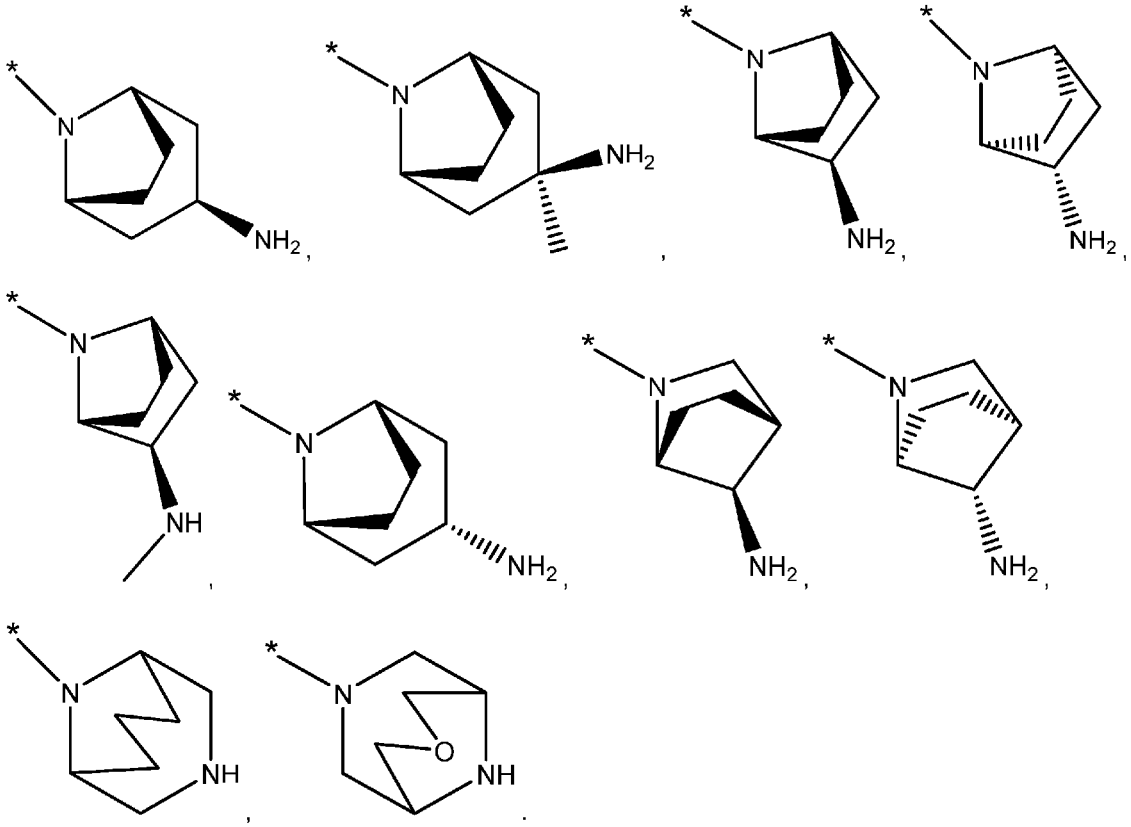
[0094] In the compound represented by formula (I), b is an integer selected from 0, 1 and 2.

[0095] In the compound represented by formula (I), c is an integer selected from 0, 1 and 2;

[0096] Preferable embodiments includes the portion Z being represented by any one of the formulas below:

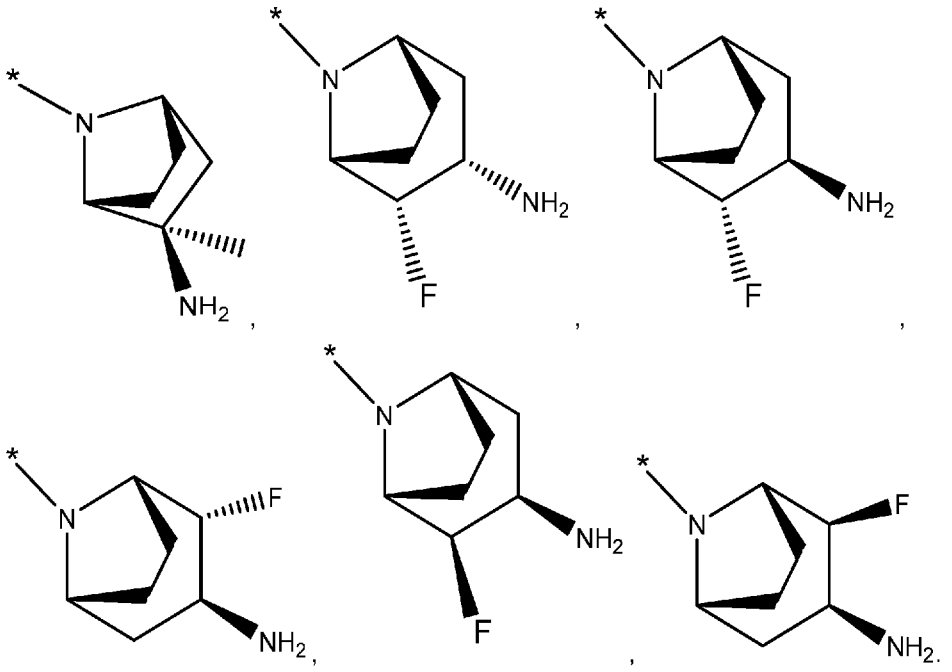
[0097]

[Chem.13]



[0098] Another preferable embodiments includes the portion Z being represented by any one of the formulas below:

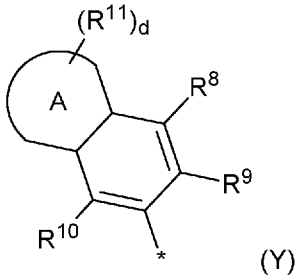
[0099] [Chem.14]



[0100] In the compound represented by formula (I) of the present invention, the following

portion (hereafter refered to as portion Y):

[0101] [Chem.15]



(Y)

[0102] wherein Ring A, R^8, R^9, R^{10}, R^{11} and d are as defined above;

is an aromatic or non-aromatic fused ring containing a benzo- ring, and a five or six-membered nitrogen containing hetetocyclic ring.

[0103] In the compound represented by formula (I), Ring A represented below

[0104] [Chem.16]



[0105] forms, together with the benzo- ring to which this group is bonded, a five or six-membered nitrogen containing heterocyclic ring.

[0106] Specifically, Ring A is either:

(i) a five-membered nitrogen-containing heterocyclic ring wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S, or

(ii) a six-membered aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S; or

(iii) a six-membered non-aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N and S.

[0107] The five-membered nitrogen-containing heterocyclic ring wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S may be afive-membered aromatic nitrogen-containing heterocyclic ring or a five-membered non-aromatic nitrogen-containing heterocyclic ring. Such heterocyclic ring contains two to four carbon atoms including the two carbon atoms that is shared with the benzo- ring to which this group is bonded, one to three nitrogen atoms, and the carbon atoms that is not shared with the benzo ring (one or two carbon atoms) replaced with an oxygen atom or a sulfur atom.

[0108] Examples of five-membered aromatic nitrogen-containing heterocyclic rings include

pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, and the like.

[0109] Examples of five-membered non-aromatic nitrogen-containing heterocyclic rings include pyrrolidine, pyrazolidine, triazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and the like.

[0110] The six-membered aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S. Such heterocyclic ring contains two to five carbon atoms including the two carbon atoms that is shared with the benzo- ring to which this group is bonded, one to three nitrogen atoms, and the carbon atoms that is not shared with the benzo- ring (one, two or three carbon atoms) replaced with an oxygen atom or a sulfur atom.

[0111] Examples of six-membered aromatic nitrogen-containing heterocyclic ring include pyridine, pyrazine, pyrimidine, pyridazine, triazine, oxazine, thiazine, and the like.

[0112] The six-membered non-aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N and S. Such heterocyclic ring contains two to five carbon atoms including the two carbon atoms that is shared with the benzo- ring to which this group is bonded, one to three nitrogen atoms, and the carbon atoms that is not shared with the benzo- ring (one, two or three carbon atoms) replaced with a sulfur atom.

[0113] Examples of six-membered non-aromatic nitrogen-containing heterocyclic ring include piperidine, piperazine, morpholine, and the like.

[0114] In the compound represented by formula (I), R^8 represents one selected from hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl and halogen.

[0115] In the compound represented by formula (I), R^9 represents one selected from hydrogen and halogen.

[0116] In the compound represented by formula (I), R^{10} represents one selected from haloC_{1-4}alkyl, C_{1-4}alkyl, halogen, hydrogen and C_{1-4}alkoxy.

[0117] In the compound represented by formula (I), each R^{11} independently represents one selected from halogen, cyano, cyanoC_{1-4}alkyl, hydroxyl, oxo (=O), C_{1-4}alkyl optionally substituted with five- or six-membered heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxylC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulfone, amino, monoC_{1-4}alkylamino, diC_{1-4}alkylamino, aminoC_{1-4}alkyl, -C_{1-4}alkylene-C(=O)$NH_{(2-q)}$(C_{1-6}alkyl)$_q$), -C_{1-4}alkylene-NHC(=O)C_{1-6}alkyl, sulfonamide, sulfonamideC_{1-4}alkyl, 3 to 6 membered cycloalkyl, C_{1-4}alkyl substituted with 3 to 6 membered cycloalkyl, five- or six-membered unsaturated heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, N, or S, and optionally substituted four- to six-membered saturated heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S where the optional substituent is selected from C_{1-4}alkyl.

[0118] When R^{11} is oxo (=O), the atomic bonding between R^{11} and Ring A is a double bond. In other cases where R^{11} is a monovalent group, the atomic bonding between R^{11} and Ring A is a single bond.

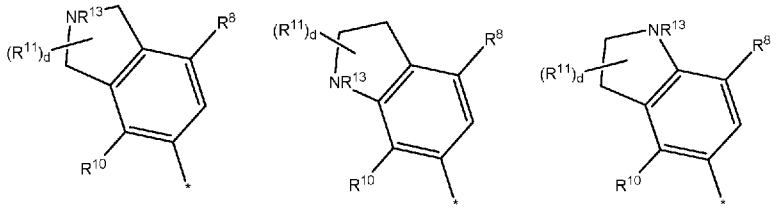
[0119] In the compound represented by formula (I), q is an integer selected from 0, 1 and 2.

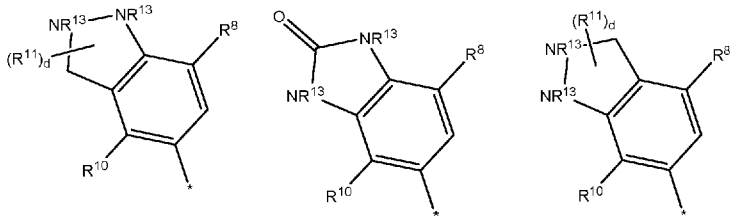
[0120] In the compound represented by formula (I), d is an integer selected from 0, 1 and 2.

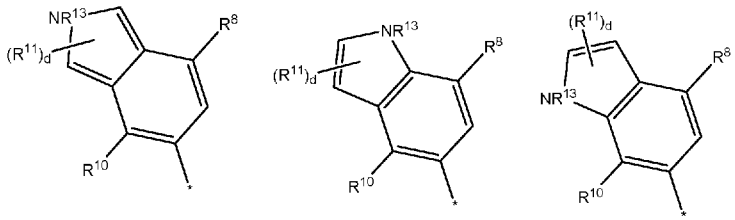
[0121] Preferable embodiments includes the portion Y being represented by any one of the formulas below:

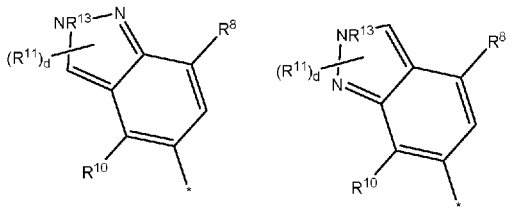
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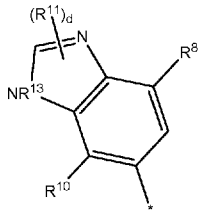
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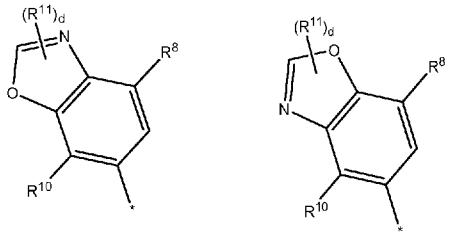
A 

B 

C 

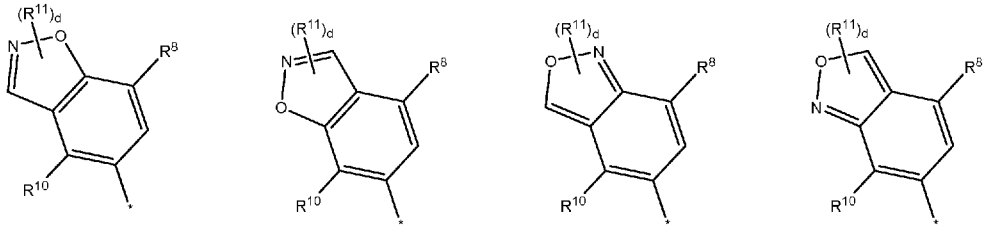
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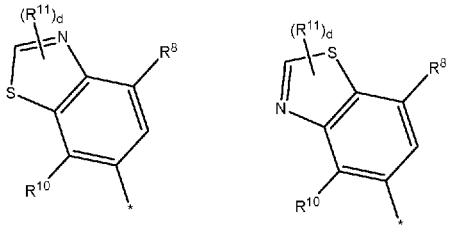
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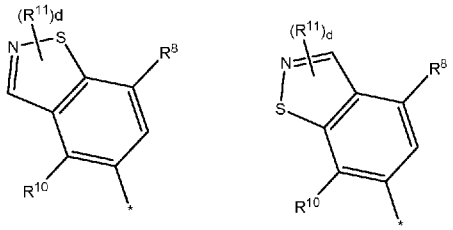
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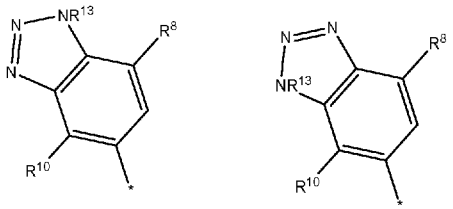
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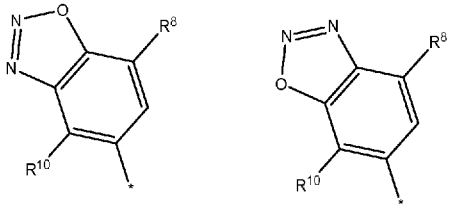
[Chem.18]

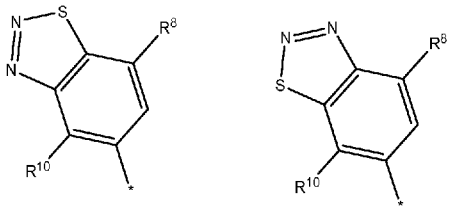
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H 

I 

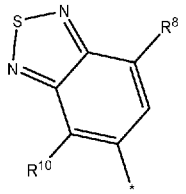
J 

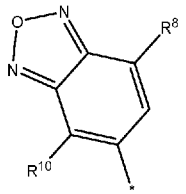
K 

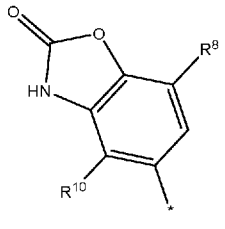
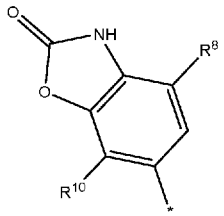
L 

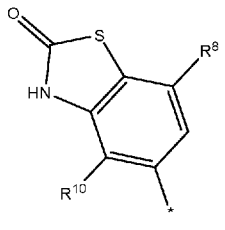
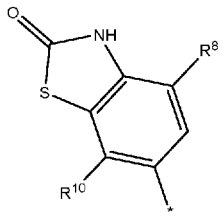
[0124]

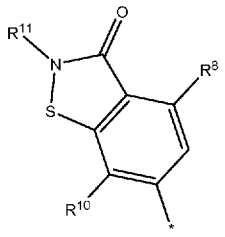
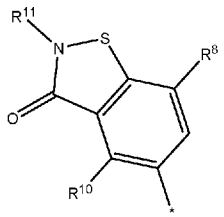
[Chem.19]

M 

N 

O  

P  

Q  

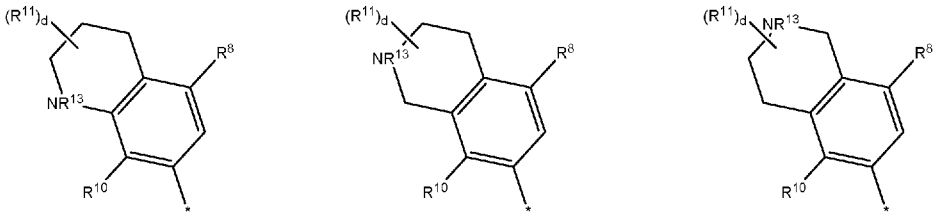
[0125] wherein R^8, R^{10}, R^{11} and d are as defined above;

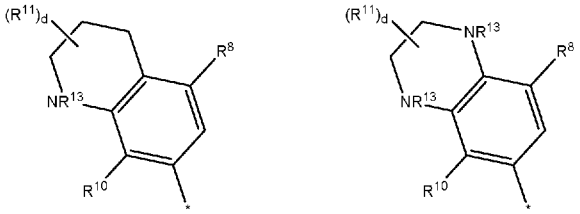
R^{13} are independently selected from hydrogen, cyano, cyanoC_{1-4}alkyl, C_{1-4}alkyl optionally substituted with five- or six-membered heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxylC_{1-4}alkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{1-4}alkylsulfone, aminoC_{2-4}alkyl, -C_{1-4}alkylene-C(=O)$NH_{(2-q)}$(C_{1-6}alkyl)$_q$), -C_{1-4}alkylene-NHC(=O)C_{1-6}alkyl , sulfoneamideC_{1-4}alkyl, 3 to 6 membered cycloalkyl, C_{1-4}alkyl substituted with 3 to 6 membered cycloalkyl, five- or six-membered unsaturated heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, N, or S, and optionally substituted four- to six-membered saturated heterocyclic group

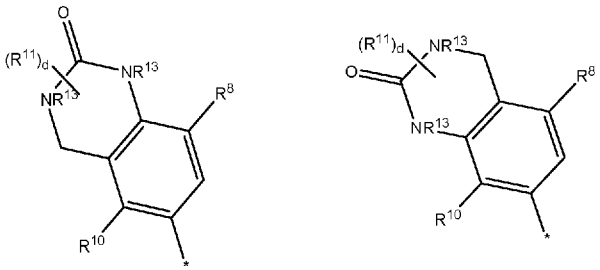
containing 1 or 2 heteroatoms selected from O, N, or S where the optional substituent is selected from C_{1-4}alkyl.

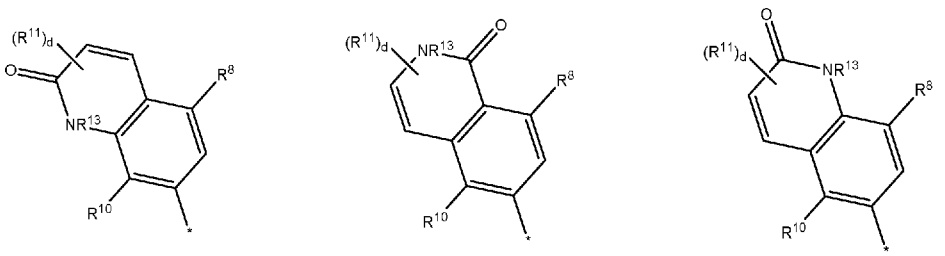
[0126] Other preferable embodiments include the portion Y being represented by any one of the formulas below:

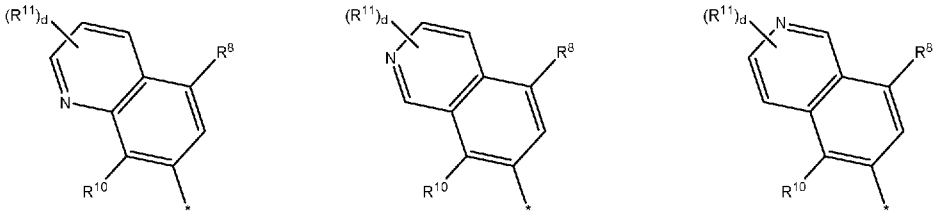
[0127] [Chem.20]

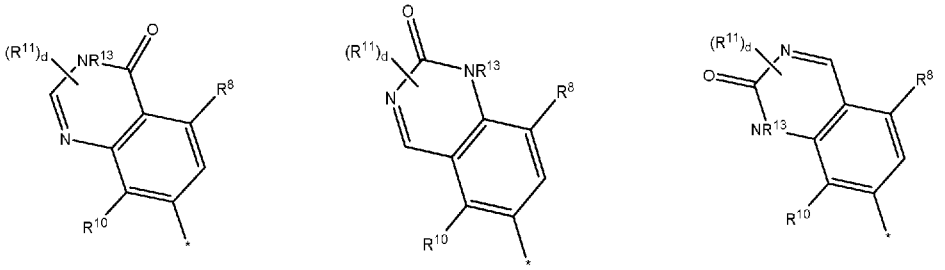
A 

B 

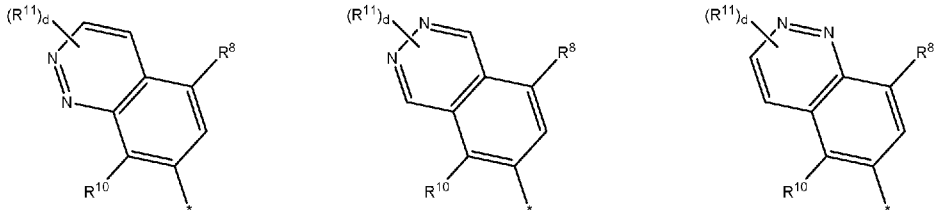
C 

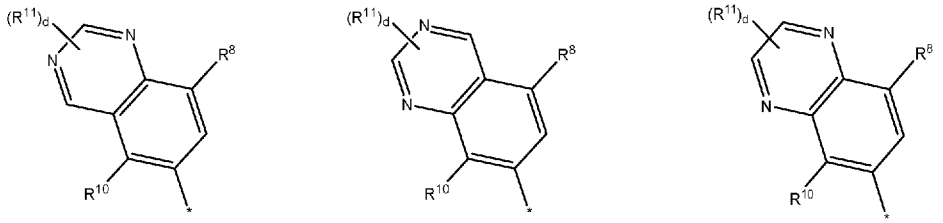
D 

E 

F 

[0128] [Chem.21]

G 

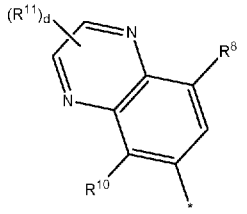
H 

[0129] wherein R^8, R^{10}, R^{11} and d are as defined above;

R^{13} are independently selected from hydrogen, cyano, cyanoC_{1-4}alkyl, C_{1-4}alkyl optionally substituted with five- or six-membered heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxylC_{1-4}alkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{1-4}alkylsulfone, aminoC_{2-4}alkyl, -C_{1-4}alkylene-C(=O)$NH_{(2-q)}$(C_{1-6}alkyl)$_q$), -C_{1-4}alkylene-NHC(=O)C_{1-6}alkyl, sulfoneamideC_{1-4}alkyl, 3 to 6 membered cycloalkyl, C_{1-4}alkyl substituted with 3 to 6 membered cycloalkyl, five- or six-membered unsaturated heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, N, or S, and optionally substituted four- to six-membered saturated heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S where the optional substituent is selected from C_{1-4}alkyl.

[0130] Other preferable embodiments include the portion Y being represented by any one of the formulas below:

[0131] [Chem.22]

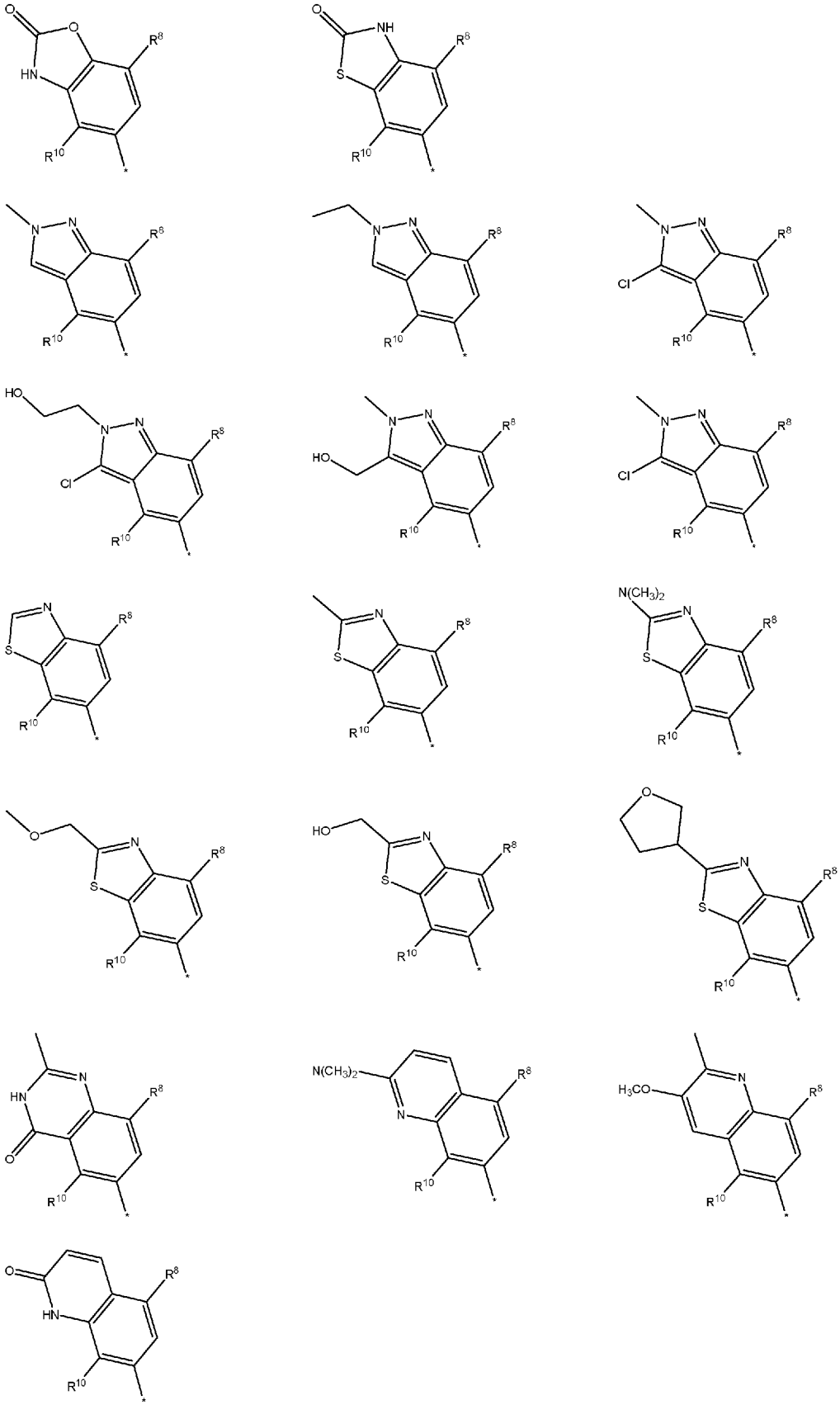
I 

[0132] wherein R^8, R^{10}, R^{11} and d are as defined above;

[0133] More preferable embodiments includes the portion Y being represented by any one of the formulas below:

[0134]

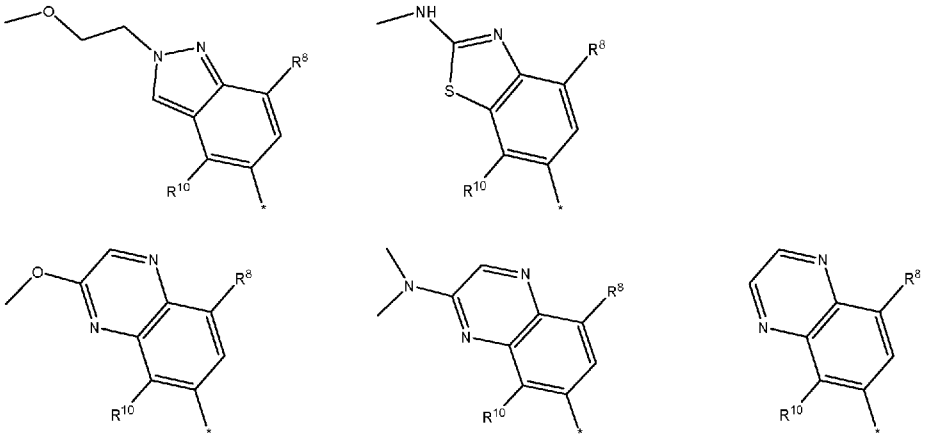
[Chem.23]



[0135] wherein R^8 and R^{10} are as defined above.

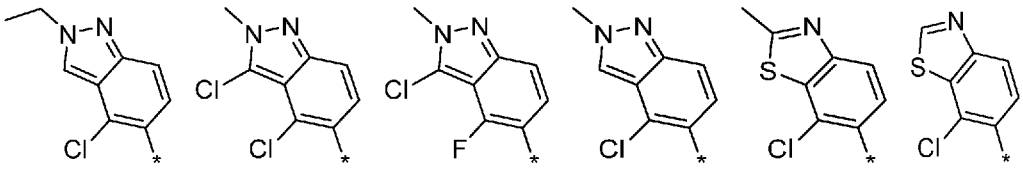
[0136] More preferable embodiments includes the portion Y being represented by any one of the formulas below:

[0137] [Chem.24]



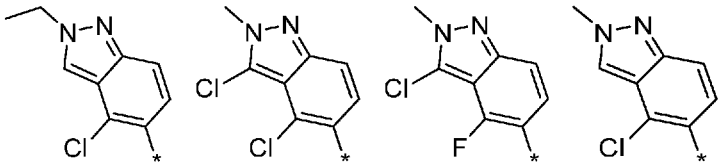
[0138] More preferable embodiments include the portion Y being represented by any one of the formulas below:

[0139] [Chem.25]



[0140] Particularly preferable embodiments include the portion Y being represented by any one of the formulas below:

[0141] [Chem.26]



[0142] The following are examples of preferable compounds of the present invention:

2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-amino-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(2-(tert-butyl)-4-chloro-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(1-amino-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(hydroxymethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(2-hydroxyethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-((1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(2,5-diazabicyclo[2.2.2]octan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,8-diazaspiro[4.5]decan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(piperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,7-diazabicyclo[4.2.0]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,9-diazaspiro[5.5]undecan-9-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,7-diazaspiro[3.5]nonan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,4R)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-amino-3,3-difluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4R)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4S)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-amino-3-(hydroxymethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(1-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-methoxypiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-methyl-5-(2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6,7-difluoro-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-methoxy-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-(2-hydroxy-2-methylpropyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2,7-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(1H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
3-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(6-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-7-chlorobenzo[d]thiazol-2-yl)-N,N-dimethylacetamide,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2,3-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-methoxy-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-(fluoromethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-3-(difluoromethyl)-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-(hydroxymethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,4S,7S)-7-(methylamino)-2-azabicyclo[2.2.1]heptan-2-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
endo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,

3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{3,8-diazabicyclo[3.2.1]octan-8-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R,3S)-1-amino-3-hydroxy-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
exo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{2,7-diazaspiro[3.5]nonan-7-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R)-1-amino-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R,3R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-(1,4-diazepan-1-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-[(1R,2R,5R)-2-amino-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-(4-aminoazepan-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

rel-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2-ethyl-2H-indazole-3-carbonitrile, .
6-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((3R,4S)-4-amino-3-fluoropiperidin-1-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(rac-(1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,2S,4R)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-5-(3,4,7-trichloro-2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-methoxyquinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-(dimethylamino)quinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
6-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

rac-6-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(5-chloroquinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(ethylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-(2-methoxyethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(isopropylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-4-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(7-chloro-2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(endo)-3-amino-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(3R,4S)-4-amino-3-fluoropiperidin-1-yl]-5-(7-chloro-1,3-benzothiazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1S,6R)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1R,5R)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1S,5S)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1S,5R)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1R,5S)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

,

2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-7-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,

2-[(endo)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,

rac-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{2,6-diazaspiro[3.4]octan-6-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,

2-[(1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,

2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one, and

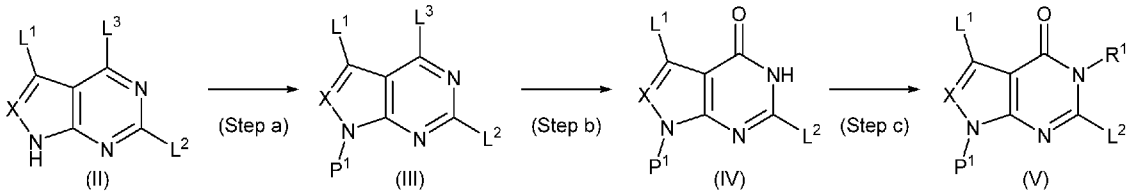
2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one.

[0143] METHODS FOR THE PREPARATION OF COMPOUNDS OF FORMULA (I)

Compounds of the formula (I) can be prepared in accordance with synthetic methods well known to the skilled person.

[0144] According to a further aspect of the invention there is provided a process for preparing a compound of formula (I), or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof, which comprises:

[0145] [Chem.27]



[0146] (wherein P^1 is a protecting group, L^1, L^2 and L^3 are leaving groups, R^1 and X are as defined above). L^1, L^2, and L^3 can be, for example, any of chrolide, bromide and iodide.

[0147] (Step a)

In this step, the compound of formula (II) is protected to produce the compound of formula (III).

[0148] The compounds of formula (II) were either commercially available, or are prepared using methods analogous to those described in the examples.

[0149] Examples of the protecting group represented by P^1 in the compound of formula (III) include ((2-trimethylsilyl)ethoxy)methyl (SEM) or tetrahydro-2H-pyran-2-yl (THP).

[0150] The process typically comprises, reacting a compound of formula (II) with ((2-trimethylsilyl)ethoxy)methylchloride (SEMCl) in a suitable solvent, a suitable base at a suitable temperature. Examples of suitable bases are sodium hydride, triethylamine or N,N-diisopropylethylamine. Examples of suitable solvents are tetrahydrofuran or

N,N-dimethylformamide. The amount of SEMCl used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (II). The amount of the base used is generally 1 to 100 moles, preferably 1 to 10 moles, per mole of the compound represented by formula (II).

[0151] The process typically comprises, reacting a compound of formula (II) with 3,4-dihydro-2H-pyran in a suitable solvent, a suitable acid at a suitable temperature. Examples of suitable acids are p-toluenesufonic acid monohydrate or camphorsulfonic acid. Examples of suitable solvents are tetrahydrofuran or methylene chloride. The amount of 3,4-dihydro-2H-pyran used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (II). The amount of the acid used is generally 0.001 to 100 moles, preferably 0.01 to 10 moles, per mole of the compound represented by formula (II).

[0152] The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 150°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 minutes to 4 days.

The thus-obtained compound of formula (III) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0153] (Step b)

In this step, the compound of formula (III) is hydroxylated to produce the compound of formula (IV).

[0154] The process typically comprises, reacting a compound of formula (III) with a suitable base in a suitable solvent at a suitable temperature. Examples of suitable base are sodium hydroxide or potassium hydroxide. Examples of suitable solvents are tetrahydrofuran, 1,2-dimethoxyethane or 1,4-dioxane with water.

[0155] The amount of the base used is usually 0.1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (III).

[0156] The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 150°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0157] The thus-obtained compound of formula (IV) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0158] (Step c)

In this step, the compound of formula (IV) is reacting with an alkylating agent such as iodomethane to produce the compound of formula (V).

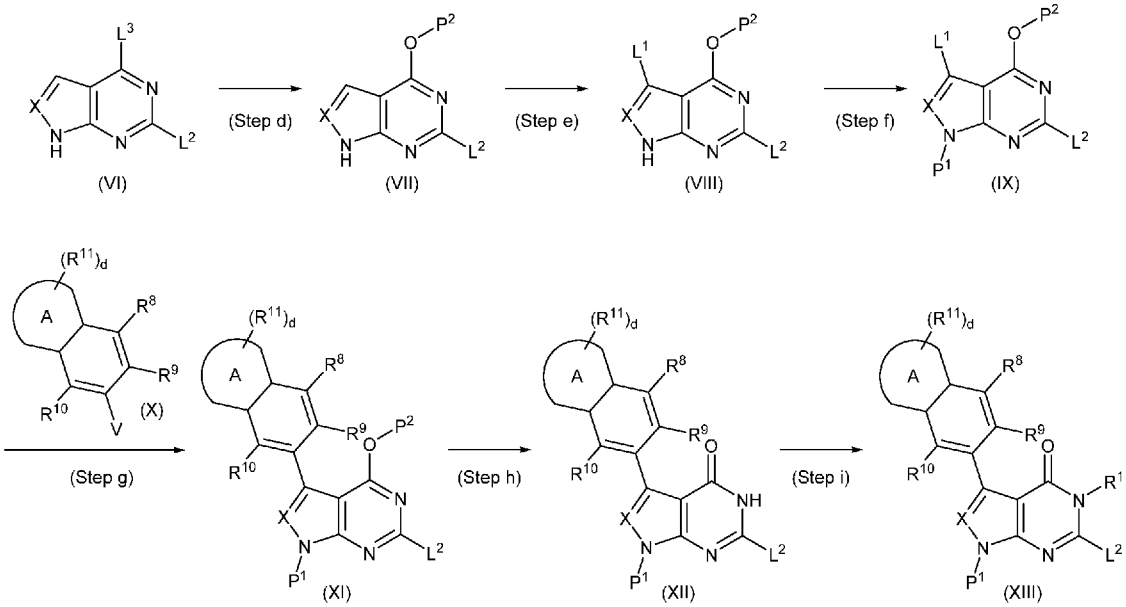
[0159] The process typically comprises, reacting a compound of formula (IV) with iodomethane and a suitable base in a suitable solvent at a suitable temperature. Examples of suitable base are potassium carbonate or cesium carbonate. Examples of suitable solvents are N,N-dimethylformamide or N-methyl-2-pyrrolidinone.

[0160] The amount of iodomethane used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (IV). The amount of the base used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (IV).

[0161] The reaction temperature generally ranges from 0 to 200°C, preferably 0 to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0162] The thus-obtained compound of formula (V) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0163] [Chem.28]



[0164] (wherein P^1, P^2 are protecting groups, L^1, L^2 and L^3 are leaving groups, V represents a metal or metaloid residue (such as boronic acid, pinacol boronate), Ring A, R^1, R^8, R^9, R^{10}, R^{11}, X and d are as defined above).

[0165] (Step d)

In this step, the compound of formula (VI) is reacting with an alcohol P^2-OH to produce the compound of formula (VII).

[0166] The compounds of formula (VI) were either commercially available, or are prepared using methods analogous to those described in the examples.

[0167] The process typically comprises, reacting a compound of formula (VI) with an alcohol such as 4-methoxybenzyl alcohol and a suitable base in a suitable solvent at a suitable temperature. Examples of suitable base are potassium tert-butoxide or sodium tert-butoxide. Examples of suitable solvents are tetrahydrofuran or 1,4-dioxane.

[0168] The amount of the alcohol used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (VI). The amount of the base used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (VI).

[0169] The reaction temperature generally ranges from 0 to 200°C, preferably 0 to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0170] The thus-obtained compound of formula (VII) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0171] (Step e)

In this step, the compound of formula (VII) is halogenated to produce the compound of formula (VIII) where L^1 is halogen.

[0172] The process typically comprises, reacting a compound of formula (VII) with a halogenating reagent in a suitable solvent at a suitable temperature. Examples of halogenating reagents are N-bromosuccinimide or N-iodosuccinimide. Examples of suitable solvents are tetrahydrofuran or N,N-dimethylformamide.

[0173] The amount of the halogenating reagent used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (VII).

[0174] The reaction temperature generally ranges from -78 to 100°C, preferably -20 to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0175] The thus-obtained compound of formula (VIII) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0176] (Step f)

This step can be performed in a similar manner as in step a.

[0177] (Step g)

In this step, the compound of formula (IX) is subjected to a coupling reaction with the compound of formula (X) to produce the compound of formula (XI).

[0178] The compounds of formula (X) were either commercially available, or are prepared using methods analogous to those described in the examples.

[0179] The process typically comprises, reacting a compound of formula (IX) with a compound of formula (X) with a suitable catalyst, a suitable base in a suitable solvent at a suitable temperature.

[0180] Examples of suitable catalysts are [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, tetrakistriphenylphosphine palladium or tris(dibenzylideneacetone)dipalladium(0) with a suitable ligand (such as triphenylphosphine, tri-tert-butylphosphine, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl). Another example of a suitable catalyst is (di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(ii). Examples of suitable base are sodium carbonate, potassium carbonate or potassium phosphate. Examples of suitable solvents are tetrahydrofuran, 1,2-dimethoxyethane or 1,4-dioxane with water).

[0181] The amount of a compound of formula (X) used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (IX). The amount of the catalyst used is usually 0.0001 to 1 moles, and preferably 0.001 to 0.5 moles, per mole of the compound represented by formula (IX). The amount of the ligand used is usually 0.0001 to 4 moles, and preferably 0.001 to 2 moles, per mole of the compound represented by formula (IX).The amount of the base used is usually 0.1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (IX).

[0182] The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 150°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0183] The thus-obtained compound of formula (XI) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0184] (Step h)

In this step, the compound of formula (XI) is deprotected to produce the compound of formula (XII).

[0185] The process typically comprises, reacting a compound of formula (XI) with 2,3-dichloro-5,6-dicyano-p-benzoquinone in a suitable solvent at a suitable temperature. Example of suitable solvent is dichloromethane.

[0186] The amount of 2,3-dichloro-5,6-dicyano-p-benzoquinone used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (XI).

The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 100°C. The reaction time generally ranges from 5 minutes to 7 days,

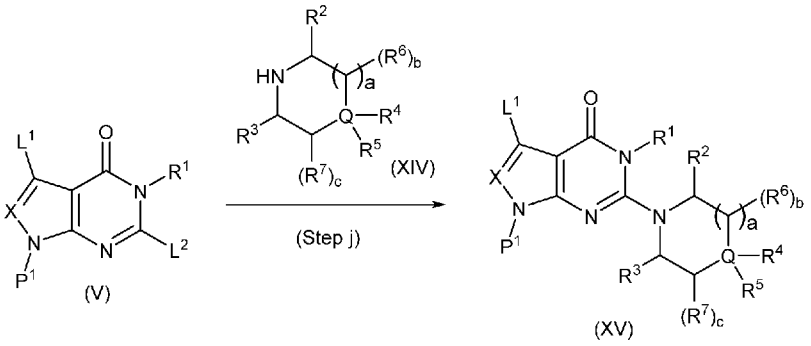
preferably 30 min to 4 days.

[0187] The thus-obtained compound of formula (XII) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0188] (Step i)

This step can be performed in a similar manner as in step c.

[0189] [Chem.29]



[0190] (wherein P^1 is a protecting group, L^1, L^2 are leaving groups, R^1, R^2, R^3, R^4, R^5, R^6, R^7, Q, X, a, b and c are as defined above).

[0191] (Step j)

In this step, the compound of formula (V) is subjected to a coupling reaction with the compound of formula (XIV) to produce the compound of formula (XV).

Optionally this is performed in the presence of an activating agent.

[0192] The compounds of formula (XIV) were either commercially available, or are prepared using methods analogous to those described in the examples.

[0193] The process typically comprises, reacting a compound of formula (V) with a compound of formula (XIV) and suitable base in a suitable solvent at a suitable temperature. Example of a suitable base is N,N-diisopropylethylamine. Examples of suitable solvents are N-methyl-2-pyrrolidinone or N,N-dimethylformamide.

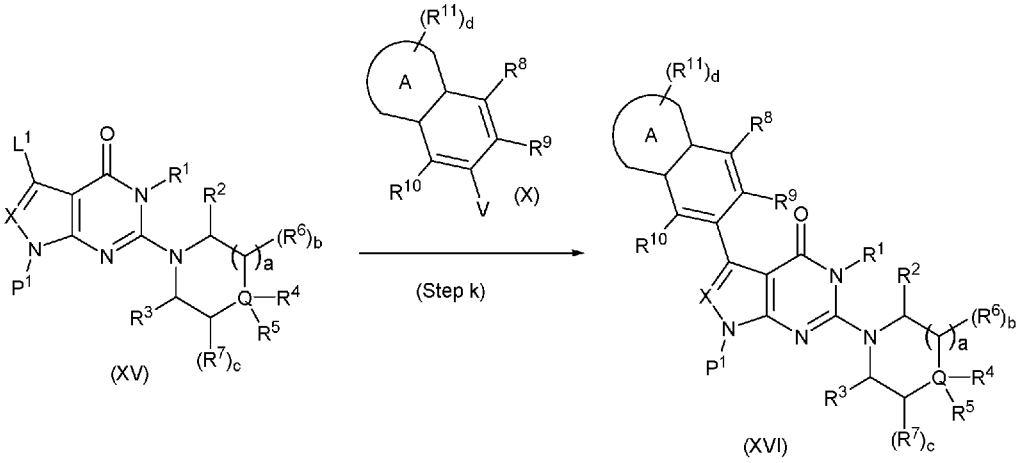
[0194] The amount of a compound of formula (XIV) used is usually 1 to 100 moles, and preferably 1 to 10 moles, per mole of the compound represented by formula (V). The amount of the base used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (V).

[0195] The reaction temperature generally ranges from room temperature to 200°C, preferably room temperature to 150°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0196] The thus-obtained compound of formula (XV) can be subjected to the subsequent step after or without isolation or purification by known separation and purification

means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0197] [Chem.30]

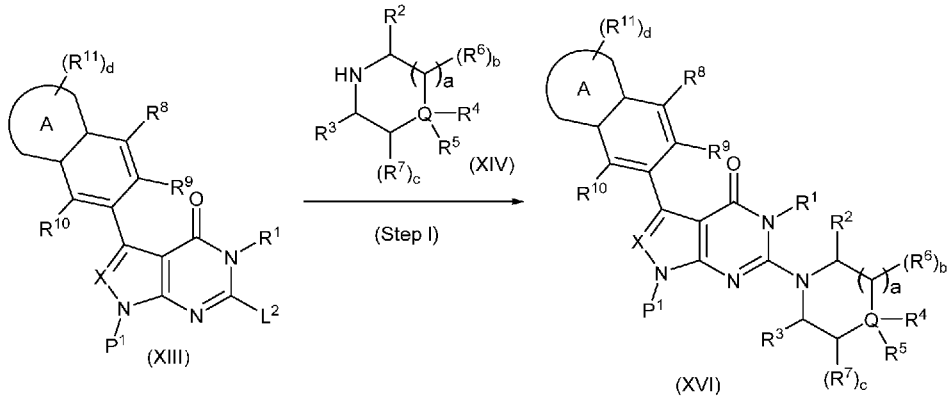


[0198] (wherein P^1 is a protecting group, L^1 is a leaving group, V represents a metal or metaloid residue (such as boronic acid or pinacol boronate), Ring A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Q, X, a, b, c and d are as defined above).

[0199] (Step k)

This step can be performed in a similar manner as in step g.

[0200] [Chem.31]



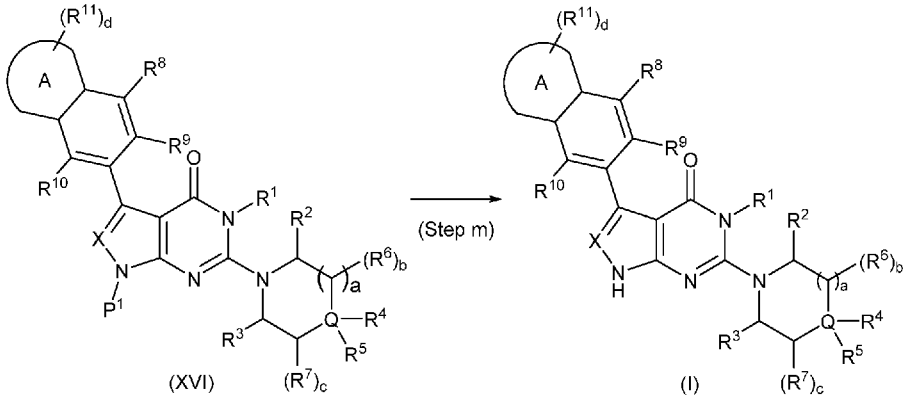
[0201] (wherein P^1 is a protecting group, L^2 is a leaving group, Ring A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Q, X, a, b, c and d are as defined above).

[0202] (Step l)

This step can be performed in a similar manner as in step j.

[0203]

[Chem.32]



[0204] (wherein P^1 is a protecting group, Ring A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Q, X, a, b, c and d are as defined above).

[0205] (Step m)

In this step, the compound of formula (XVI) is deprotected to produce the compound of formula (I).

[0206] Process typically comprises any suitable deprotection reaction, the conditions of which will depend upon the nature of the protecting group. When the protecting group P^1 represents ((2-trimethylsilyl)ethoxy)methyl group (SEM), such a deprotection reaction will typically comprise the use of a suitable acid in a suitable solvent, followed by removal of the hydroxymethyl adduct formed during the acid deprotection of the SEM protecting group with ethylenediamine or sodium hydroxide. For example, the acid may suitably comprise of trifluoroacetic acid or hydrogen chloride and the solvent may suitably comprise dichloromethane, chloroform, N,N-dimethylformamide or methanol. Optionally a mixture of solvents may be used, for example water and methanol. The second step involves concentration in vacuo, followed by dissolving the crude material in a suitable solvent such as methanol and treatment with a suitable scavenging reagent such as ethylenediamine or sodium hydroxide.

[0207] The amount of the acid used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (XVI). The amount of the scavenging reagent used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (XVI).

[0208] The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0209] Where the protecting group is a tetrahydro-2H-pyran-2-yl group (THP), a strong acid such as hydrochloric acid may be used in a suitable solvents such as methanol at a suitable temperature.

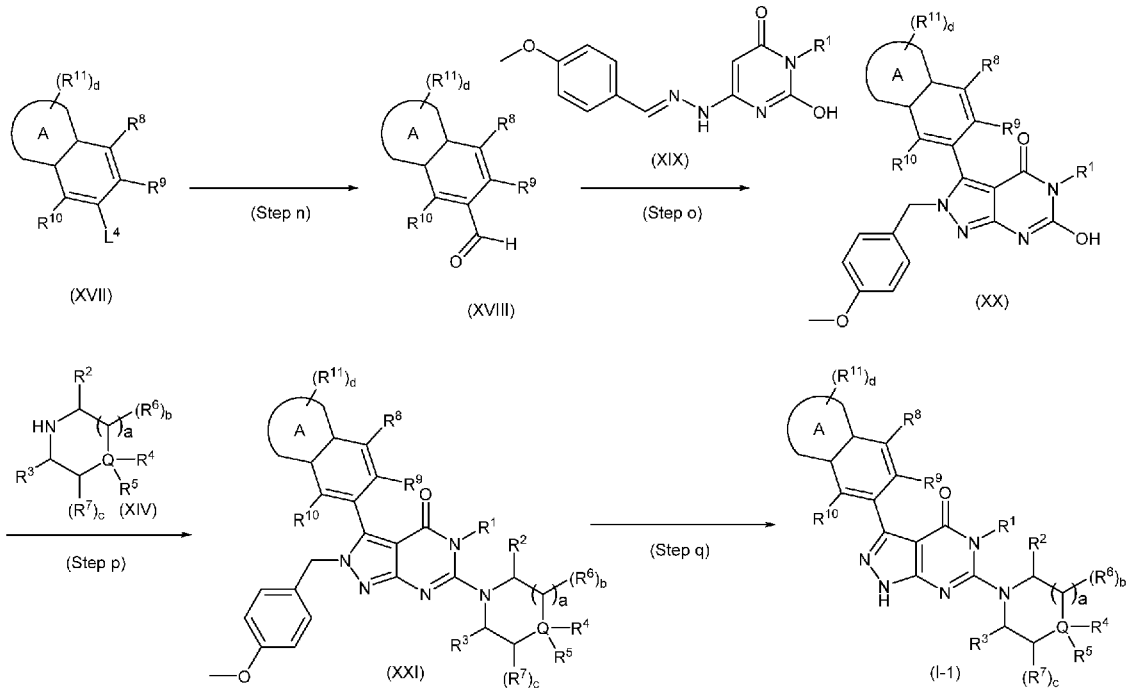
[0210] The amount of the acid used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (XVI).

[0211] The reaction temperature generally ranges from 0 to 200°C, preferably room temperature to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0212] The thus-obtained compound of Formula (I) can be isolated and purified by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0213] The deprotection may be carried out in accordance with the procedures described herein as general procedures for preparation of compounds of formula (I).

[0214] [Chem.33]



[0215] (wherein L^4 is a leaving group, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, Ring A, Q, a, b, c and d are as defined above). L^4 can be, for example, any of bromide, iodide and trifluoromethanesulfonate.

[0216] (Step n)

In this step, the compound of formula (XVII) is subjected to a formylation to produce the compound of formula (XVIII).

[0217] The process typically comprises, reacting a compound of formula (XVII) with an organometallic reagent such as i-PrMgCl and a formylating agent such as N,N-dimethylformamide in a suitable solvent at a suitable temperature. Example of a suitable solvent is tetrahydrofuran.

[0218] The amount of i-PrMgCl used is usually 1 to 10 moles, and preferably 1 to 5 moles,

per mole of the compound represented by formula (XVII). The amount of N,N-dimethylformamide used is usually 1 to 20 moles, and preferably 1 to 10 moles, per mole of the compound represented by formula (XVII).

[0219] The reaction temperature generally ranges from 0 to 100°C, preferably 0 to 60°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0220] The thus-obtained compound of formula (XVIII) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0221] (Step o)

In this step, the compound of formula (XVIII) is subjected to a cyclization reaction with the compound of formula (XIX) to produce the compound of formula (XX).

[0222] The process typically comprises, reacting a compound of formula (XVIII) and a compound of formula (XIX) with a suitable base in a suitable solvent at a suitable temperature. Example of a suitable base is piperidine. Examples of suitable solvents are N,N-dimethylformamide and isopropanol.

[0223] The amount of a compound of formula (XVIII) used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (XIX). The amount of the base used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (XIX).

[0224] The reaction temperature generally ranges from 0 to 100°C, preferably 0 to 60°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0225] The thus-obtained compound of formula (XX) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0226] Compounds of formula (XIX) are known or prepared my methods analogous to those described in the literature.

[0227] (Step p)

In this step, the compound of formula (XX) is subjected to a coupling reaction with the compound of formula (XIV) to produce the compound of formula (XXI).

[0228] The compounds of formula (XIV) were either commercially available, or are prepared using methods analogous to those described in the examples.

[0229] The process typically comprises, reacting a compound of formula (XX) with a compound of formula (XIV), an activating agent such as PyBOP and suitable base in a suitable solvent at a suitable temperature. Examples of suitable bases are DBU or

N,N-diisopropylethylamine. Examples of suitable solvents are N-methyl-2-pyrrolidinone or N,N-dimethylformamide.

[0230] The amount of a compound of formula (XVIII) used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (XX). The amount of PyBOP used is usually 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound represented by formula (XX). The amount of the base used is usually 1 to 20 moles, and preferably 1 to 10 moles, per mole of the compound represented by formula (XX).

[0231] The reaction temperature generally ranges from 0 to 100°C, preferably 0 to 60°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0232] The thus-obtained compound of formula (XXI) can be subjected to the subsequent step after or without isolation or purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0233] (Step q)

In this step, the compound of formula (XXI) is deprotected to produce the compound of formula (I-1).

[0234] The process typically comprises, reacting a compound of formula (XXI) with a suitable acid in a suitable solvent at a suitable temperature. Example of a suitable acid is trifluoromethanesulfonic acid. Examples of suitable solvents are dichloromethane or chloroform.

[0235] The amount of trifluoromethanesulfonic acid used is usually 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound represented by formula (XXI).

[0236] The reaction temperature generally ranges from 0 to 200°C, preferably 0 to 100°C. The reaction time generally ranges from 5 minutes to 7 days, preferably 30 min to 4 days.

[0237] The thus-obtained compound of Formula (I-1) can be isolated and purified by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0238] The deprotection may be carried out in accordance with the procedures described herein as general procedures for preparation of compounds of formula (I-1).

[0239] In any of the above steps, protection of a substituent, and removal or conversion of the protecting group, can be suitably performed. For example, for functional groups such as amino, imino, hydroxy, carboxy, carbonyl, and amide groups, as well as functional groups having an active proton, such as indole, protected reagents can be used, or a protecting group can be introduced into such a functional group according to a usual method; afterward, the protecting group can be removed in an appropriate step

in each production method.

[0240] The protecting group of an amino group or protecting group of an imino group is not particularly limited, insofar as it has a protecting function. Examples of such protecting groups include aralkyl groups, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl, trityl, and cumyl; lower alkanoyl groups, such as formyl, acetyl, propionyl, butyryl, pivaloyl, trifluoroacetyl, and trichloroacetyl; benzoyl; arylalkanoyl groups, such as phenylacetyl and phenoxyacetyl; lower alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, and tert-butoxycarbonyl; aralkyloxycarbonyl groups, such as p-nitrobenzyloxycarbonyl and phenethyloxycarbonyl; lower alkylsilyl groups, such as trimethylsilyl and tert-butyldimethylsilyl; tetrahydropyranyl; trimethylsilylethoxymethyl; lower alkylsulfonyl groups, such as methylsulfonyl, ethylsulfonyl, and tert-butylsulfonyl; lower alkylsulfinyl groups, such as tert-butylsulfinyl; arylsulfonyl groups, such as benzenesulfonyl and toluenesulfonyl; and imido groups, such as phthalimido. In particular, trifluoroacetyl, acetyl, tert-butoxycarbonyl, benzyloxycarbonyl, trimethylsilylethoxymethyl, cumyl, and the like are preferable.

[0241] The protecting group of a hydroxy group is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include lower alkyl groups, such as methyl, ethyl, propyl, isopropyl, and tert-butyl; lower alkylsilyl groups, such as trimethylsilyl and tert-butyldimethylsilyl; lower alkoxymethyl groups, such as methoxymethyl and 2-methoxyethoxymethyl; tetrahydropyranyl; trimethylsilylethoxymethyl; aralkyl groups, such as benzyl, p-methoxybenzyl, 2,3-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, and trityl; and acyl groups, such as formyl, acetyl, and trifluoroacetyl. In particular, methyl, methoxymethyl, tetrahydropyranyl, trimethylsilylethoxymethyl, tert-butyldimethylsilyl, and acetyl are preferable.

[0242] The protecting group of a carboxy group is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include lower alkyl groups, such as methyl, ethyl, propyl, isopropyl, and tert-butyl; halo-lower-alkyl groups, such as 2,2,2-trichloroethyl; lower alkenyl groups, such as allyl; trimethylsilylethoxymethyl; and aralkyl groups, such as benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl, and trityl. In particular, methyl, ethyl, tert-butyl, allyl, benzyl, p-methoxybenzyl, trimethylsilylethoxymethyl, and the like are preferable.

[0243] The protecting group of a carbonyl group is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include ethylene ketal, trimethylene ketal, dimethyl ketal, ethylene acetal, trimethylene acetal, dimethyl acetal, and like ketals and acetals.

[0244] The protecting group of an amide group or the protecting group of a functional group

having an active proton, such as indole, is not particularly limited, insofar as it has a protecting function. Examples of such protecting groups include lower alkyl groups, such as methyl, ethyl, propyl, isopropyl, and tert-butyl; lower alkylsilyl groups, such as trimethylsilyl and tert-butyldimethylsilyl; lower alkoxymethyl groups, such as methoxymethyl and 2-methoxyethoxymethyl; tetrahydropyranyl; trimethylsilylethoxymethyl; aralkyl groups, such as benzyl, p-methoxybenzyl, 2,3-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, and trityl; and acyl groups, such as formyl, acetyl, and trifluoroacetyl. In particular, methyl, methoxymethyl, tetrahydropyranyl, trimethylsilylethoxymethyl, tert-butyldimethylsilyl, and acetyl are preferable.

[0245] The method for removing such a protecting group may vary depending on the type of protecting group, stability of the target compound (I), etc. For example, the following methods can be used: solvolysis using an acid or a base according to the method disclosed in a publication (Protective Groups in Organic Synthesis, third edition, T.W. Green, John Wiley & Sons (1999)) or a similar method, i.e., a method comprising reacting with 0.01 moles or a large excess of an acid, preferably trifluoroacetic acid, formic acid, or hydrochloric acid, or an equimolar to large excessive molar amount of a base, preferably potassium hydroxide or calcium hydroxide; chemical reduction using a metal hydride complex etc.; or catalytic reduction using a palladium-carbon catalyst, Raney nickel catalyst, etc.

[0246] The compound of the present invention can be easily isolated and purified by common isolation and purification means. Examples of such means include solvent extraction, recrystallization, preparative reversed-phase high-performance liquid chromatography, column chromatography, preparative thin-layer chromatography, and the like.

[0247] When the compound of the present invention has isomers such as optical isomers, stereoisomers, rotational isomers, and tautomers, any of the isomers and mixtures thereof is included within the scope of the compound of the present invention, unless otherwise specified. For example, when the compound of the present invention has optical isomers, the optical isomer separated from a racemic mixture is also included within the scope of the compound of the present invention, unless otherwise specified. Each of such isomers can be obtained as a single compound by known synthesis and separation means (e.g., concentration, solvent extraction, and column chromatography, recrystallization).

[0248] As stated above, unless otherwise specified, the compound of the present invention includes all of the enantiomers and mixtures thereof. The compound of the present invention may be a mixture of R and S enantiomers. Such a mixture may be a mixture comprising 55% or more, 60% or more, 65% or more, 70% or more, 75% or more,

80% or more, 85% or more, 90% or more, 95% or more, or 99% or more of R enantiomer; a mixture comprising 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or 99% or more of S enantiomer; or the like.

[0249] Methods for chiral resolution include, for example: a diastereomer method of causing a chiral resolving agent to act on the compound of the present invention to form a salt, and resolving one of the enantiomers using a solubility difference etc. of the obtained salt; a preferential crystallization method of adding one of the enantiomers to a super-saturated solution of a racemate as a seed for crystallization; and column chromatography such as HPLC using a chiral column. A chiral resolving agent that can be used in the diastereomer method can be appropriately selected from, for example, acid resolving agents such as tartaric acid, malic acid, lactic acid, mandelic acid, 10-camphorsulfonic acid, and derivatives thereof; and basic resolving agents such as brucine, strychnine, quinine, and like alkaloid compounds, amino acid derivatives, cinchonidine, and α-methylbenzylamine. One of the enantiomers of the compound of the present invention alone can be obtained not only by obtaining the compound of the present invention as a mixture of enantiomers and then conducting chiral resolution as above, but also by obtaining one enantiomer of the compound of the present invention through chiral resolution as above or by other methods, and using it as a synthetic raw material of the compound of the present invention. Furthermore, methods for obtaining one of the enantiomers of the compound of the present invention or its raw material compound include a method of preferentially obtaining one of the enantiomers by adjusting reaction conditions for a catalyst or the like in a reaction step of generating asymmetric carbon.

[0250] Compounds of formula (I) may optionally be converted to a pharmacologically acceptable salt. The compound of the present invention or a salt thereof may be in the form of crystals. Single crystals and polymorphic crystal mixtures are included within the scope of the compound of the present invention or a salt thereof. Such crystals can be produced by crystallization according to a crystallization method known per se in the art. The compound of the present invention or a salt thereof may be a solvate (e.g., a hydrate) or a non-solvate. Any of such forms are included within the scope of the compound of the present invention or a salt thereof. Compounds labeled with one or more isotopes (e.g., ^{2}H, ^{3}H, ^{14}C, ^{35}S, and ^{125}I) are also included within the scope of the compound of the present invention or a salt thereof.

[0251] The salts of the compounds of the present invention or of the intermediates thereof refer to common salts used in the field of organic chemistry. Examples of such salts include base addition salts to a carboxy group when the compound has a carboxy group, and acid addition salts to an amino or basic heterocyclic group when the

compound has an amino or basic heterocyclic group.

[0252] Examples of base addition salts include alkali metal salts, such as sodium salts and potassium salts; alkaline earth metal salts, such as calcium salts and magnesium salts; ammonium salts; and organic amine salts, such as trimethylamine salts, triethylamine salts, dicyclohexylamine salts, ethanolamine salts, diethanolamine salts, tri-ethanolamine salts, procaine salts, and N,N'-dibenzylethylenediamine salts.

[0253] Examples of acid addition salts include inorganic acid salts, such as hydrochloride, sulfate, nitrate, phosphate, and perchlorate; organic acid salts, such as acetate, formate, maleate, fumarate, tartrate, citrate, ascorbate, and trifluoroacetate; and sulfonates such as methanesulfonate, isethionate, benzenesulfonate, and p-toluenesulfonate.

Also encompassed by formula (I) are any pro-drugs of the compounds of the formula (I). By "prodrugs" is meant for example any compound that is converted in vivo into a biologically active compound of the formula (I). Such prodrugs can, for example, be produced by replacing appropriate functionalities present in the compounds of the formula (I) with certain moieties known to those skilled in the art. In one embodiment, certain compounds of the formula (I) may themselves act as prodrugs of other of the compounds of the formula (I). In one embodiment formula (I) does not include prodrugs of the compounds of the formula (I) within its scope.

[0254] Due to their excellent SHP2 inhibitory activity, the compounds of the present invention or salts thereof are useful as a pharmaceutical preparation for prophylaxsis or treatment of a disease or condition mediated by SHP2.

[0255] Examples of the "a disease or condition mediated by SHP2" include diseases or condition whose incidence can be reduced, and whose symptoms can be remitted, relieved, and/or completely cured by eliminating, suppressing, and/or inhibiting SHP2 function. Such diseases may encompass diseases in which SHP2 activity/ existence/status is abnormal associated with aberrant RAS-ERK signalling pathway or receptor tyrosine kinase signalling pathway status, or diseases in which SHP2 activity/ existence/status is abnormal associated with aberrant immune response status. Examples of "a disease or condition mediated by SHP2" include, but are not limited to, malignant tumors etc.

[0256] The type of malignant tumor to be treated by the compound or a salt thereof of the present invention is not particularly limited. Examples of such malignant tumors include head and neck cancers, esophagus cancer, gastric cancer, colon cancer, rectum cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, biliary tract cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, cervical cancer, en-dometrial cancer, renal cancer, bladder cancer, prostate cancer, testicular tumor, os-teosarcoma, soft-tissue sarcoma, leukemia, myelodysplastic syndrome, chronic myelo-proliferative disease, malignant lymphoma, multiple myeloma, skin cancer, brain

tumor, mesothelioma, and the like.

[0257] When the compounds or salts thereof of the present invention are used as pharmaceutical preparations, a pharmaceutically acceptable carrier can be added, if required, thereby forming a suitable dosage form according to prevention and treatment purposes. Examples of the dosage form include oral preparations, injections, suppositories, ointments, patches, and the like; preferably oral preparations. Such dosage forms can be formed by methods conventionally known to persons skilled in the art.

[0258] As the pharmaceutically acceptable carrier, various conventional organic or inorganic carrier materials used as preparation materials may be blended as an excipient, binder, disintegrant, lubricant, or coating agent in solid preparations; or as a solvent, solubilizing agent, suspending agent, isotonizing agent, pH adjuster/buffer, or soothing agent in liquid preparations. Moreover, pharmaceutical preparation additives, such as antiseptics, antioxidants, colorants, sweeteners, and stabilizers, may also be used, if required.

[0259] When a solid preparation for oral administration is prepared, optionally an excipient, a binder, a disintegrator, a lubricant, a colorant, a sweetener, and the like may be added to the compound of the present invention; and the resulting mixture may be formulated into tablets, coated tablets, granules, powders, capsules, etc., according to an ordinary method.

[0260] When an injection is prepared, a pH adjuster, a buffer, a stabilizer, an isotonizing agent, a local anesthetic, and the like may be added, as necessary, to the compound of the present invention; and the resulting mixture may be formulated into subcutaneous, intramuscular, and intravenous injections according to an ordinary method.

[0261] The amount of the compound of the present invention to be incorporated in each of such dosage unit forms depends on the condition of the patient to whom the compound is administered, the dosage form, etc. . In general, in the case of an oral agent, an injection, and a suppository, the amount of the compound of the present invention is preferably 0.05 to 1000 mg, 0.01 to 500 mg, and 1 to 1000 mg, respectively, per dosage unit form.

[0262] The amount of the active compound administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. An effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 0.01 to about 40 mg/kg/day, in single or divided doses. For example, the daily dose of the compound of the present invention for an adult (body weight: 50 kg) may be generally about 0.05 to about 5000 mg, and preferably about 0.5 to about 2000 mg. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still

larger doses may be used without causing any harmful side effect. Such larger doses typically may be divided into several smaller doses for administration throughout the day. The total daily dose may be administered in single or divided doses. At the physician's discretion, the total daily dose may fall outside of the typical range based on an average human subject e.g., those having a weight of about 50 to about 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Examples

[0263] Synthetic Methods

By following methods similar and/or analogous to general procedures below, the compounds set out below were prepared.

[0264] The following synthetic procedures are provided for illustration of the methods used; for a given preparation or step the precursor used may not necessarily derive from the individual batch synthesised according to the step in the description given.

[0265] Where a compound is described as a mixture of two diastereoisomers / epimers, the configuration of the stereocentre is not specified and is represented by straight lines.

[0266] As understood by a person skilled in the art, compounds synthesised using the protocols as indicated may exist as a solvate e.g. hydrate, and/or contain residual solvent or minor impurities. Compounds isolated as a salt form, may be integer stoichiometric i.e. mono- or di-salts, or of intermediate stoichiometry.

[0267] Some of the compounds below are isolated as the salt, for example depending on the acid used in the purification method. Some compounds are isolated as the free base.

[0268] Compounds containing a single stereocentre are typically isolated as a single isomer using preparative chiral HPLC (as described in general methods); at (or towards) the final stage of the synthetic sequence. In these cases the stereochemistry is designated in accordance with IUPAC, using 'hashed' or 'solid' wedged lines. Unless stated otherwise, a straight line at a stereocentre indicates the compound exists as a mixture of both isomers.

[0269] Compounds containing a second stereocentre are typically isolated as a single isomer by preparative achiral and/or chiral HPLC.

[0270] The optical isomers may be characterised by their optical activity (i.e. as + and - isomers, or d and l isomers). The stereocentre can also assigned as "R or S" according to the nomenclature developed by Cahn, Ingold and Prelog, see Advanced Organic Chemistry by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, Angew. Chem. Int. Ed. Engl., 1966, 5, 385-415.

[0271] Optical isomers can be separated by a number of techniques including chiral chro-

matography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

[0272] As an alternative to chiral chromatography, optical isomers of basic compounds can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulfonic acid, separating the diastereoisomeric salts by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base. Likewise, optical iomers of acidic compounds can be separated by forming diastereoisomeric salts with chiral amines such as Brucine, Cinchonidine, quinine etc.

[0273] Additionally enantiomeric separation can be achieved by covalently linking a enantiomerically pure chiral auxiliary onto the compound and then performing diastereisomer separation using conventional methods such as chromatography. This is then followed by cleavage of the aforementioned covalent linkage to generate the appropriate enantiomerically pure product. Examples could include making menthol esters of an acidic compound.

[0274] Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers.

[0275] Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

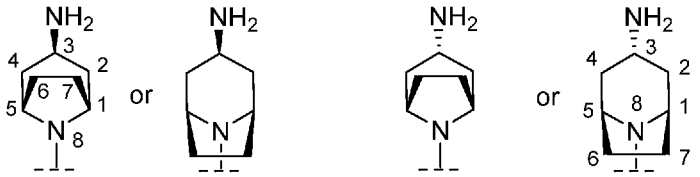
[0276] Compounds encompassing double bonds can have an E (entgegen) or Z (zusammen) stereochemistry at said double bond. Substituents on bivalent cyclic or (partially) saturated radicals may have either the cis- or trans-configuration. The terms cis and trans when used herein are in accordance with Chemical Abstracts nomenclature (J. Org. Chem. 1970, 35 (9), 2849-2867), and refer to the position of the substituents on a ring moiety.

[0277] Of special interest are those compounds of formula (I) which are stereochemically pure. When a compound of formula (I) is for instance specified as R, this means that the compound is substantially free of the S isomer. If a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z

isomer. The terms cis, trans, R, S, E and Z are well known to a person skilled in the art.

[0278] The terms exo and endo refer to the stereochemistry of a bridged bicycloalkane, such as a substituted tropane, described in PAC, 1996, 68, 2193, basic terminology of stereochemistry (IUPAC Recommendations 1996). If a substituent, e.g. the amino group, is orientated towards the highest numbered bridge it is given the description exo; if it is orientated away from the highest numbered bridge it is given the description endo. Where there are two substituents on the same carbon atom, the terms exo and endo refer to the higher priority substituent. The figure below illustrates the pictorial representation of how the amino tropane is defined in this patent.

[0279] [Chem.34]



[0280] EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples. Compounds are named, for example, using an automated naming package such as AutoNom (MDL), using IUPAC rules or are as named by the chemical supplier. In the examples, the following abbreviations are used.

[0281]

[Math.1]

Ac	acetyl
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BuLi	butyllithium
t-BuOK	potassium *tert*-butoxide
t-BuONa	sodium *tert*-butoxide
Cbz	carboxybenzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol
LDA	lithium diisopropylamide
i-PrMgCl	isopropylmagnesium chloride
MeCN	acetonitrile

[0282] [Math.2]

MeOH	methanol
min.	minutes
MS	mass spectrometry
MTBE	*tert*-butyl methyl ether
NaOMe	sodium methoxide
NBS	*N*-bromosuccinimde
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
PMB	*p*-methoxybenzyl
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RT	room temperature
Sat.	saturated
SEM	(2-(trimethylsilyl)ethoxy)methyl
SEMCl	2-(trimethylsilyl)ethoxymethyl chloride
TBAF	tetrabutylammonium fluoride
TBSCl	*tert*-butyldimethylsilyl chloride
TEA	triethylamine
TBME	*tert*-butyl methyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsCl	*p*-toluenesulfonyl chloride
Z-chloride	benzyl chloroformate

[0283] Synthetic Methods

All starting materials and solvents were obtained either from commercial sources or prepared according to the literature citation. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate. Hydrogenations were performed on a Parr hydrogenator, a Thales H-cube flow reactor

under the conditions stated or under a balloon of hydrogen. Microwave reactions were performed in Biotage(Registered Trademark) Initiator, a CEM Discover and Smithcreator microwave reactor, heating to a constant temperature using variable power microwave irradiation. Normal phase column chromatography was routinely carried out on an automated flash chromatography system such as CombiFlash Companion or CombiFlash RF system using pre-packed silica (230-400 mesh, 40-63 μm) cartridges. SCX was purchased from Supelco and treated with 1M hydrochloric acid prior to use. Unless stated otherwise the reaction mixture to be purified was first diluted with MeOH and made acidic with a few drops of AcOH. This solution was loaded directly onto the SCX and washed with MeOH. The desired material was then eluted by washing with a solvent such as 1% NH_3 in MeOH. NH_2 ion exchange silica gel purification was done with Strata NH_2 (55 μm, 70 Å) columns, loaded directly onto the NH_2 column and eluting with a solvent such as methanol. Biotage(Registered Trademark) SNAP Ultra silica gel columns and Biotage(Registered Trademark) KP-NH SNAP silica gel columns were purchased from Biotage(Registered Trademark). Reverse phase purification was done using Biotage(Registered Trademark) SNAP Ultra C18 silica gel columns and were purchased from Biotage(Registered Trademark).

[0284] NMR Data

^1H NMR spectra were acquired on a Bruker Avance III spectrometer at 400 MHz, an AL400 (400 MHz; produced by JEOL), a Mercury 400 (400 MHz; produced by Agilent Technologies, Inc.), a 500 MHz Bruker Avance III HD NMR Spectrometer or a Bruker Avance NEO NMR spectrometer (400 MHz) Either the central peaks of chloroform-d, dimethylsulfoxide-d_6 or an internal standard of tetramethylsilane were used as references. For NMR data, where the number of protons assigned is less than the theoretical number of protons in the molecule, it is assumed that the apparently missing signal(s) is/are obscured by solvent and/or water peaks. In addition, where spectra were obtained in protic NMR solvents, exchange of NH and/or OH protons with solvent occurs and hence such signals are normally not observed.

[0285] Analytical and Preparative LC-MS systems

Analytical LC-MS system and method description

In the following examples, compounds were characterised by mass spectroscopy using the systems and operating conditions set out below. Where atoms with different isotopes are present and a single mass quoted, the mass quoted for the compound is the monoisotopic mass (i.e. ^{35}Cl; ^{79}Br etc.).

[0286]

[Math.3]

Shimadzu Nexera

HPLC System:	Shimadzu SIL-30AC autosampler / 2x Shimadzu LC-30AD pumps
Mass Spec Detector:	Shimadzu LCMS-2020 single quadrupole MS
Second Detector:	Shimadzu SPD-M20A diode array detector

MS Operating Conditions

Qarray DC voltage:	20V on ES Pos (-20V on ES Neg)
Drying gas flow:	20.0 L/min
DL Temperature:	300 ° C
Heat Block Temperature:	350 ° C
Nebulising Gas Flow:	1.5 L/min
Scan Range:	100-750 amu
Ionisation Mode:	ElectroSpray Positive-Negative switching

[0287]

[Math.4]

Agilent 1290 Infinity II - 6130 LC-MS system

HPLC System:	Agilent 1290 Infinity II
Mass Spec Detector:	Agilent 6130 single quadrupole
Second Detector:	Agilent 1290 Infinity II Diode Array Detector

MS Operating Conditions

Capillary voltage:	3000V
Fragmentor/Gain:	70
Gain:	1
Drying gas flow:	13.0 L/min
Gas Temperature:	350 ° C
Nebuliser Pressure:	40 psig
Scan Range:	150-1000 amu
Sheath Gas Temperature:	360 ° C
Sheath Gas Flow:	10.0 L/min
Nozzle Voltage:	300 (+ve mode) / 1750 (-ve mode)
Ionisation Mode:	Agilent Jet Stream Electrospray Positive-Negative switching

[0288] LCMS spectra were alternatively measured with an SQD manufactured by Waters Corporation under the following two conditions, and the $[M+H]^+$ values were shown.

[0289]

[Math.5]

MS detection: ESI positive

UV detection: 254 nm

Column flow rate: 0.5 mL/min

Mobile phase: water/acetonitrile (0.1% formic acid)

Injection volume: 1 μL

Method

Column: Acguity BEH, 2.1×50 mm, 1.7 μm

Gradient:

Time (min)	water/acetonitrile (0.1% formic acid)
0	95/5
0.1	95/5
2.1	5/95
3.0	STOP

[0290] Preparative LC-MS system and method description

Preparative LC-MS is a standard and effective method used for the purification of small organic molecules such as the compounds described herein. The methods for the liquid chromatography (LC) and mass spectrometry (MS) can be varied to provide better separation of the crude materials and improved detection of the samples by MS. Optimisation of the preparative gradient LC method will involve varying columns, volatile eluents and modifiers, and gradients. Methods are well known in the art for optimising preparative LC-MS methods and then using them to purify compounds. Such methods are described in Rosentreter U, Huber U.; Optimal fraction collecting in preparative LC-MS; J Comb Chem.; 2004; 6(2), 159-64 and Leister W, Strauss K, Wisnoski D, Zhao Z, Lindsley C., Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries; J Comb Chem.; 2003; 5(3); 322-9.

[0291] Several systems for purifying compounds via preparative LC-MS are described below although a person skilled in the art will appreciate that alternative systems and

methods to those described could be used. From the information provided herein, or employing alternative chromatographic systems, a person skilled in the art could purify the compounds described herein by preparative LC-MS.

[0292] Mass Directed Purification LC-MS System

Preparative LC-MS is a standard and effective method used for the purification of small organic molecules such as the compounds described herein. The methods for the liquid chromatography (LC) and mass spectrometry (MS) can be varied to provide better separation of the crude materials and improved detection of the samples by MS. Optimisation of the preparative gradient LC method will involve varying columns, volatile eluents and modifiers, and gradients. Methods are well known in the art for optimising preparative LC-MS methods and then using them to purify compounds. Such methods are described in Rosentreter U, Huber U.; Optimal fraction collecting in preparative LC/MS; J Comb Chem.; 2004; 6(2), 159-64 and Leister W, Strauss K, Wisnoski D, Zhao Z, Lindsley C., Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries; J Comb Chem.; 2003; 5(3); 322-9.

[0293] One such system for purifying compounds via preparative LC-MS is described below although a person skilled in the art will appreciate that alternative systems and methods to those described could be used. In particular, normal phase preparative LC based methods might be used in place of the reverse phase methods described here. Most preparative LC-MS systems utilise reverse phase LC and volatile acidic modifiers, since the approach is very effective for the purification of small molecules and because the eluents are compatible with positive ion electrospray mass spectrometry. Employing other chromatographic solutions e.g. normal phase LC, alternatively buffered mobile phase, basic modifiers etc as outlined in the analytical methods described above could alternatively be used to purify the compounds.

[0294]

[Math.6]

Agilent 1260 LC-MS preparative system

Hardware:

Autosampler: G2260A Prep ALS

Pumps: 2x G1361A Prep Pumps for preparative flow gradient, G1311C Quat Pump VL for pumping modifier in prep flow and G1310B Iso Pump for make-up pump flow

UV detector: G1365C 1260 MWD

MS detector: G6120B Quadrupole LC-MS

Fraction Collector: 2x G1364B 1260 FC-PS

G1968D Active Splitter

Software:

Agilent OpenLab C01.06

Agilent MS operating conditions:

Capillary voltage:	3000 V
Fragmentor/Gain:	70/1
Drying gas flow:	12.0 L/min
Drying Gas Temperature:	275 ° C
Nebuliser Pressure:	40 psig
Vaporizer Temperature:	200 ° C
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive

[0295]

[Math.7]

Columns:

1. Waters XBridge Prep C18 5m OBD 100x19mm

   Typically used for ammonium bicarbonate-based methods
2. Waters SunFire Prep C18 OBD 5m 100x19mm

   Typically used for TFA-based methods
3. Waters XBridge Prep Phenyl 5m OBD 100x19mm

   Typically used for neutral pH ammonium acetate-based methods
4. Supelco Ascentis RP-Amide 5m 100x21.2mm

   Typically used for formic acid-based methods
5. Phenomenex Synergi Fusion-RP 4m 100x21.2mm

   Typically used for formic acid-based methods

Eluents:

Solvent A: Water

Solvent B: Acetonitrile

Solvent C: Choice of available modifiers:

2.5% Trifluoroacetic acid in water
2.5% Formic acid in water
250mM ammonium bicarbonate in water pH 9.4
250mM ammonium acetate

Make up solvent:

90:10 Methanol:Water + 0.2% Formic Acid (for all chromatography types)

[0296] Methods:

According to the analytical trace the most appropriate preparative chromatography type was chosen. A typical routine was to run an analytical LC-MS using the type of chromatography (low or high pH) most suited for compound structure. Once the analytical trace showed good chromatography a suitable preparative method of the same type was chosen. Typical running conditions for both low and high pH chromatography methods were:

Flow rate: 25 mL/min

Gradient: Generally all gradients had an initial 0.4 min step with 95% A + 5% B

(with additional modifier C). Then according to analytical trace a 6.6 min gradient was chosen in order to achieve good separation (e.g. from 5% to 50% B for early retaining compounds; from 35% to 80% B for middle retaining compounds and so on)
Wash: 1.6 minute wash step was performed at the end of the gradient
Make Up flow rate: 0.8 mL/min

[0297] Solvent:

All compounds were usually dissolved in 100% MeOH or 100% DMSO

From the information provided someone skilled in the art could purify the compounds described herein by preparative LC-MS.

[0298] [Math.8]

Waters Fractionlynx system

Hardware:

2767 Dual Loop Autosampler/Fraction Collector

2525 preparative pump

CFO (column fluidic organiser) for column selection

RMA (Waters reagent manager) as make up pump

Waters ZQ Mass Spectrometer

Waters 2996 Photo Diode Array detector

Waters ZQ Mass Spectrometer

Software:

Masslynx 4.1

Waters MS running conditions:

Capillary voltage:	3.5 kV (3.2 kV on ES Negative)
Cone voltage:	25 V
Source Temperature:	120 °C
Multiplier:	500 V
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive or ElectroSpray Negative

[0299] Alternatively Reverse phase preparative HPLC column chromatography was performed at the following conditions.

[0300] [Math.9]

Column:	CAPCELL PAK C18 AQ manufactured by SHISEIDO, 30x50 mm, 5 μm
UV detection:	254 nm
Column flow rate:	40 mL/min
Mobile phase:	water/acetonitrile (0.1% formic acid)
Injection volume:	1.0 mL
Basic gradient method:	water/acetonitrile 0%-50% (8 minutes)

[0301] Achiral Preparative Chromatography

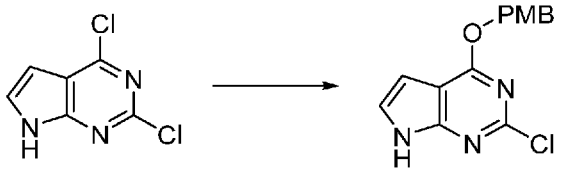
The compound examples described have undergone HPLC purification, where indicated, using methods developed following recommendations as described in Snyder L. R., Dolan J. W., High-Performance Gradient Elution The Practical Application of the Linear-Solvent-Strength Model, Wiley, Hoboken, 2007.

[0302] Chiral Preparative Chromatography

Preparative separations using Chiral Stationary Phases (CSPs) are the natural technique to apply to the resolution of enantiomeric mixtures. Equally, it can be applied to the separation of diastereomers and achiral molecules. Methods are well known in the art for optimising preparative chiral separations on CSPs and then using them to purify compounds. Such methods are described in Beesley T. E., Scott R.P.W.; Chiral Chromatography; Wiley, Chichester, 1998.

[0303] Preparation 1: 2-Chloro-4-((4-methoxybenzyl)oxy)-7H-pyrrolo[2,3-d]pyrimidine

[0304] [Chem.35]

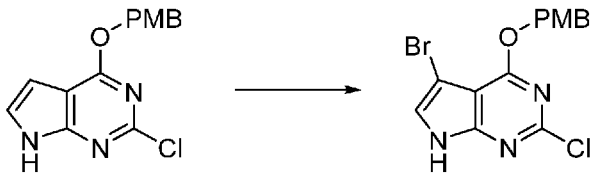


[0305] To a solution of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (2.5 g, 13.3 mmol) and 4-methoxybenzyl alcohol (1.99 mL, 16.0 mmol) in 1,4-dioxane (37.5 mL) was added potassium tert-butoxide (5.97 g, 53.2 mmol) at RT. The mixture was stirred at RT for 1 h. Sat. NH_4Cl was added at RT. The precipitate was collected, washed with water and EtOAc, and dried at 50 °C overnight under reduced pressure to give the title compound (3.14 g). MS: $[M+H]^+$ = 290, 292.

[0306] Preparation 2:
5-Bromo-2-chloro-4-((4-methoxybenzyl)oxy)-7H-pyrrolo[2,3-d]pyrimidine

[0307]

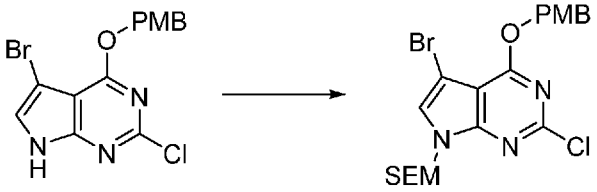
[Chem.36]



[0308] To a solution of 2-chloro-4-((4-methoxybenzyl)oxy)-7H-pyrrolo[2,3-d]pyrimidine (3.14 g, 10.8 mmol) in DMF (31.4 mL) was added NBS (2.12 g, 11.9 mmol) at -20 °C. The mixture was stirred at -20 °C for 30 min. Sat. sodium thiosulfate (30 mL) and EtOAc (15 mL) were added. The mixture was stirred at RT for 30 min. The precipitate was collected, washed with water, and dried at 50 °C overnight under reduced pressure to give the title compound (3.78 g). MS: $[M+H]^+$ = 368, 370.

[0309] Preparation 3:
5-Bromo-2-chloro-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

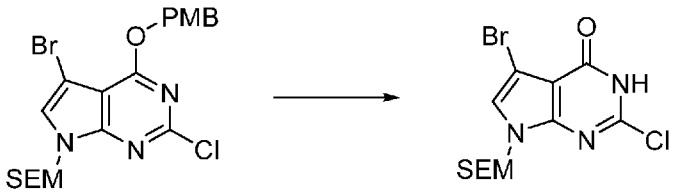
[0310] [Chem.37]



[0311] To a solution of 5-bromo-2-chloro-4-((4-methoxybenzyl)oxy)-7H-pyrrolo[2,3-d]pyrimidine (2.0 g, 5.43 mmol) in DMF (40 mL) were added sodium hydride (60% in mineral oil, 0.26 g, 6.51 mmol) and SEMCl (1.14 mL, 6.51 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Sat. NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 20 - 60% EtOAc/hexane) to give the title compound (2.68 g). MS: $[M+H]^+$ = 498, 500.

[0312] Preparation 4:
5-Bromo-2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

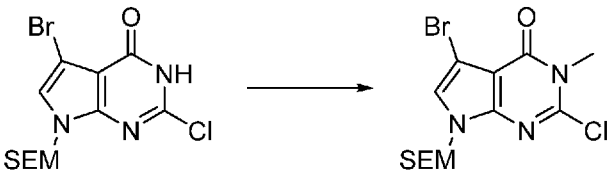
[0313] [Chem.38]



[0314] To a solution of 5-bromo-2-chloro-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (1.6 g, 3.21 mmol) in DCM (30.4 mL) were added 2,3-dichloro-5,6-dicyano-p-benzoquinone (2.18 g, 9.62 mmol) and water (1.6 mL) at RT. The mixture was stirred at RT for 3 days. $CHCl_3$ and sat. $NaHCO_3$ were added at RT. The mixture was filtered through a pad of Celite, and washed with $CHCl_3$ and water. The filtrate was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give the title compound (0.746 g). MS: $[M+H]^+$ = 378, 380.

[0315] Preparation 5:
5-Bromo-2-chloro-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

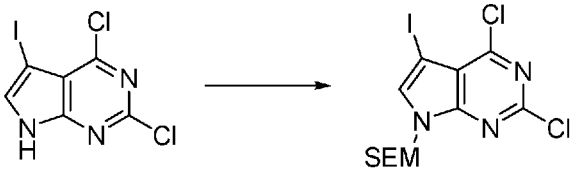
[0316] [Chem.39]



[0317] To a solution of 5-bromo-2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (0.746 g, 1.97 mmol) in DMF (7.46 mL) were added K_2CO_3 (0.544 g, 3.94 mmol) and iodomethane (0.245 mL, 3.94 mmol) at RT. The mixture was stirred at RT for 30 min, poured into water, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give the title compound (0.7 g). MS: $[M+H]^+$ = 392, 394.

[0318] Preparation 6:
2,4-Dichloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

[0319] [Chem.40]

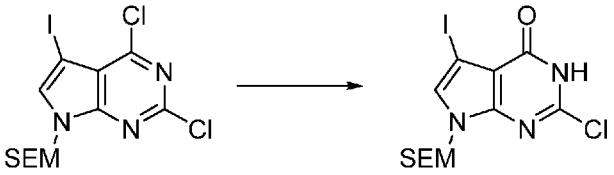


[0320] To a mixture of 2,4-dichloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (1 g, 3.18 mmol) and DIPEA (1.66 mL, 9.55 mmol) in THF (10 mL) were added SEMCl (1.13 mL, 6.37

mmol) at RT. The mixture was stirred at RT for 2 h, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 30% EtOAc/hexane) to give the title compound (1.5 g). MS: $[M+H]^+$ = 444, 446.

[0321] Preparation 7:
2-Chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

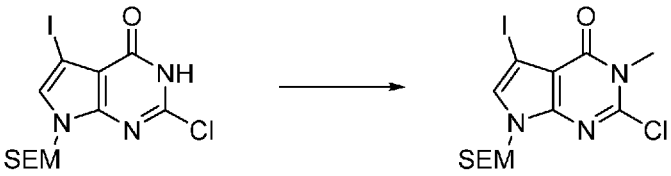
[0322] [Chem.41]



[0323] To a mixture of 2,4-dichloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (0.3 g, 0.67 mmol) in 1,4-dioxane (4 mL) was added 4 M KOH (1 mL, 4 mmol) at RT. The mixture was stirred at 60 °C overnight, cooled to RT, acidified with aq. HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 70% EtOAc/hexane) to give the title compound (0.17 g). MS: $[M+H]^+$ = 426, 428.

[0324] Preparation 8:
2-Chloro-5-iodo-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0325] [Chem.42]

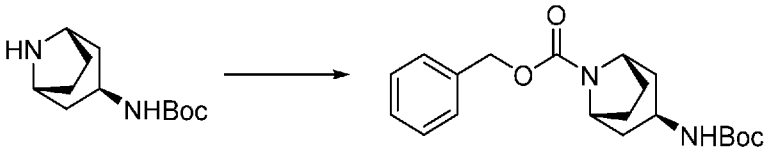


[0326] To a mixture of 2-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (0.17 g, 0.40 mmol) and K_2CO_3 (0.11 g, 0.79 mmol) in NMP (1 mL) was added iodomethane (0.05 mL, 0.79 mmol) at RT. The mixture was stirred at RT for 3 h, diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 50% EtOAc/hexane) to give the title compound (0.15 g). MS: $[M+H]^+$ = 440, 442.

[0327] Preparation 9: Benzyl

[endo-3-(tert-butoxycarbonyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate

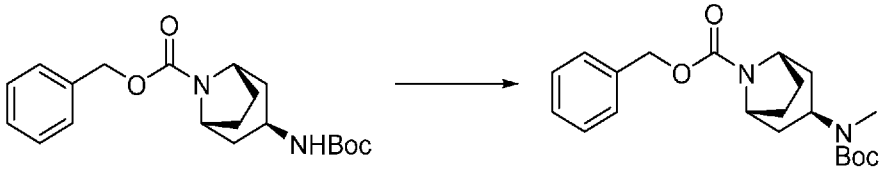
[0328] [Chem.43]



[0329] To a suspension of tert-butyl (endo-8-azabicyclo[3.2.1]octan-3-yl)carbamate (1.0 g, 4.4 mmol) and TEA (1.2 equiv., 5.3 mmol) in THF (5.0 mL) and DCM (3.0 mL) was added Z-chloride (0.69 mL, 4.9 mmol) at 0 °C in an ice bath. The ice bath was removed and the mixture was stirred at RT for 1 h. Z-chloride (0.13 mL, 0.88 mmol) was added to the mixture at RT and the mixture was stirred at RT for additional 3 h. To the mixture were added dil. HCl aq. and EtOAc, and the mixture was extracted with EtOAc (X3). The organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue (a pale yellow oil, 1.7 g) was purified by column chromatography on silica gel (gradient elution, 0 - 8% MeOH/ $CHCl_3$) to give the title compound (1.4 g, 4.0 mmol, 91% Yield) as a colorless solid. MS: $[M+H]^+ = 361$.

[0330] Preparation 10: Benzyl [endo-3-(tert-butoxycarbonyl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate

[0331] [Chem.44]

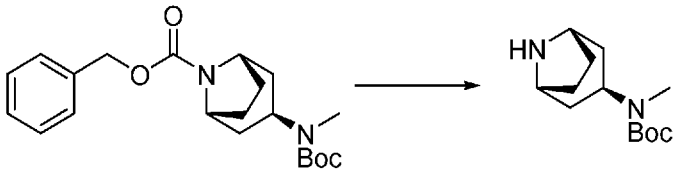


[0332] To benzyl [endo-3-(tert-butoxycarbonyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (1.4 g, 4.0 mmol) in DMF (5.0 mL) was added sodium hydride (60% in mineral oil, 0.24 g, 5.99 mmol) at 0 °C and the mixture was stirred at 0 °C for 40 min. Iodomethane (0.50 mL, 7.99 mmol) was added to the mixture at 0 °C and the ice bath was removed in 5 min. After stirred at RT for 30 min, sodium hydride (60% in mineral oil, 32 mg, 0.799 mmol) and iodomethane (0.12 mL, 2.00 mmol) were added to the mixture and the mixture was stirred at RT for additional 30 min. To the mixture were added dil. aqueous citric acid solution and EtOAc, and the mixture was extracted with EtOAc. The organic extracts were washed with water and brine, and dried over Na_2SO_4. Concentration of the filtrate gave the crude product (a yellow oil, 1.7g), which was purified by column chromatography on silica gel (gradient elution, 0 - 70% EtOAc/hexane) to

give the title compound (879 mg, 2.3 mmol, 58% Yield) as a colorless oil. MS: $[M+H]^+ = 375$.

[0333] Preparation 11: tert-Butyl (endo-8-azabicyclo[3.2.1]octan-3-yl)(methyl)carbamate

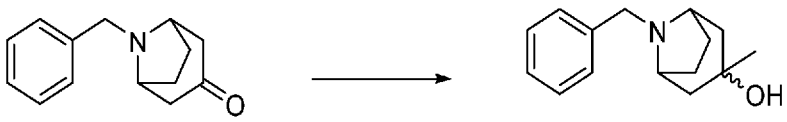
[0334] [Chem.45]



[0335] Benzyl [endo-3-(tert-butoxycarbonyl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (875 mg, 2.3 mmol) and 10% Pd-C (M) Wet (500 mg) was suspended in MeOH (5.0 mL) and the mixture was substituted with H_2. The mixture was stirred at RT for 3 h. The reaction mixture was applied to a pad of Celite and the filtrate was concentrated. The residue was dissolved in MeOH and was again applied to a pad of Celite and the filtrate was concentrated to give the title compound (556 mg, 2.3 mmol, 99% Yield) as a pale yellow oil-solid. MS: $[M+H]^+ = 241$.

[0336] Preparation 12: 8-Benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-ol

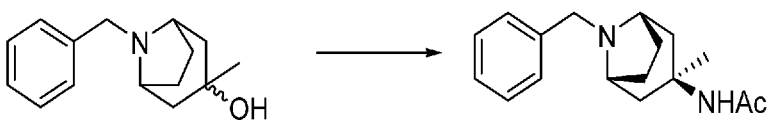
[0337] [Chem.46]



[0338] To a solution of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one (4.28 g, 19.9 mmol) in THF (47.0 mL) was added 3.0 mol/L methylmagnesium chloride in THF solution (29.4 mL, 88.4 mmol) under MeCN-dry ice bath, and the reaction was stirred for 30 min at this temperature and then 20 h at RT. Sat. NH_4Cl solution was added at 0 °C and the mixture was extracted with EtOAc. The combined organic layers were washed with water and sat. sodium chloride solution, and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel (NH silica gel, gradient elution, 20-50% $CHCl_3$/hexane), to give the title compound (4.50 g). MS: $[M+H]^+ = 232$.

[0339] Preparation 13: N-(endo-8-Benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)acetamide

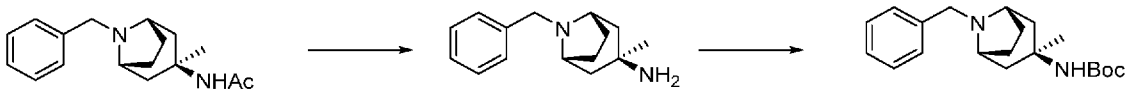
[0340] [Chem.47]



[0341] To a solution of 8-benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-ol (4.28 g, 18.48 mmol) in acetonitrile (26 mL) was added conc. sulfuric acid (18 mL) dropwise over 15 min. at 0 °C, and stirred for 18 h at RT. The reaction mixture was poured into ice (ca. 200 g), and basified (ca pH 10) with 5 mol/L sodium hydroxide solution (ca. 100 mL). The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and sat. sodium chloride solution, and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed at reduced pressure. The residue was washed with diethylether and petrol, to give the title compound (2.45 g). MS: $[M+H]^+ = 273$.

[0342] Preparation 14: tert-Butyl N-(endo-8-benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate

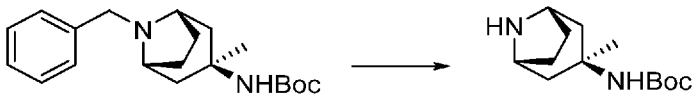
[0343] [Chem.48]



[0344] To N-(endo-8-benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)acetamide was added 6 mol/L hydrochloric acid (80 mL) and the mixture was stirred for 11 days at 140 °C. The reaction mixture was basified with 4 mol/L sodium hydroxide solution at 0 °C, and 1,4-dioxane (20 mL), and di-tert-butyl dicarbonate (3.93 g, 18.0 mmol) was added. The reaction was stirred for 1 h at 0 °C, and for 18 h at RT. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and sat. sodium chloride solution, and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel (gradient elution, 0-10% MeOH/DCM) to give the title compound (3.05 g). MS: $[M+H]^+ = 331$.

[0345] Preparation 15: tert-Butyl N-(endo-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate

[0346] [Chem.49]

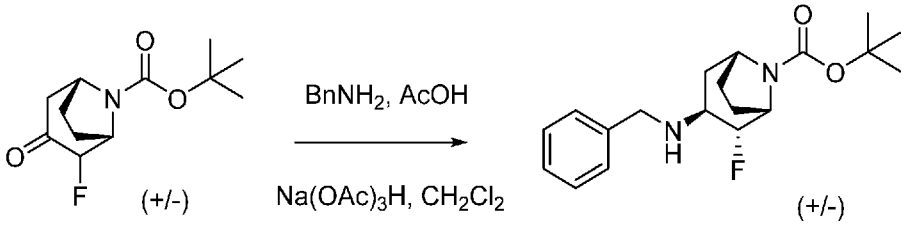


[0347] $Pd(OH)_2/C$ (10 wt% Pd, 637 mg, 0.454 mmol) was added to a solution of tert-butyl N-(endo-8-benzyl-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate (3.0 g, 9.08 mmol) in MeOH (20 mL) and the reaction was subjected to hydrogenation at ambient pressure and RT for 24 h. The reaction was filtered through Celite and the filtrate evaporated. The residue was triturated with diethyl ether to give the title compound (1.86 g). MS: $[M+H]^+ = 241$.

[0348] Preparation 16: rac-tert-Butyl

(1S,2R,3S,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0349] [Chem.50]

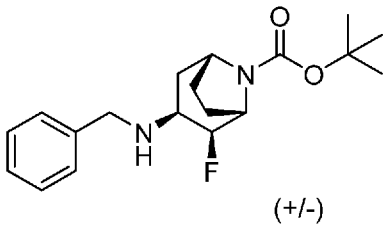


[0350] Sodium triacetoxyborohydride (41 g, 193 mmol) was added portion wise to a solution of (±)-tert-butyl 2-fluoro-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (34.8 g, 129 mmol), acetic acid (11.0 ml, 192 mmol) and benzylamine (20 ml, 183 mmol) in dichloromethane (500 mL) then stirred at room temperature overnight. The mixture was diluted with 10% sodium hydrogen carbonate (500 mL) then extracted with dichloromethane (3 x 500 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was recrystallised from ethyl acetate : isohexane (800 mL, 1:3), to give the title compound (11.6 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.39-7.27 (m, 4H), 7.27-7.19 (m, 1H), 4.51 (br d, 1H), 4.38-4.21 (m, 1H), 4.13-4.04 (m, 1H), 3.83-3.65 (m, 2H), 2.80 (dd, 1H), 2.48-2.33 (m, 1H), 2.09 (s, 1H), 2.03-1.88 (m, 2H), 1.86-1.69 (m, 2H), 1.56 (d, 1H), 1.37 (s, 9H).

[0351] The filtrate was concentrated under reduced pressure then purified by column chromatography on silica gel (gradient elution, 0-50% EtOAc/isohexane), to afford the following compounds:

[0352] Preparation 17: rac-tert-Butyl (1S,2S,3S,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0353] [Chem.51]

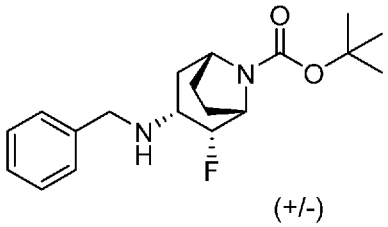


[0354] To give the title compound (3.8 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.42-7.28 (m, 4H), 7.29-7.18 (m, 1H), 4.68 (dt, 1H), 4.16-4.04 (m, 1H), 4.05-3.94 (m, 1H), 3.82 (dd, 1H), 3.63 (dd, 1H), 3.29-3.20 (m, 1H), 2.44-2.31 (m, 1H), 2.21-2.04 (m, 2H), 1.97-1.87 (m, 1H), 1.89-1.61 (m, 3H), 1.39 (s, 9H).

[0355] Praparation 18: rac-tert-Butyl (1S,2R,3R,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0356]

[Chem.52]

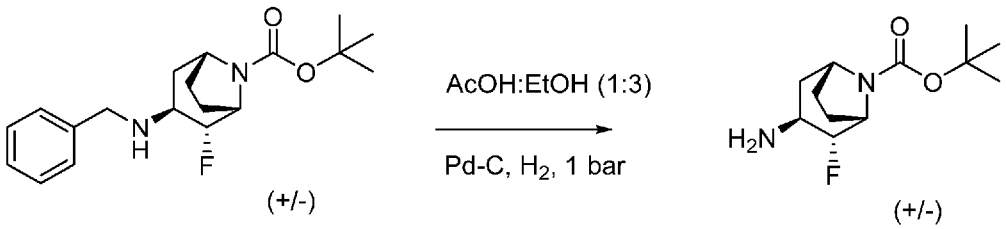


(+/-)

[0357] To give 14 g of a colourless oil which was purified by column chromatography on silica gel (gradient elution, 0-50% EtOAc/isohexane), to give the title compound (11.9 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.38-7.26 (m, 4H), 7.26-7.15 (m, 1H), 4.66 (dt, 1H), 4.48-4.24 (m, 1H), 4.19-4.06 (m, 1H), 3.77 (d, 1H), 3.72 (d, 1H), 2.96-2.72 (m, 1H), 1.95-1.64 (m, 4H), 1.61-1.43 (m, 3H), 1.38 (s, 9H).

[0358] Preparation 19: rac-tert-Butyl (1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0359] [Chem.53]

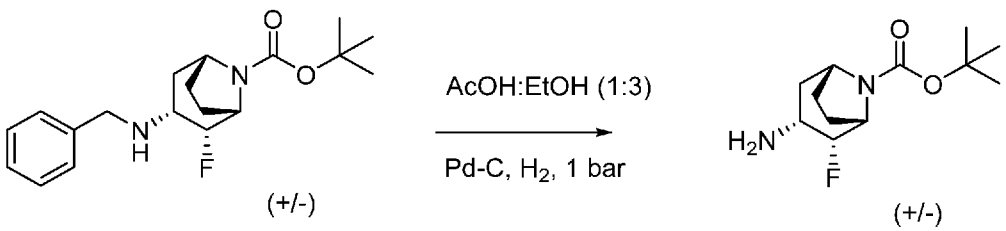


(+/-) (+/-)

[0360] rac-tert-Butyl (1S,2R,3S,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (18.5 g, 55.3 mmol) and 10% palladium on carbon (JM Type 39, 57.3% moisture) (4.0 g, 1.605 mmol) were dissolved in acetic acid/ethanol (1:3, 200 mL) and stirred under hydrogen at 1 bar for 2 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with sodium bicarbonate slurry (10 g in 100 mL) then extracted with chloroform/IPA (9:1, 3 x 100 mL). The combined organic phases were concentrated under reduced pressure, to give the title compound (13.5 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.39-4.15 (m, 2H), 4.07 (m, 1H), 3.11 (dd, 1H), 2.12-1.88 (m, 4H), 1.83-1.65 (m, 4H), 1.37 (s, 9H).

[0361] Preparation 20: rac-tert-Butyl (1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0362] [Chem.54]

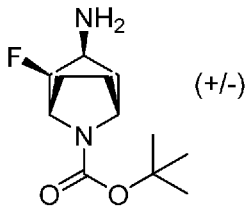


(+/-) (+/-)

[0363] The title compound was prepared similar fashion to rac-tert-butyl (1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate using rac-tert-butyl (1S,2R,3R,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (11 g, 32.9 mmol), to give the title compound (8.25 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.37 (dt, 2H), 4.38-4.33 (m, 1H), 4.16-4.09 (m, 1H), 2.95 (dddd, 1H), 1.88-1.76 (m, 3H), 1.66-1.46 (m, 4H), 1.41 (d, J = 0.5 Hz, 9H).

[0364] Praparation 21: rac-tert-Butyl (1S,2S,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

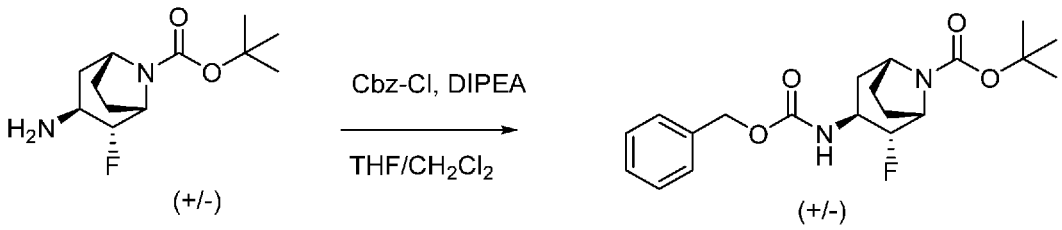
[0365] [Chem.55]



[0366] The title compound was prepared similar fashion to rac-tert-butyl (1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate using rac-tert-butyl (1S,2S,3S,5R)-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (6.0 g, 17.0 mmol), to give the title compound (4.0 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.53 (dt, 1H), 4.13-4.03 (m, 1H), 4.03-3.91 (m, 1H), 3.64-3.53 (m, 1H), 2.50-2.40 (m, 1H), 2.22-2.05 (m, 1H), 1.97-1.49 (m, 6H), 1.39 (d, 9H).

[0367] Preparation 22: rac-tert-Butyl (1S,2R,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0368] [Chem.56]

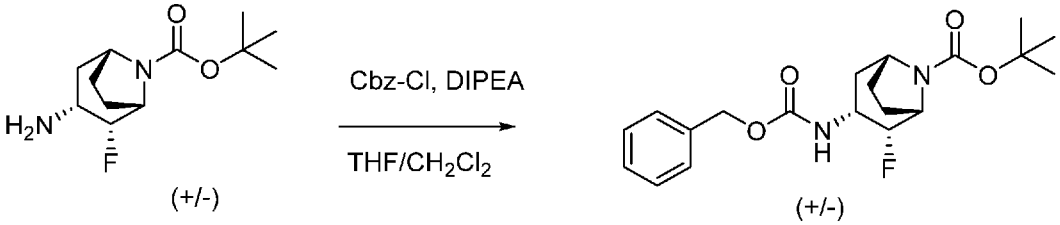


[0369] Benzyl chloroformate (10 mL, 70.0 mmol) was added to a cooled (0 °C) solution of rac-tert-butyl (1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (13.5 g, 52.5 mmol) and DIPEA (27 mL, 155 mmol) in THF/DCM (375 mL: 1:4) then stirred at room temperature overnight. Water (400 mL) was added then the mixture was extracted with dichloromethane (3 x 400 mL) and combined organic phases were con-

centrated under reduced pressure. The crude product was purified by chromatography on silica gel (0-30% EtOAc/isohexane). The purified oil was purified again by column chromatography on silica gel (gradient elution, 0-10% EtOAc/DCM), to give the title compound (19.5 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.46-7.39 (m, 1H), 7.39-7.34 (m, 4H), 7.34-7.29 (m, 1H), 5.07 (d, 1H), 5.02 (d, 1H), 4.51 (br d,1H), 4.38-4.20 (m, 1H), 4.16-4.06 (m, 1H), 3.64-3.49 (m, 1H), 2.23-2.11 (m, 1H), 1.94-1.79 (m, 2H), 1.78-1.66 (m, 2H), 1.49-1.43 (m, 1H), 1.38 (s, 9H).

[0370] Preparation 23: rac-tert-Butyl (1S,2R,3R,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

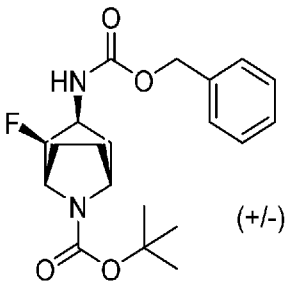
[0371] [Chem.57]



[0372] The title compound was prepared similar fashion to rac-tert-butyl (1S,2R,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate using rac-tert-butyl (1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (8.25 g, 32.1 mmol), to give the title compound (10.9 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.46-7.26 (m, 6H), 5.11-4.94 (m, 2H), 4.54 (dt, 1H), 4.43-4.26 (m, 1H), 4.20-4.06 (m, 1H), 3.92-3.72 (m, 1H), 1.99-1.69 (m, 3H), 1.70-1.48 (m, 3H), 1.38 (s, 9H).

[0373] Preparation 24: rac-tert-Butyl (1S,2S,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[0374] [Chem.58]

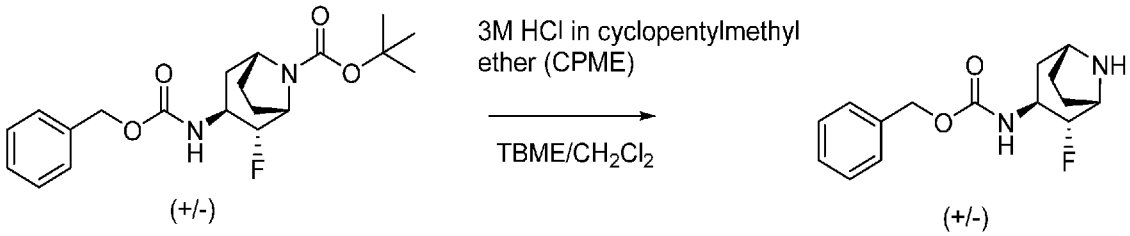


[0375] The title compound was prepared similar fashion to rac-tert-butyl (1S,2R,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate using rac-tert-butyl (1S,2S,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (4.0 g, 15.5

mmol), to give the title compound (5.45 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.41-7.35 (m, 4H), 7.35-7.28 (m, 1H), 7.14-6.93 (m, 1H), 5.23-4.89 (m, 2H), 4.85-4.65 (m, 1H), 4.22-4.07 (m, 2H), 4.07-3.97 (m, 1H), 2.29-2.17 (m, 1H), 2.08-2.02 (m, 1H), 1.99-1.79 (m, 2H), 1.80-1.64 (m, 2H), 1.40 (s, 9H).

[0376] Preparation 25: rac-Benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

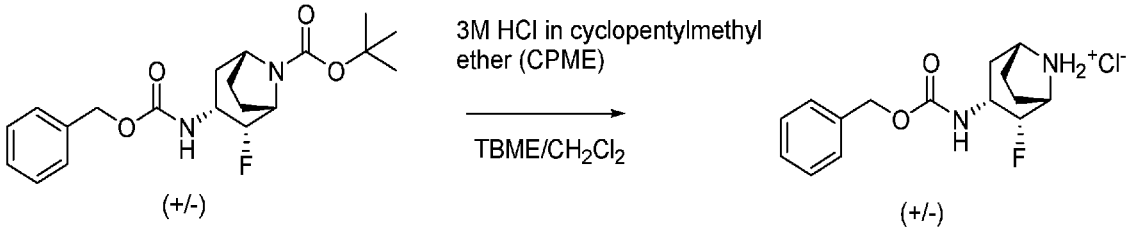
[0377] [Chem.59]



[0378] 3.0 M hydrogen chloride in cyclopentyl methyl ether (130 mL, 390 mmol) was added to a solution of rac-tert-butyl (1S,2R,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (14.5 g, 36.4 mmol) in tert-butyl methyl ether (15 mL) then stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure then partitioned between dichloromethane (200 mL) and saturated sodium hydrogen carbonate solution (200 mL). The organic layer was concentrated under reduced pressure then purified by column chromatography on silica gel (gradient elution, 0-10% (0.7 M Ammonia/MeOH)/DCM), to give the title compound (6.0 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.41-7.28 (m, 5H), 7.28-7.20 (m, 1H), 5.10-4.97 (m, 2H), 4.29 (ddd, 1H), 3.69-3.51 (m, 1H), 3.41 (dd, 1H), 3.37-3.29 (m, 1H), 2.30-2.09 (m, 1H), 2.10-1.97 (m, 1H), 1.77-1.63 (m, 2H), 1.64-1.47 (m, 2H), 1.30-1.14 (m, 1H).

[0379] Preparation 26: rac-Benzyl N-[(1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride

[0380] [Chem.60]

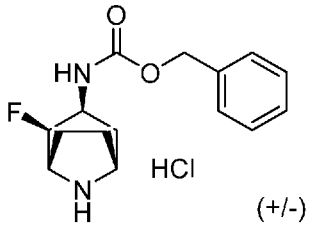


[0381] 3.0 M hydrogen chloride in cyclopentyl methyl ether (100 mL, 300 mmol) was added to a suspension of (±)-tert-butyl (1S,2S,3R,5R)-3-(((benzyloxy)carbonyl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (10.9 g, 27.4 mmol) in tert-butyl methyl ether (15 mL) and

dichloromethane (10 mL) then stirred at room temperature for 18 h. The resulting precipitate was collected by filtration to give the title compound (8.8 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.28-9.22 (m, 1H), 9.22-8.29 (m, 1H), 7.74-7.59 (m, 1H), 7.42-7.35 (m, 4H), 7.35-7.29 (m, 1H), 5.07 (d, 1H), 5.04 (d, 1H), 4.83 (dt,1H), 4.22-4.12 (m, 1H), 3.99-3.92 (m, 1H), 3.92-3.75 (m, 1H), 2.08-1.86 (m, 4H), 1.86-1.68 (m, 2H).

[0382] Preparation 27: rac-Benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride

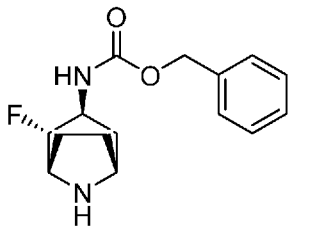
[0383] [Chem.61]



[0384] rac-tert-Butyl (1S,2S,3S,5R)-3-{[(benzyloxy)carbonyl]amino}-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (5.45 g, 14.26 mmol) was dissolved in dichloromethane (5 mL) then stirred with 3.0 M hydrogen chloride in cyclopentyl methyl ether (50 mL) at room temperature for 4 h. TBME (c.a. 10mL) was added dropwise whilst still stirring until the turbidity persisted, then the mixture was stirred overnight. The resulting precipitate was collected by filtration then washed with TBME (10 mL) and isohexane (10 mL), to give the title compound (3.9 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.08-9.28 (m, 2H), 7.46-7.14 (m, 6H), 5.21-5.00 (m, 3H), 4.27-4.15 (m, 1H), 4.13-4.04 (m, 1H), 3.96-3.88 (m, 1H), 2.42 (ddd, 1H), 2.36-2.26 (m, 1H), 2.16 (ddd, 1H), 2.04-1.90 (m, 2H), 1.89-1.78 (m, 1H).

[0385] Preparation 28: Benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (Fast eluting isomer)

[0386] [Chem.62]

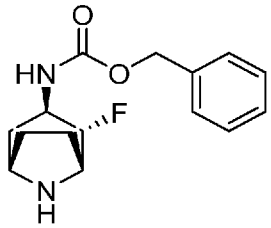


[0387] rac-Benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (5.82 g) was dissolved in methanol (150 mL) then purified by chiral preparative supercritical fluid chromatography (Lux A1 column, (21.2mm x 250mm, 5um); 40 °C, Flow Rate 50 mL/min, BPR 100 BarG, Detection at 210 nm, Injection Volume 200 uL (30

mg), 35:65 MeOH:CO_2 (0.2% v/v NH_3)). Pure fractions were combined then evaporated, to give the title compound (2.58 g) as the faster eluting enantiomer. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.41-7.28 (m, 5H), 7.28-7.20 (m, 1H), 5.10-4.97 (m, 2H), 4.29 (ddd, 1H), 3.69-3.51 (m, 1H), 3.41 (dd, 1H), 3.37-3.29 (m, 1H), 2.30-2.09 (m, 1H), 2.10-1.97 (m, 1H), 1.77-1.63 (m, 2H), 1.64-1.47 (m, 2H), 1.30-1.14 (m, 1H).

[0388] Preparation 29: Benzyl N-[(1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (Slow eluting isomer)

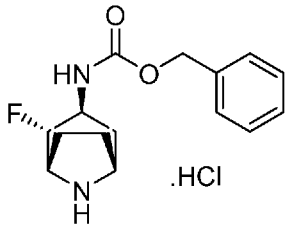
[0389] [Chem.63]



[0390] rac-Benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (5.82 g) was dissolved in methanol (150 mL) then purified by chiral preparative super-critical fluid chromatography (Lux A1 column, (21.2mm x 250mm, 5um); 40 °C, Flow Rate 50 mL/min, BPR 100 BarG, Detection at 210 nm, Injection Volume 200 uL (30 mg), 35:65 MeOH:CO_2 (0.2% v/v NH_3)). Pure fractions were combined then evaporated, to give the title compound (2.99 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.41-7.28 (m, 5H), 7.28-7.20 (m, 1H), 5.10-4.97 (m, 2H), 4.29 (ddd, 1H), 3.69-3.51 (m, 1H), 3.41 (dd, 1H), 3.37-3.29 (m, 1H), 2.30-2.09 (m, 1H), 2.10-1.97 (m, 1H), 1.77-1.63 (m, 2H), 1.64-1.47 (m, 2H), 1.30-1.14 (m, 1H).

[0391] Preparation 30: Benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride

[0392] [Chem.64]

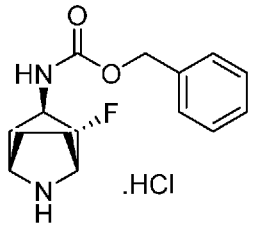


[0393] Fast eluting isomer benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (3.8 g) was dissolved in dichloromethane (10 mL) then treated with 3.0 M hydrogen chloride in cyclopentyl methyl ether (10 ml, 30.0 mmol), to give a white solid which was recrys-tallised in acetonitrile (50 mL), to give the title compound (2.2 g). ^{1}H NMR (500 MHz,

DMSO-d_6) δ: 9.34 (br s, 2H), 7.76-7.56 (m, 1H), 7.45-7.27 (m, 5H), 5.09 (d, 1H), 5.04 (d, 1H), 4.95-4.77 (m, 1H), 4.17-4.06 (m, 1H), 3.98-3.87 (m, 1H), 3.77-3.60 (m, 1H), 2.33 (ddd, 1H), 2.18 (q, 1H), 2.03-1.89 (m, 3H), 1.79 (d, 1H).

[0394] Preparation 31: Benzyl N-[(1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride

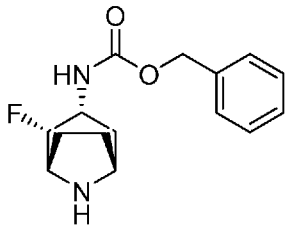
[0395] [Chem.65]



[0396] Slow eluting isomer benzyl N-[(1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (3.8 g) was dissolved in dichloromethane (10 mL) then treated with 3.0 M hydrogen chloride in cyclopentyl methyl ether (10 ml, 30.0 mmol), to give a white solid which was recrystallised in acetonitrile (50 mL), to give the title compound (3.2 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.34 (br s, 2H), 7.76-7.56 (m, 1H), 7.45-7.27 (m, 5H), 5.09 (d, 1H), 5.04 (d, 1H), 4.95-4.77 (m, 1H), 4.17-4.06 (m, 1H), 3.98-3.87 (m, 1H), 3.77-3.60 (m, 1H), 2.33 (ddd, 1H), 2.18 (q, 1H), 2.03-1.89 (m, 3H), 1.79 (d, 1H).

[0397] Preparation 32: Benzyl N-[(1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (Fast eluting isomer)

[0398] [Chem.66]

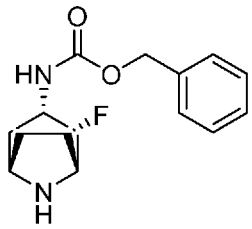


[0399] rac-Benzyl N-[(1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (8.8 g) was dissolved in methanol (50 mg mL^{-1}) then purified by chiral preparative supercritical fluid chromatography (Lux C2 (4.6mm x 250mm, 5um) ; 40 °C, Flow Rate 50 mL/min, BPR 100 BarG, Detection at 210 nm, Injection Volume 500 uL (25 mg), 35:65 EtOH:CO_2 (0.2% v/v NH3)). Pure fractions were combined then evaporated, to give the title compound (4.04 g) as the faster eluting enantiomer. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.08-7.57 (m, 2), 7.53 (d, 1H), 7.41-7.28 (m, 5H), 5.04 (d, 1H), 5.02 (d, 1H), 4.67 (dt, 1H), 3.99-3.89 (m, 1H), 3.85-3.67 (m, 2H), 1.97-1.59 (m, 6H).

(compound isolated as a partial hydrochloride salt)

[0400] Preparation 33: Benzyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (Slow eluting isomer)

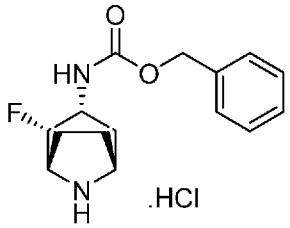
[0401] [Chem.67]



[0402] rac-Benzyl N-[(1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (8.8 g) was dissolved in methanol (50 mg mL^{-1}) then purified by chiral preparative super-critical fluid chromatography (Lux C2 (4.6mm x 250mm, 5um) ; 40 °C, Flow Rate 50 mL/min, BPR 100 BarG, Detection at 210 nm, Injection Volume 500 uL (25 mg), 35:65 EtOH:CO_2 (0.2% v/v NH3)). Pure fractions were combined then evaporated, to give the title compound (4.01 g) as the slower eluting enantiomer. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.47-7.28 (m, 6H), 5.97-4.75 (m, 2H), 5.08-4.99 (m, 2H), 4.52 (dt, 1H), 3.82-3.72 (m, 1H), 3.73-3.65 (m, 2H), 3.59-3.51 (m, 1H), 1.85-1.72 (m, 2H), 1.72-1.50 (m, 3H). (compound isolated as a partial hydrochloride salt)

[0403] Preparation 34: Benzyl N-[(1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate, hydrochloride salt

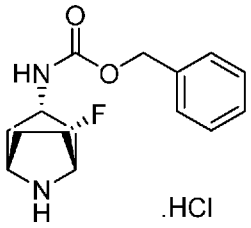
[0404] [Chem.68]



[0405] Partial HCl salt of benzyl ((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate (faster eluting enantiomer) (4.0 g, 13.65 mmol) was slurried in a minimal amount of dichloromethane (10 mL) and tert-butyl methyl ether (50 mL) then treated with 3M hydrogen chloride solution in cyclopentyl methyl ether (7 ml, 21.00 mmol). The mixture was slurried overnight then collected by filtration, to give the title compound (4.19 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.3-8.10 (br m, 2H), 7.65 (d, 1H), 7.46-7.24 (m, 5H), 5.18-4.94 (m, 2H), 4.82 (d, J = 47.7 Hz, 1H), 4.25-4.09 (m, 1H), 3.99-3.90 (m, 1H), 3.90-3.75 (m, 1H), 2.08-1.73 (m, 6H). $[\alpha]^{20}_D$ = 15.47° (c 1.00, MeOH).

[0406] Preparation 35: Benzyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate, hydrochloride salt

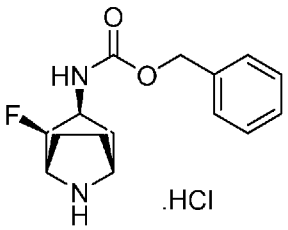
[0407] [Chem.69]



[0408] Benzyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (slow eluting isomer) (4.0 g, 13.65 mmol) was slurried in a minimal amount of dichloromethane (10 mL) and tert-butyl methyl ether (50 mL) then treated with 3M hydrogen chloride solution in cyclopentyl methyl ether (7 mL, 21.00 mmol). The mixture was slurried overnight then collected by filtration, to give the title compound (4.23 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.3-8.10 (br m, 2H), 7.65 (d, 1H), 7.46-7.24 (m, 5H), 5.18-4.94 (m, 2H), 4.82 (d, J = 47.7 Hz, 1H), 4.25-4.09 (m, 1H), 3.99-3.90 (m, 1H), 3.90-3.75 (m, 1H), 2.08-1.73 (m, 6H). $[\alpha]^{20}_D$ = -11.88° (c 1.05, MeOH).

[0409] Preparation 36: Benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride (Fast eluting isomer)

[0410] [Chem.70]

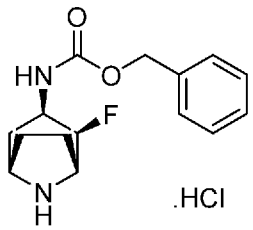


[0411] rac-Benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (3.83 g) was dissolved in methanol (50 mg mL-1) then purified by chiral preparative supercritical fluid chromatography (Lux A1 (4.6mm x 250mm, 5um) ; 40 °C, Flow Rate 50 mL/min, BPR 125 BarG, Detection at 210 nm, Injection Volume 1000 uL (50 mg), 50:50 MeOH:CO_2 (0.7% v/v DEA)). Benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate was isolated as the faster eluting enantiomer). Pure fractions were combined then evaporated. The residue was then dissolved in dichloromethane (5 mL) then added dropwise to a stirred mixture of tert-butyl methyl ether (20 mL), isohexane (20 mL) and 3.0 M hydrogen chloride in cyclopentyl methyl ether (2 mL, 6.00 mmol) to give a solid which was re-

crystallised in acetonitrile (15 mL), to give the title compound (1.15 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.82-9.29 (m, 2H), 7.62-6.86 (m, 6H), 5.25-4.87 (m, 3H), 4.29-4.13 (m, 1H), 4.13-4.00 (m, 1H), 3.98-3.85 (m, 1H), 2.42 (ddd, J = 14.1, 9.7, 4.7 Hz, 1H), 2.33-2.23 (m, 1H), 2.22-2.11 (m, 1H), 2.03-1.86 (m, 2H), 1.87-1.73 (m, 1H).

[0412] Preparation 37: Benzyl N-[(1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride (Slow eluting isomer)

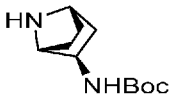
[0413] [Chem.71]



[0414] rac-Benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate was subjected to chiral preparative supercritical fluid chromatography (as above) and isolated as the slow eluting enantiomer. Pure fractions were combined then evaporated. The residue was then dissolved in dichloromethane (5 mL) then diluted with tert-butyl methyl ether (20 mL) and treated with 3.0 M hydrogen chloride in cyclopentyl methyl ether (2 ml, 6.00 mmol) to give a sticky suspension. The suspension was diluted with isohexane (30 mL) stirred for 18 h and collected by filtration, to give the title compound (1.5 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.82-9.29 (m, 2H), 7.62-6.86 (m, 6H), 5.25-4.87 (m, 3H), 4.29 - 4.13 (m, 1H), 4.13-4.00 (m, 1H), 3.98-3.85 (m, 1H), 2.42 (ddd, J = 14.1, 9.7, 4.7 Hz, 1H), 2.33-2.23 (m, 1H), 2.22-2.11 (m, 1H), 2.03-1.86 (m, 2H), 1.87-1.73 (m, 1H).

[0415] Preparation 38: tert-Butyl ((1R,2R,4S)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0416] [Chem.72]



[0417] Step 1

rac-tert-Butyl ((1S,2S,4R)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate hydrochloride (36 mg) was dissolved in DCM (2.89 mL). TEA (0.040 mL) and benzyl chloroformate (0.025 mL) were added thereto at RT, followed by stirring at RT for 1 h. The solvent was distilled off, and chloroform and water were added thereto. The mixture was extracted twice with chloroform and washed with water and saturated saline. The solvent was distilled off, and the residue was purified by silica gel column chromatography (gradient elution: hexane/EtOAc) to give benzyl rac-(1S,2S,4R)-

2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate. rac-Benzyl (1S,2S,4R)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate was obtained as a 10 mg/mL ethanol solution, and separation was performed under the following conditions.

Column: Daicel CHIRALPAK IC 2.0 x 25 cm

Mobile phase: hexane/2-propanol = 85/15

Flow rate: 12.5 mL/min

[0418] Retention time of each isomer:

Benzyl (1R,2R,4S)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate: 16.93 minutes

Benzyl (1S,2S,4R)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate: 23.82 minutes.

[0419] Chiral analysis conditions:

Column: CHIRALPAK IC 4.6 x 150 mm

Mobile phase: hexane/2-propanol = 85/15

Flow rate: 1.0 mL/min

[0420] Retention time of each isomer:

Benzyl (1R,2R,4S)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate: 6.972 minutes

Benzyl (1S,2S,4R)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate: 9.895 minutes.

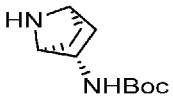
[0421] Step 2

Benzyl (1R,2R,4S)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate (93 g) and 10% Pd/C (10 g) were suspended in methanol (1.0 L). The mixture was stirred at RT for 5 h under a hydrogen atmosphere (50 psi). The reaction solution was filtrated, and the filtrate was concentrated to give the title compound. MS: $[M+H]^+$ = 213. ^{1}H-NMR (DMSO-d6) δ: 6.96-6.92 (1H, m), 3.63-3.56 (1H, m), 3.41-3.38 (1H, m), 3.35-3.32 (1H, m), 1.79-1.72 (1H, m), 1.67-1.61 (1H, m), 1.42-1.30 (11H, m), 1.27-1.19 (1H, m), 0.98-0.93 (1H, m).

[0422] Preparation 39: tert-Butyl ((1S,2S,4R)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0423]

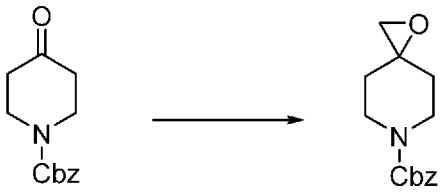
[Chem.73]



[0424] In accordance with Step 2 of Preparation 38, except that benzyl (1S,2S,4R)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate obtained in Step 1 of Preparation 38 was used in place of benzyl (1R,2R,4S)-2-((tert-butoxycarbonyl)amino)-7-azabicyclo[2.2.1]heptane-7-carboxylate, the title compound was obtained. MS: $[M+H]^+ = 213$. ^{1}H-NMR (DMSO-d6) δ: 6.97-6.93 (1H, m), 3.63-3.57 (1H, m), 3.42-3.38 (1H, m), 3.36-3.32 (1H, m), 1.79-1.72 (1H, m), 1.67-1.61 (1H, m), 1.43-1.30 (11H, m), 1.28-1.20 (1H, m), 0.99-0.92 (1H, m).

[0425] Preparation 40: Benzyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

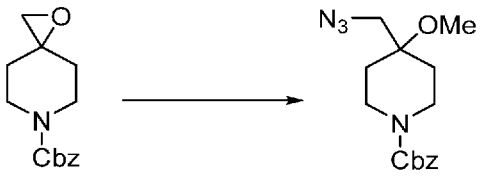
[0426] [Chem.74]



[0427] To a mixture of benzyl 4-oxopiperidine-1-carboxylate (11.7 g, 50 mmol) and trimethylsulfoxonium iodide (12.1 g, 55 mmol) in DME (200 mL) was added potassium tert-butoxide (6.17 g, 55 mmol), and stirred at 100 °C for 5 h. Water was added at RT and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : hexane = 1 : 5 to 1 : 2) to give the title compound (7.58 g). MS: $[M+H]^+ = 248$.

[0428] Preparation 41: Benzyl 4-(azidomethyl)-4-methoxypiperidine-1-carboxylate

[0429] [Chem.75]

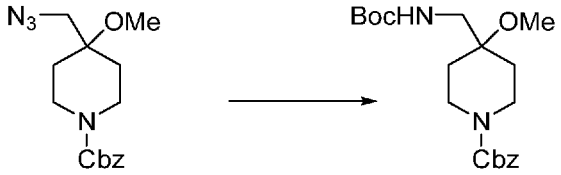


[0430] To a solution of benzyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (1.24 g, 5.0 mmol) in MeOH (30 mL) and water (6 ml) were added sodium azide (1.63 g., 25 mmol) and NH_4Cl (535 mg, 10 mmol) and stirred at 90 °C for 14 h. The solvent was removed under reduced pressure, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4,

filtered, and concentrated in vacuo. The residue in THF (15 mL) was added sodium hydride (55% in mineral oil, 262 mg, 6.0 mmol) at 0 °C, and stirred for 15 min., and added iodomethane (0.40 mL, 6.5 mmol) and stirred at RT for 15 h. Sat. NH_4Cl was added at 0 °C, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : hexane = 1 : 5 to 1 : 2) to give the title compound (1.16 g). MS: $[M+H]^+ = 305$.

[0431] Preparation 42: Benzyl 4-(((tert-butoxycarbonyl)amino)methyl)-4-methoxypiperidine-1-carboxylate

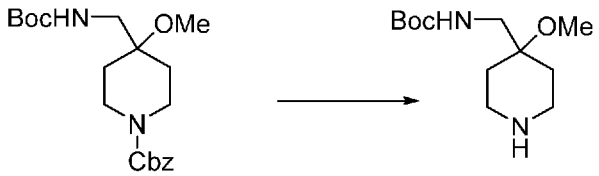
[0432] [Chem.76]



[0433] To a solution of benzyl 4-(azidomethyl)-4-methoxypiperidine-1-carboxylate (1.07 g, 3.5 mmol) in THF (15 mL) and water (0.63 mL, 35 mmol) was added triphenylphosphine (1.84 g, 7.0 mmol) at RT, and stirred at 45 °C for 15 h. The mixture was added 2 M NaOH (3.5 mL, 7.0 mmol) and di-tert-butyl dicarbonate (918 mg, 4.2 mmol) at 0 °C and stirred at RT for 2 h. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : hexane = 1 : 3 to 2 : 3) to give the title compound (1.32 g). MS: $[M+H]^+ = 379$.

[0434] Preparation 43: tert-Butyl ((4-methoxypiperidin-4-yl)methyl)carbamate

[0435] [Chem.77]

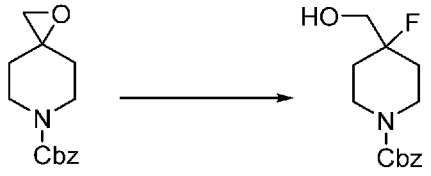


[0436] To a solution of benzyl 4-(((tert-butoxycarbonyl)amino)methyl)-4-methoxypiperidine-1-carboxylate (1.14 g, 3.0 mmol) in THF (15 mL) was added 10% palladium on carbon (46.7% wet, 280 mg, 0.12 mmol) and stirred for 1 h under hydrogen atmosphere. The mixture was added MeOH (15 mL) and stirred for 6 h under hydrogen atmosphere. After the reaction mixture was filtered by celite, the solvent was removed at reduced pressure to give the

title compound (742 mg). MS: $[M+H]^+$ = 245.

[0437] Preparation 44: Benzyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

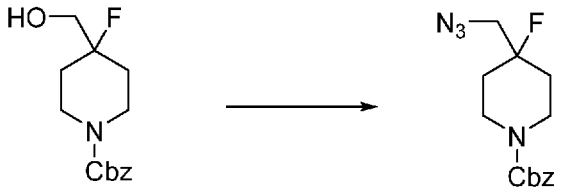
[0438] [Chem.78]



[0439] To a solution of benzyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (2.47 g, 10.0 mmol) in DCM (15 mL) was added pyridine polyfluoride hydrofluoride (2.0 mL, 14 mmol) in DCM (5 mL) at -10 °C and stirred at RT for 2 h. Sat. $NaHCO_3$ was added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : $CHCl_3$ = 1 : 10 to 1 : 3) to give the title compound (1.71 g). MS: $[M+H]^+$ = 268.

[0440] Preparation 45: Benzyl 4-(azidomethyl)-4-fluoropiperidine-1-carboxylate

[0441] [Chem.79]

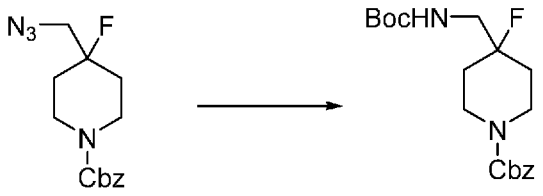


[0442] To a solution of benzyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (1.60 g, 6.0 mmol) in DCM (20 mL) were added Et_3N (1.68 mL, 12 mmol) and methanesulfonyl chloride (0.56 mL, 7.2 mmol) at RT, and stirred for 1 h. Water was added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue in DMF (15 mL) was added sodium azide (1.94 g, 30 mmol) and stirred at 110 °C for 48 h. Water was added at RT, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : hexane = 1 : 5 to 1 : 2) to give the title compound (1.20 g). MS: $[M+H]^+$ = 293.

[0443] Preparation 46: Benzyl 4-(((tert-butoxycarbonyl)amino)methyl)-4-fluoropiperidine-1-carboxylate

[0444]

[Chem.80]



[0445] To a solution of benzyl 4-(azidomethyl)-4-fluoropiperidine-1-carboxylate (1.02 g, 3.5 mmol) in THF (15 mL) and water (0.63 mL, 35 mmol) was added triphenylphosphine (1.84 g, 7.0 mmol) at RT, and stirred at 45 °C for 15 h. To the mixture were added 2 M NaOH (3.5 mL, 7.0 mmol) and di-tert-butyl dicarbonate (918 mg, 4.2 mmol) at 0 °C and stirred at RT for 6 h. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc : hexane = 1 : 3 to 2 : 3) to give the title compound (1.24 g). MS: $[M+H]^+ = 367$.

[0446] Preparation 47: tert-Butyl ((4-fluoropiperidin-4-yl)methyl)carbamate

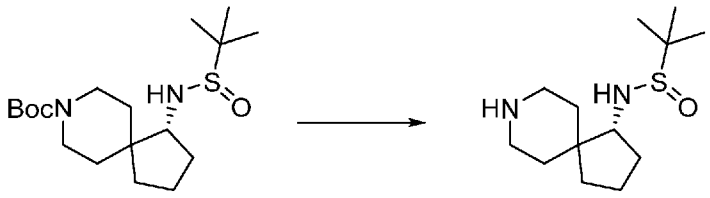
[0447] [Chem.81]



[0448] To a solution of benzyl 4-(((tert-butoxycarbonyl)amino)methyl)-4-fluoropiperidine-1-carboxylate (1.10 g, 3.0 mmol) in THF (15 mL) and MeOH (15 mL) was added 10% palladium on carbon (46.7% wet, 345 mg, 0.15 mmol) and stirred for 8 h under hydrogen atmosphere. After the reaction mixture was filtered by celite, the solvent was removed at reduced pressure to give the title compound (718 mg). MS: $[M+H]^+ = 233$.

[0449] Preparation 48: 2-Methyl-N-((R)-8-azaspiro[4.5]decan-1-yl)propane-2-sulfinamide

[0450] [Chem.82]

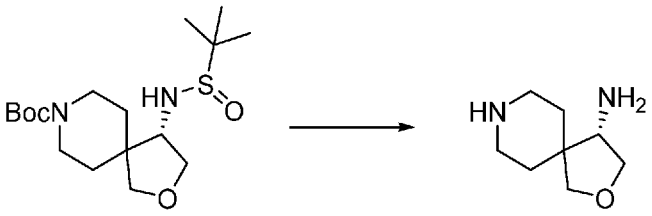


[0451] To a solution of tert-butyl (1R)-1-((tert-butylsulfinyl)amino)-8-azaspiro[4.5]decane-8-carboxylate (0.10 g, 0.28 mmol) prepared by the method as described in WO2016203405 in $CHCl_3$ (1 mL) was

added TFA (0.20 mL, 2.6 mmol) at RT. The mixture was stirred at RT for 2 h. The volatiles were removed under reduced pressure, and the resulting crude 2-methyl-N-((R)-8-azaspiro[4.5]decan-1-yl)propane-2-sulfinamide salt was used without further purification. MS: $[M+H]^+ = 259$.

[0452] Preparation 49: (S)-2-oxa-8-azaspiro[4.5]decan-4-amine

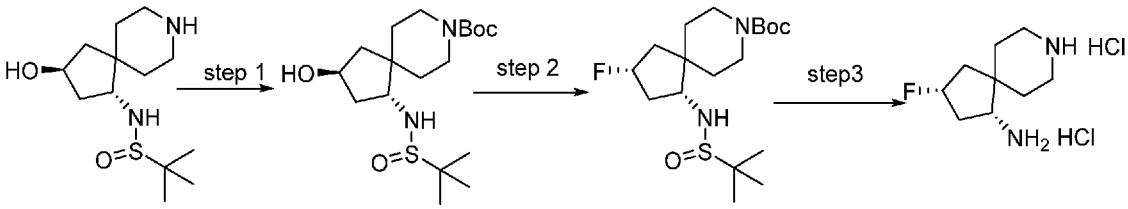
[0453] [Chem.83]



[0454] To a solution of tert-butyl (4S)-4-((tert-butylsulfinyl)amino)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (0.10 g, 0.28 mmol) prepared by the method as described in WO2016203405 in MeOH (1 mL) was added 4M HCl in 1,4-dioxane (0.70 mL, 2.8 mmol) at RT. The mixture was stirred at 50 °C for 30 min, and cooled to RT. The volatiles were removed under reduced pressure, the residue was azeotroped with toluene and the resulting crude (S)-2-oxa-8-azaspiro[4.5]decan-4-amine salt was used without further purification. MS: $[M+H]^+ = 157$.

[0455] Preparation 50: (1R,3R)-3-Fluoro-8-azaspiro[4.5]decan-1-amine dihydrochloride

[0456] [Chem.84]



[0457] Step 1: (1R,3S)-tert-Butyl 1-(1,1-dimethylethylsulfinamido)-3-hydroxy-8-azaspiro[4.5]decane-8-carboxylate

N-((1R,3S)-3-Hydroxy-8-azaspiro[4.5]decan-1-yl)-2-methylpropane-2-sulfinamide (950 mg, 3.46 mmol) was dissolved in THF (5 mL) and Boc_2O (754 mg, 3.46 mmol) was added. The solution was stirred at 50 °C for 4 hours before being concentrated. The crude material was purified by chromatography on silica gel (12 g cartridge, 0-10% MeOH/DCM) to afford (1R,3S)-tert-butyl 1-(1,1-dimethylethylsulfinamido)-3-hydroxy-8-azaspiro[4.5]decane-8-carboxylate (210 mg, 0.53 mmol, 15 % yield) as a colourless solid. MS: $[M+Na]^+ = 397$.

[0458] Step 2: (1R,3R)-tert-Butyl 1-(1,1-dimethylethylsulfinamido)-3-fluoro-8-azaspiro[4.5]decane-8-carboxylate

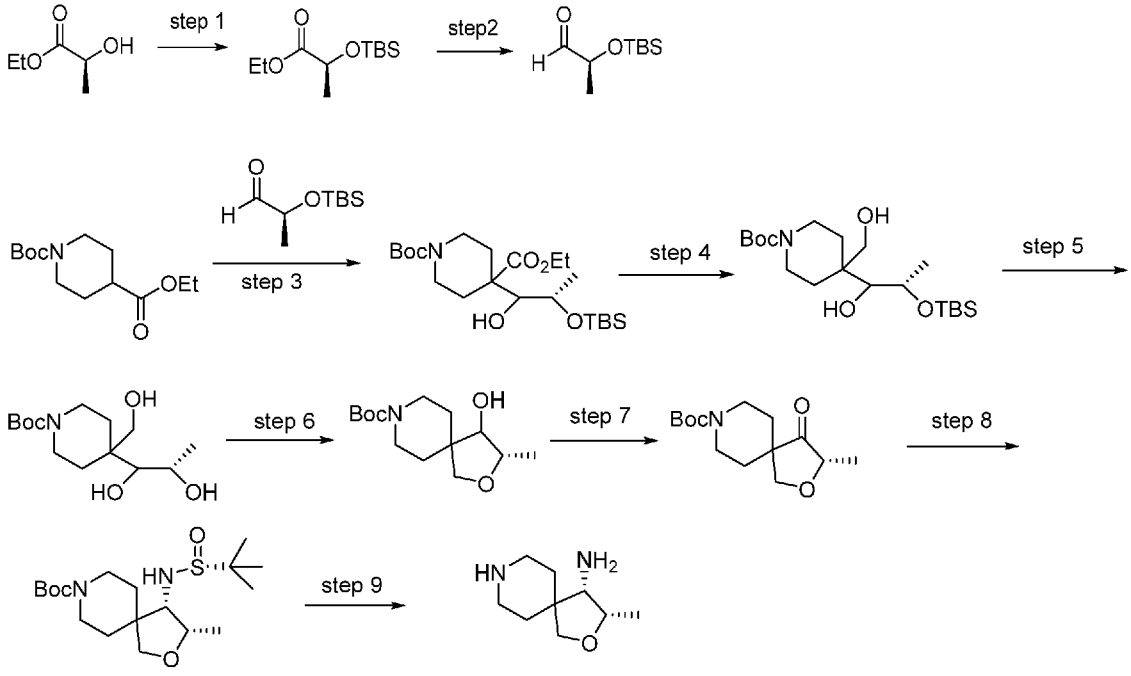
(1R,3S)-tert-Butyl 1-(1,1-dimethylethylsulfinamido)-3-hydroxy-8-azaspiro[4.5]decane-8-carboxylate (200 mg, 0.53 mmol) was dissolved in DCM (2.5 mL) and the solution cooled to 0 °C. Deoxofluor (50% wt in toluene) (0.35 mL, 0.934 mmol) was added dropwise and the mixture stirred at room temperature for 3 hours. A further portion of deoxofluor (50% wt in toluene) (0.35 mL, 0.934 mmol) was added and the reaction was stirred at 0 °C for 3 hours and then ambient temperature for 30 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and the mixture stirred for 15 minutes. The organic phase was isolated and the aqueous phase was further extracted with DCM (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material as an orange oil. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-10% MeOH/DCM) to afford (1R,3R)-tert-butyl 1-(1,1-dimethylethylsulfinamido)-3-fluoro-8-azaspiro[4.5]decane-8-carboxylate (135 mg, 0.32 mmol, 60% yield) as a pale orange gum. MS: $[M+Na]^+ = 399$.

[0459] Step 3: (1R,3R)-3-Fluoro-8-azaspiro[4.5]decan-1-amine dihydrochloride

HCl (4M in dioxane) (1.0 mL) was added to (1R,3R)-tert-butyl 1-(1,1-dimethylethylsulfinamido)-3-fluoro-8-azaspiro[4.5]decane-8-carboxylate (130 mg, 0.345 mmol) and the mixture stirred at room temperature. A further portion of HCl (4M in dioxane) (1.0 mL) was added and the reaction was stirred at room temperature for 1 hour 30 minutes. The mixture was concentrated to give orange solids. The crude material was used directly in subsequent steps.

[0460] Preparation 51: (3S,4S)-3-Methyl-2-oxa-8-azaspiro[4.5]decan-4-amine hydrochloride

[0461] [Chem.85]



[0462] Step 1: Ethyl (2S)-2-[(tert-butyldimethylsilyl)oxy]propanoate

The reaction mixture of ethyl (2S)-2-hydroxypropanoate (95.0 g, 0.8 mol) in DCM (1 L) was cooled to 0 °C, then imidazole (81.6 g, 1.2 mol) and TBSCl (133.3 g, 0.88 mol) were added, stirred at ambient temperature for about 1.5 h. The reaction mixture was poured into water (1.0 L), extracted with DCM (2 x 500 mL), then washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet.ether/EtOAc=50/1 to 20/1) to give the product (180.0 g, 97%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.33 (s, 1H), 4.22 (s, 2H), 1.44 (d, 3H), 1.32 (t, 3H), 0.97 (s, 9H), 0.15 (s, 6H).

[0463] Step 2: (2S)-2-[(tert-Butyldimethylsilyl)oxy]propanal

A solution of ethyl (2S)-2-[(tert-butyldimethylsilyl)oxy]propanoate (131.0 g, 0.56 mol) in toluene (800 mL) was cooled to -60 °C , DIBAL-H (1.5 M, 560 mL, 0.85 mol) was dropwise added, then stirred at -60 °C for 2 h. The reaction mixture was poured into water (800 mL), extracted with EtOAc (2 x 500 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the crude product. It was used in the next step without purification.

[0464] Step 3: 1-tert-Butyl 4-ethyl 4-[(2S)-2-[(tert-butyldimethylsilyl)oxy]-1-hydroxypropyl]piperidine-1,4-dicarboxylate

A solution of diisopropylamine (65.0 g, 0.64mol) in THF (400 mL) was cooled to -20 °C. n-BuLi (2.5 M, 224 mL, 0.56 mol) was added dropwise, then stirred at -10 °C for 1 h. 1-tert-Butyl 4-ethyl piperidine-1,4-dicarboxylate (110.0 g, 0.43 mol) in THF (200 mL) was added dropwise at -10 °C, then stirred at -10 °C to ambient temperature for 1 h under N_2. (2S)-2-[(tert-Butyldimethylsilyl)oxy]propanal (120.0 g, 0.64 mol) in THF (200 mL) was added dropwise at -10 °C, then stirred at -10 °C to 0 °C for 2 h. The reaction mixture was poured into sat. NH_4Cl (1L), extracted with EtOAc (2 x 500 mL), the combined EtOAc phase was washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet.ether/EtOAc=50/1 to 30/1 to 20/1) to give the product (70.0 g, 37%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29-4.09 (m, 2H), 4.06-3.88 (m, 2H), 3.79 (d, 1H), 3.60-3.48 (m, 1H), 2.78 (s, 2H), 2.66-2.25 (m, 1H), 2.24-1.94 (m, 2H), 1.74 (m, 2H), 1.50-1.37 (m, 9H), 1.34-1.18 (m, 5H), 1.12 (d, 3H), 0.91 (s, 10H), 0.04 (s, 6H).

[0465] Step 4: tert-Butyl 4-[(2S)-2-[(tert-butyldimethylsilyl)oxy]-1-hydroxypropyl]-4-(hydroxymethyl)piperidne-1-carboxylate

To the solution of 1-tert-butyl 4-ethyl 4-[(2S)-2-[(tert-butyldimethylsilyl)oxy]-1-hydroxypropyl]piperidine-1,4-dicarboxylate (70.0 g, 0.157 mol) in THF (700 mL) was added $LiBH_4$ (2 M, 118 mL, 0.236 mol) at 0 °C , then stirred at ambient temperature overnight. The mixture was poured into water

(500 mL), stirred at ambient temperature for 20 min, extracted with EtOAc (2 x 300 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the crude product (60.0 g). It was used in the next step without purification.

[0466] Step 5: tert-Butyl 4-[(2S)-1,2-dihydroxypropyl]-4-(hydroxymethyl)piperidine-1-carboxylate

To a cooled (0 °C) solution of tert-butyl 4-[(2S)-2-[(tert-butyldimethylsilyl)oxy]-1-hydroxypropyl]-4-(hydroxymethyl)piperidn e-1-carboxylate (60.0 g, 0.149 mol) in THF (600 mL), TBAF (1 M, 223 mL, 0.223 mol) was added, and stirred at ambient temperature for 2 h. $NaHCO_3$ (aq. 600 mL) was added, stirred at ambient temperature for 10 min, extracted with EtOAc (2 x 300 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (DCM/MeOH=100/1 to 50/1 to 30/1) to give the product (37.0g, 86%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.02-3.87 (m, 1H), 3.74 (m, 4H), 3.36 (d, 4H), 3.10 (s, 2H), 1.66 (s, 3H), 1.40 (s, 10H), 1.31 (s, 3H).

[0467] Step 6: tert- Butyl (3S)-4-hydroxy-3-methyl-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

To an ice cooled solution of tert-butyl 4-[(2S)-1,2-dihydroxypropyl]-4-(hydroxymethyl)piperidine-1-carboxylate (37.0 g, 0.127 mol) in THF (400 mL) was added NaH (17.8 g, 0.44 mol) in portions, then a solution of TsCl (25.5 g, 0.134 mol) in THF (200 mL) was added and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into ice and NH_4 Cl (aq. 600 mL), extracted with EtOAc (3 x 400 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (DCM/MeOH=100/1 to 50/1 to 30/1) to give the product (20.0 g, 58%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94-3.57 (m, 4H), 3.45 (d, 1H), 2.96 (s, 2H), 1.70 (s, 3H), 1.42 (s, 10H), 1.29 (m, 4H).

[0468] Step 7: tert-Butyl (3S)-3-methyl-4-oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

To an ice cooled solution of tert-butyl (3S)-4-hydroxy-3-methyl-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (20.0 g, 0.074 mol) in DCM (200 mL) was added DMP (37.5 g, 0.088 mol) in portions. The reaction mixture was stirred at ambient temperature for 1h, poured into $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the product (19.0 g, 95%) as a yellow oil. It was used in the next step directly.

[0469] Step 8: tert-Butyl (3S,4S)-3-methyl-4-[(2-methylpropane-2-sulfinyl)amino]-2-oxa-8-azaspiro[4.5]decane -8-carboxylate

To the solution of tert-butyl (3S)-3-methyl-4-oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (11.0 g, 0.04 mol) in

THF (250 mL) was added (R)-2-methylpropane-2-sulfinamide (9.9 g, 0.08 mol), $Ti(OEt)_4$ (36.5 g, 0.16 mol) and the reaction mixture was stirred at 75 °C for overnight. The reaction mixture was cooled to -10 °C, $LiBH_4$ (2 M, 30 mL, 0.06mol) was dropwise added, then stirred at -10 °C for 1h. The reaction mixture was poured into ice and NH_4Cl (aq. 300 mL) and EtOAc (300 mL), stirred at ambient temperature for 20 min, then filtered through celite. The reaction mixture was extracted with EtOAc (2 x 300 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet. ether/ EtOAc=10/1 to 5/1 to 3/1 to 2/1) to give the product (7.0 g, 47%). ^1H NMR (400 MHz, DMSO-d_6) δ: 5.07 (d, J = 11.0 Hz, 1H), 4.06 (s, 1H), 3.74 (m, 3H), 3.37 (d, 3H), 2.84 (s, 2H), 1.69-1.50 (m, 2H), 1.39 (s, 11H), 1.15 (s, 9H), 1.06 (m, 3H).

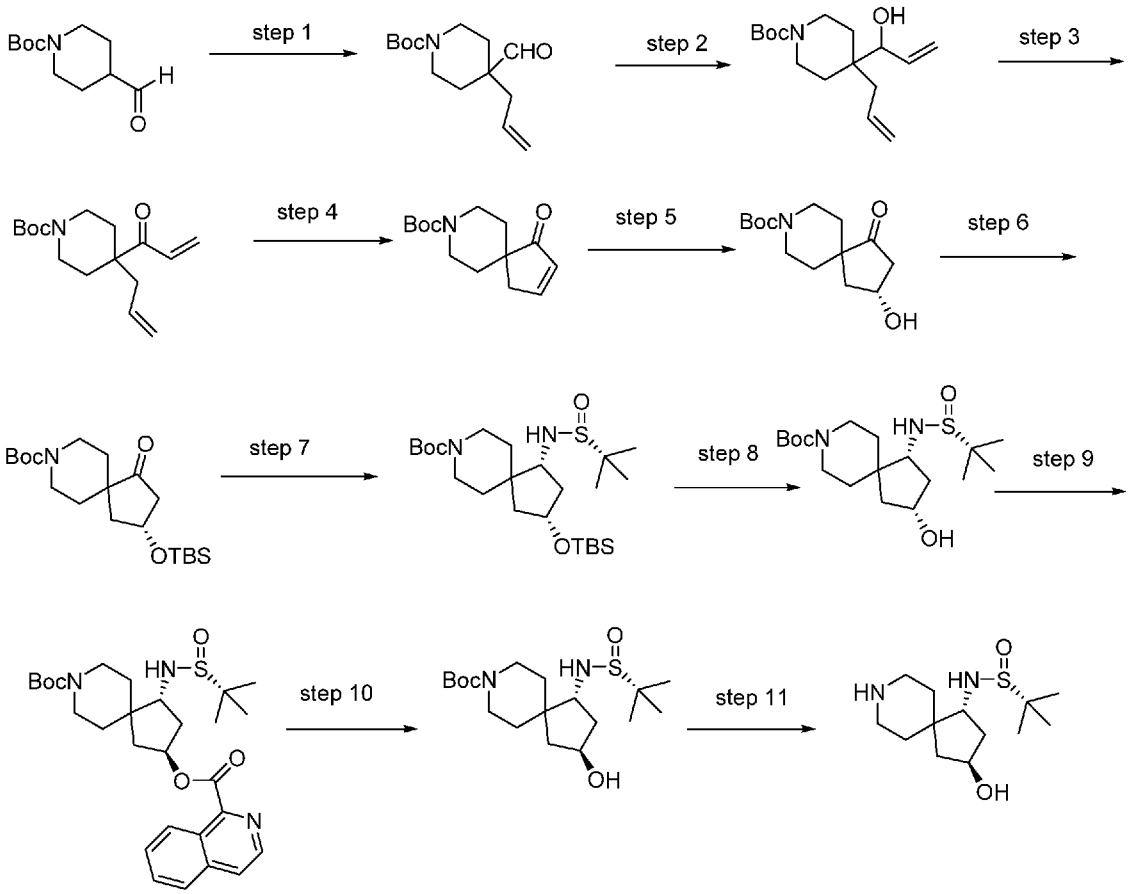
[0470] Step 9: (3S,4S)-3-Methyl-2-oxa-8-azaspiro[4.5]decan-4-amine hydrochloride

To the solution of tert-butyl (3S,4S)-3-methyl-4-[(2-methylpropane-2-sulfinyl)amino]-2-oxa-8-azaspiro[4.5]decane -8-carboxylate (5.8 g, 15.5 mmol) in MeOH (20 mL) was added HCl/dioxane (4M, 39 mL, 155 mmol), then stirred at 50 °C for 2 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The crude product was dissolved in water (50mL), extracted with EtOAc (3 x 40mL). The aqueous phase was freeze dried to give the HCl salt of the product (4.0 g) as a yellow solid. MS: $[M+H]^+$ = 171. ^1H NMR (400 MHz, DMSO-d_6) δ: 4.44 (m, 1H), 4.05-3.88 (m, 2H), 3.67 (s, 1H), 3.58-3.39 (m, 2H), 3.22-3.01 (m, 2H), 1.98 (m, 4H), 1.34 (s, 3H).

[0471] Preparation 52: N-((1R,3S)-3-Hydroxy-8-azaspiro[4.5]decan-1-yl)-2-methylpropane-2-sulfinamide

[0472]

[Chem.86]



[0473] Step 1: tert-Butyl 4-formyl-4-(prop-2-en-1-yl)piperidine-1-carboxylate

A solution of tert-butyl 4-formylpiperidine-1-carboxylate (300.0 g, 1.40 mol) in THF (3 L) was cooled to -25 °C, allylbromide (187.7 g, 1.55 mol) was added, then t-BuOK (173.0 g, 1.55 mol) in portions, then stirred at -25 °C ~ -15 °C for 45 min. The reaction mixture was poured into ice and NH_4Cl (aq. 3L), extracted with EtOAc (2 x 2L), washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet.ether/EtOAc=50/1 to 20/1 to 10/1) to give the product (210.0 g, 60%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 5.58 (s, 1H), 5.03 (s, 2H), 3.76 (s, 2H), 2.90 (s, 2H), 2.21 (s, 2H), 1.89 (s, 2H), 1.43 (s, 9H).

[0474] Step 2: tert-Butyl
4-(1-hydroxyprop-2-en-1-yl)-4-(prop-2-en-1-yl)piperidine-1-carboxylate

A solution of tert-butyl 4-formyl-4-(prop-2-en-1-yl)piperidine-1-carboxylate (250.0 g, 0.99 mol) in THF (2.5 L) was cooled to -60 °C , vinylmagnesium bromide (1.18 L, 1.18 mol) was added, then stirred at ambient temperature for 1 h. The mixture was poured into NH_4Cl (aq. 3L), extracted with EtOAc (2 x 2L), washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the product (270.0 g, 97%) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.00-5.78 (m, 2H), 5.28-5.15 (m, 2H), 5.11-4.99 (m,

2H), 3.98 (d, 1H), 3.79-3.56 (m, 2H), 3.09 (s, 2H), 2.24 (ddd, 7.5 Hz, 2H), 1.86 (d, 1H), 1.65-1.49 (m, 2H), 1.45-1.38 (m, 11H).

[0475] Step 3: tert-Butyl 4-(prop-2-en-1-yl)-4-(prop-2-enoyl)piperidine-1-carboxylate

A solution of tert-butyl 4-(1-hydroxyprop-2-en-1-yl)-4-(prop-2-en-1-yl)piperidine-1-carboxylate (286.0 g, 1.01 mol) in DCM (1.5 L) was cooled to 0 °C, DMP (471.0 g, 1.1 mol) was added and stirred at ambient temperature for 2 h. The reaction mixture was poured into $NaHCO_3$ / Na_2SO_3 (1:1, 2 L), extracted with DCM (1 L), the combined DCM phase was washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the crude product (840.0 g) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ: 6.88-6.70 (m, 1H), 6.37 (d, 1H), 5.68 (d, 1H), 5.55 (d, 1H), 5.02 (t, 2H), 3.74 (s, 2H), 2.93 (s, 2H), 2.28 (s, 2H), 2.06 (s, 2H), 1.43 (s, 11H).

[0476] Step 4: tert-Butyl 1-oxo-8-azaspiro[4.5]dec-2-ene-8-carboxylate

To a solution of tert-butyl 4-(prop-2-en-1-yl)-4-(prop-2-enoyl)piperidine-1-carboxylate (256.0 g, 0.91 mol) in toluene (3 L) was added dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)(tricyclohexylphosphine)ruthenium(II) (31.1 g, 0.037 mol) and stirred at 85 °C for 3 h. The reaction mixture was concentrated in vacuo, purified by silica column (pet.ether/EtOAc=50/1 to 30/1 to 15/1) to give the product (370.0 g) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (s, 1H), 6.16 (s, 1H), 4.08 (s, 2H), 2.90 (s, 2H), 2.60 (s, 2H), 1.72 (m, 2H), 1.46 (s, 9H), 1.25 (s,2H).

[0477] Step 5: tert-Butyl (3R)-3-hydroxy-1-oxo-8-azaspiro[4.5]decane-8-carboxylate

A mixture of CuCl (1.55 g, 0.0156 mol), (S)-TolBINAP (10.6 g, 0.0156 mol), t-BuONa (1.5 g, 0.0156 mol) in THF (900mL) was stirred at ambient temperature for 30 min. Bis(pinacolato)diboron (145.3g, 0.572 mol) in THF (400 mL) was added and stirred at ambient temperature for 15 min. tert-Butyl 1-oxo-8-azaspiro[4.5]dec-2-ene-8-carboxylate (130.0 g, 0.52 mol) in (THF 200 mL) and MeOH (33.3 g, 1.04 mol) were added and the reaction mixture was stirred at ambient temperature overnight. Water (1.6 L) and $NaBO_3$ (400.0 g, 2.6 mol) were added and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was filtered, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by silica column (pet. ether/EtOAc=20/1 to 10/1 to 3/1) to give the product (100.0 g, 71%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.61 (s, 1H), 3.88 (s, 2H), 3.03 (m, 2H), 2.65 (s, 1H), 2.38 (s, 1H), 2.19 (s, 3H), 1.73 (m, 4H), 1.44 (s, 9H).

[0478] Step 6: tert-Butyl (3R)-3-[(tert-butyldimethylsilyl)oxy]-1-oxo-8-azaspiro[4.5]decane-8-carboxylate

To a solution of tert-butyl (3R)-3-hydroxy-1-oxo-8-azaspiro[4.5]decane-8-carboxylate (110.0 g, 0.4 mol) in DMF (1.0 L) were added imidazole (41.0 g, 0.6 mol), TBSCl (73.3 g, 0.48 mol) and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was poured into water (5L), extracted with EtOAc (2 x 2L) washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet.ether/EtOAc=20/1 to 10/1 to 3/1) to give the product (120.0 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.49 (s, 1H), 3.88 (s, 2H), 2.97 (s, 2H), 2.52 (s, 1H), 2.21 (s, 2H), 2.06 (s, 2H), 1.66 (s, 4H), 1.43 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H).

[0479] Step 7: tert-Butyl (1R,3R)-3-[(tert-butyldimethylsilyl)oxy]-1-[(2-methylpropane-2-sulfinyl)amino]-8-aza spiro[4.5]decane-8-carboxylate

To the solution of tert-butyl (3R)-3-[(tert-butyldimethylsilyl)oxy]-1-oxo-8-azaspiro[4.5]decane-8-carboxylate (80.0 g, 0.2 mol) in THF (1.3 L) was added (R)-2-methylpropane-2-sulfinamide (50.6 g, 0.4 mol), $Ti(OEt)_4$ (182.5 g, 0.8 mol), then stirred at 65 °C overnight. The reaction mixture was cooled to -60 °C , $LiBH_4$ (2 M, 300 mL, 0.6 mol) was added dropwise, stirred at -60 °C overnight. The reaction mixture was poured into NH_4Cl (aq. 2 L), extracted with EtOAc (2 x 1L), washed with brine, dried over Na_2SO_4, concentrated in vacuo, purified by silica column (pet.ether/EtOAc=10/1 to 3/1) to give the product (120.0 g) as a yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ: 4.30 (s, 1H), 3.94 (s, 2H), 3.58 (s, 1H), 3.28 (s, 1H), 2.82 (s, 2H), 2.30 (s, 1H), 1.76 (m, 7H), 1.38 (s, 9H),1.19 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H).

[0480] Step 8: tert-Butyl (1R,3R)-3-hydroxy-1-[(2-methylpropane-2-sulfinyl)amino]-8-azaspiro[4.5]decane-8-c arboxylate

To the solution of tert-butyl (1R,3R)-3-[(tert-butyldimethylsilyl)oxy]-1-[(2-methylpropane-2-sulfinyl)amino]-8-aza spiro[4.5]decane-8-carboxylate (135.0 g, 0.276 mol) in THF (800 mL) was added TBAF (553 mL, 0.553 mol) and stirred at ambient temperature for 4 h. The reaction mixture was poured into water (1L), extracted with EtOAc (2 x 500 mL), washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the crude product (100.0 g, 97%) as a yellow oil. It was used in the next step without purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.05 (s, 1H), 4.67 (s, 1H), 4.04 (s, 1H), 3.82 (s, 2H), 3.05 (s, 1H), 2.74 (br, s, 2H), 2.10 (m, 1H), 1.67 (m, 4H), 1.42 (m, 11H), 1.24 (s, 2H), 1.09 (m, 9H).

[0481] Step 9: tert-Butyl (1R,3S)-3-(isoquinoline-1-carbonyloxy)-1-[(2-methylpropane-2-sulfinyl)amino]-8-aza spiro[4.5]decane-8-carboxylate

To the solution of tert-butyl

(1R,3R)-3-hydroxy-1-[(2-methylpropane-2-sulfinyl)amino]-8-azaspiro[4.5]decane-8-carboxylate (120.0 g, 0.32 mol) in THF (1 L) was added isoquinoline-1-carboxylic acid (166.6 g, 0.96 mol), DIAD (97.1g, 0.48 mol), TPP (125.9 g, 0.48 mol) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured into $NaHCO_3$ (aq. 2L), extracted with EtOAc (2 x 1L), washed with brine, dried over Na_2SO4, concentrated in vacuo to give the crude product, which was purified by silica column (DCM/EtOAc=50/1 to 20/1 to DCM/MeOH=20/1) to give the product (120.0 g, 71%) as a yellow solid. MS: $[M+H]^+ = 530$. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.59 (s, 1H), 8.40 (s, 1H), 8.04 (s, 2H), 7.83 (d, 2H), 5.48 (s, 1H), 5.23 (s, 1H), 3.85 (s, 2H), 3.50 (s, 1H), 2.77 (s, 2H), 2.49-2.38 (m, 1H), 2.14 (d, 2H), 1.73 (s, 2H), 1.47 (s, 1H), 1.38 (s, 9H), 1.25 (s, 3H), 1.15 - 1.11 (m, 9H).

[0482] Step 10: tert-Butyl (1R,3S)-3-hydroxy-1-[(2-methylpropane-2-sulfinyl)amino]-8-azaspiro[4.5]decane-8-carboxylate

To the solution of tert-butyl (1R,3S)-3-(isoquinoline-1-carbonyloxy)-1-[(2-methylpropane-2-sulfinyl)amino]-8-azaspiro[4.5]decane-8-carboxylate (120.0 g, 0.227 mol) in THF/H_2O (1/1, 1 L) was added LiOH · H_2O (92.9g, 2.27 mol) and stirred at ambient temperature for 2 h. The reaction mixture was poured into NH_4Cl (aq. 2L), extracted with EtOAc (2 x 1L), washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the crude product, which was purified by crystallization from EtOAc/hexane to give the product (64.0g, 75%) as a white solid. MS: $[M+H-Boc]^+ = 275$. ^1H NMR (400 MHz, DMSO-d_6) δ: 4.97 (s, 1H), 4.51 (s, 1H), 4.06 (s, 1H), 3.82 (s, 2H), 3.39 (s, 1H), 2.74 (s, 2H), 1.99 (s, 1H), 1.81 (s, 3H), 1.39 (s, 11H), 1.28-1.16 (m, 1H), 1.11 (s, 9H).

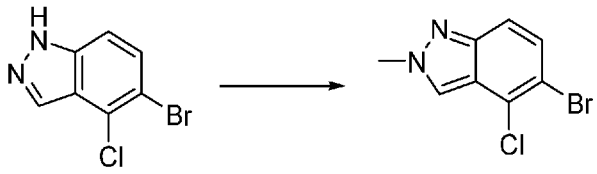
[0483] Step 11: N-[(1R,3S)-3-Hydroxy-8-azaspiro[4.5]decan-1-yl]-2-methylpropane-2-sulfinamide

To the solution of tert-butyl (1R,3S)-3-hydroxy-1-[(2-methylpropane-2-sulfinyl)amino]-8-azaspiro[4.5]decane-8-carboxylate (64.0 g, 0.171 mol) in DCM (600 mL) was added TFA (195.3 g, 1.71 mol), stirred at ambient temperature for 2 h. The reaction mixture was poured into water (2 L), extracted with Et_2O (5 x 300 mL) to remove impurities, then the pH was adjusted pH = 8 with $NaHCO_3$ (aq.), the water was freeze dried to give the product (50.0 g) as a colourless oil. MS: $[M+H]^+ = 275$. ^1H NMR (400 MHz, DMSO-d_6) δ: 5.13 (d, 1H), 4.83 (br, s, 3H), 4.08 (s, 1H), 3.44 (m, 1H), 3.15 (m, 2H), 2.78 (m, 2H), 2.01-1.64 (m, 4H), 1.40 (m, 2H), 1.25 (m, 1H), 1.15 (s, 9H).

[0484] Preparation 53: 5-Bromo-4-chloro-2-methyl-2H-indazole

[0485]

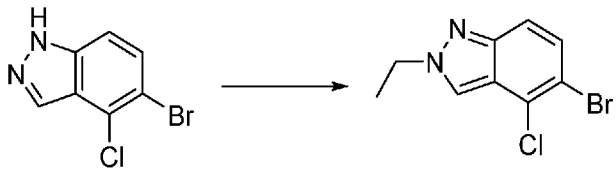
[Chem.87]



[0486] To a suspension of 5-bromo-4-chloro-1H-indazole (10.0 g, 43.2 mmol) in EtOAc (200 mL) was added trimethyloxonium tetrafluoroborate (9.58 g, 64.8 mmol) at RT. The mixture was stirred at RT for 20 h, quenched with sat. $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 50% EtOAc/hexane) to give the title compound (9.16 g). MS: $[M+H]^+$ = 245, 247.

[0487] Preparation 54: 5-Bromo-4-chloro-2-ethyl-2H-indazole

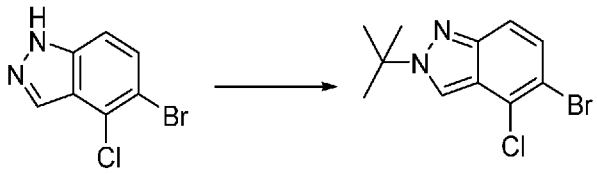
[0488] [Chem.88]



[0489] To a suspension of 5-bromo-4-chloro-1H-indazole (5.0 g, 21.6 mmol) in EtOAc (100 mL) was added triethyloxonium hexafluorophosphate (8.04 g, 32.4 mmol) at RT. The mixture was stirred at RT overnight, quenched with sat. $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 50% EtOAc/hexane) to give the title compound (5.05 g). MS: $[M+H]^+$ = 259, 261.

[0490] Preparation 55: 5-Bromo-2-(tert-butyl)-4-chloro-2H-indazole

[0491] [Chem.89]



[0492] To a suspension of 5-bromo-4-chloro-1H-indazole (0.93 g, 4.0 mmol) in toluene (8.0 mL) were added tert-butyl acetate (4.7 g, 40 mmol) and methanesulfonic acid (0.38 g, 4.0 mmol) at RT.

The mixture was stirred at 95 °C for 1 d. To the mixture was added tert-butyl acetate

(4.7 g, 40 mmol) and methanesulfonic acid (0.38 g, 4.0 mmol) and stirred for another 1 d. The mixture was diluted with EtOAc, and washed with water and brine. The organic layer was concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 20% EtOAc/hexane) to give the title compound (1.1 g). MS: $[M+H]^+$ = 287, 289.

[0493] Preparation 56: 5-Bromo-2-methyl-2H-indazole

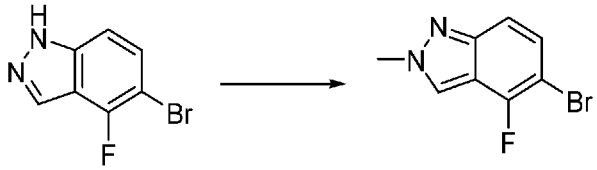
[0494] [Chem.90]



[0495] Prepared from 5-bromo-1H-indazole using similar procedure for the preparation of 5-bromo-4-chloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 211, 213.

[0496] Preparation 57: 5-Bromo-4-fluoro-2-methyl-2H-indazole

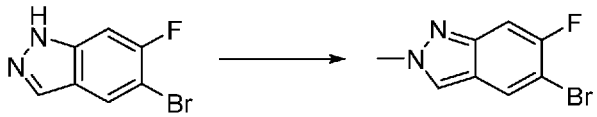
[0497] [Chem.91]



[0498] Prepared from 5-bromo-4-fluoro-1H-indazole using similar procedure for the preparation of 5-bromo-4-chloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 229, 231.

[0499] Preparation 58: 5-Bromo-6-fluoro-2-methyl-2H-indazole

[0500] [Chem.92]

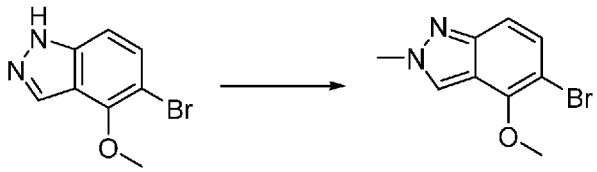


[0501] Prepared from 5-bromo-6-fluoro-1H-indazole using similar procedure for the preparation of 5-bromo-4-chloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 229, 231.

[0502] Preparation 59: 5-Bromo-4-methoxy-2-methyl-2H-indazole

[0503]

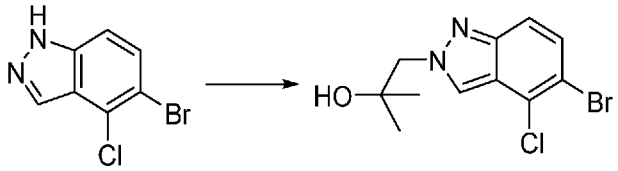
[Chem.93]



[0504] Prepared from 5-bromo-4-methoxy-1H-indazole using similar procedure for the preparation of 5-bromo-4-chloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 241, 243.

[0505] Preparation 60: 1-(5-Bromo-4-chloro-2H-indazol-2-yl)-2-methylpropan-2-ol

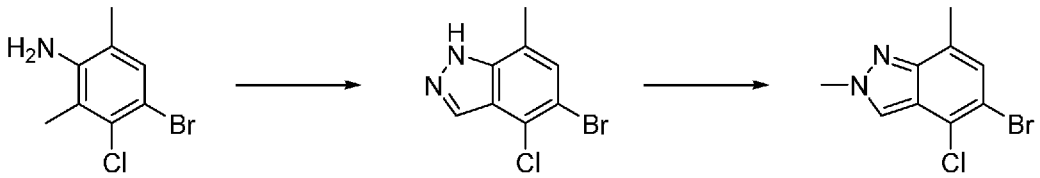
[0506] [Chem.94]



[0507] To a solution of 5-bromo-4-chloro-1H-indazole (1.0 g, 4.32 mmol) in DMF (10 mL) was added K_2CO_3 (1.19 g, 8.64 mmol) and isobutylene oxide (0.58 mL, 6.48 mmol) at RT. The mixture was stirred at 100 °C for 2 h, diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 10 - 20% EtOAc/hexane) to give the title compound (0.55 g). MS: $[M+H]^+$ = 303, 305.

[0508] Preparation 61: 5-Bromo-4-chloro-2,7-dimethyl-2H-indazole

[0509] [Chem.95]



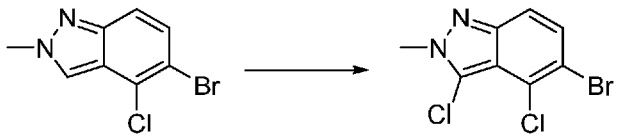
[0510] To a mixture of 4-bromo-3-chloro-2,6-dimethylaniline (4.8 g, 20 mmol), potassium acetate (3.1 g, 31 mmol), acetic acid (1.8 g, 29 mmol) and toluene (61 mL) was added tert-butyl nitrite (2.5 g, 25 mmol) at RT. The mixture was stirred at 45 °C overnight. To the mixture was added EtOAc (40 mL) and 1 M NaOH aq. (40 mL). The separated organic layer was washed with brine, and concentrated in vacuo. The residue was suspended in toluene and heptane. The precipitate was collected and dried at 50 °C under reduced pressure to give a mixture of 5-bromo-4-chloro-7-methyl-1H-indazole and 5-bromo-6-chloro-7-methyl-1H-indazole (3.4 g). MS: $[M+H]^+$ = 245, 247.

Prepared from a mixture of 5-bromo-4-chloro-7-methyl-1H-indazole and

5-bromo-6-chloro-7-methyl-1H-indazole using similar procedure for the preparation of 5-bromo-4-chloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 259, 261

[0511] Preparation 62: 5-Bromo-3 4-dichloro-2-methyl-2H-indazole

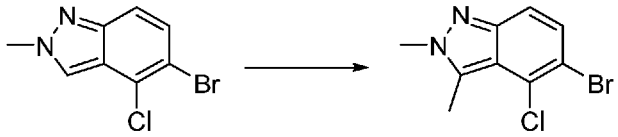
[0512] [Chem.96]



[0513] To a solution of 5-bromo-4-chloro-2-methyl-2H-indazole (5 g, 20.3 mmol) in DMF (50 mL) was added NCS (2.99 g, 22.4 mmol) at 0 °C. The mixture was stirred at RT overnight. Water (150 mL) was added at RT. The mixture was stirred at RT for 1 h. The precipitate was collected, washed with water, and dried at 60 °C for 3 h under reduced pressure to give the title compound (5.63 g). MS: $[M+H]^+$ = 279, 281.

[0514] Preparation 63: 5-Bromo-4-chloro-2,3-dimethyl-2H-indazole

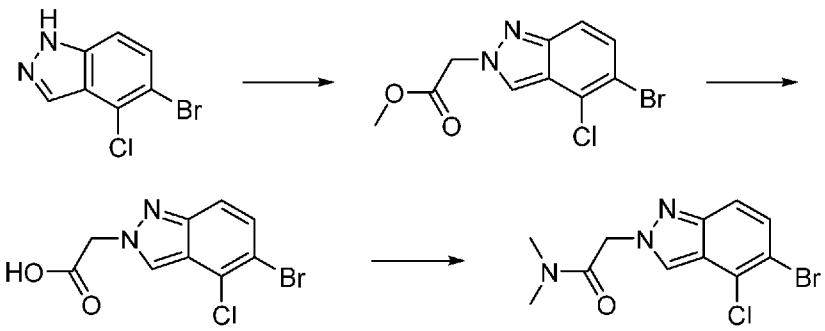
[0515] [Chem.97]



[0516] To a solution of 5-bromo-4-chloro-2-methyl-2H-indazole (500 mg, 2.03 mmol) in THF (10 mL) was added LDA (1.08 M in THF, 2.26 mL, 2.44 mmol) at -78 °C. The mixture was stirred at 0 °C for 30 min, and cooled to -78 °C. Iodomethane (0.190 mL, 3.05 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 2 h, quenched with sat. NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/ hexane) to give the title compound (442 mg). MS: $[M+H]^+$ = 259, 261.

[0517] Preparation 64: 2-(5-Bromo-4-chloro-2H-indazol-2-yl)-N,N-dimethylacetamide

[0518] [Chem.98]



[0519] Step 1

To a solution of 5-bromo-4-chloro-1H-indazole (500 mg, 2.16 mmol) and methyl glycolate (0.25 mL, 3.24 mmol) in THF (10 mL) was added DMEAD (759 mg, 3.24 mmol) and triphenylphosphine (850 mg, 3.24 mmol) at RT. The mixture was stirred at RT for 2 h. The reaction solution was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 20 - 40% EtOAc/ hexane) to give methyl 2-(5-bromo-4-chloro-2H-indazol-2-yl)acetate (190 mg). MS: $[M+H]^+$ = 303, 305.

[0520] Step 2

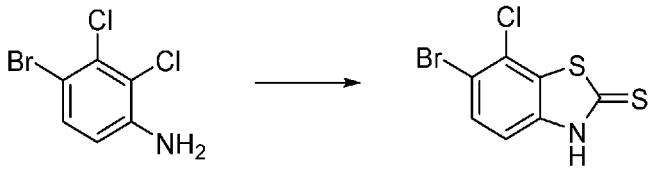
To a solution of methyl 2-(5-bromo-4-chloro-2H-indazol-2-yl)acetate (190 mg, 0.63 mmol) in THF (1.9 mL) was added a solution of LiOH (90 mg, 3.76 mmol) in water (0.95 mL) at RT. The mixture was stirred at RT for 20 min, diluted with MTBE and added 2 M NaOH. The aqueous layer was added 6 M HCl and extracted with $CHCl_3$ three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 2-(5-bromo-4-chloro-2H-indazol-2-yl)acetic acid (140 mg). MS: $[M+H]^+$ = 289, 291.

[0521] Step 3

2-(5-Bromo-4-chloro-2H-indazol-2-yl)acetic acid (140 mg, 0.48 mmol) in THF (1.4 mL) was added TEA (0.27 mL, 1.93 mmol), HATU (276 mg, 0.73 mmol) and dimethylamine hydrochloride (59 mg, 0.73 mmol) at RT. The mixture was stirred at 50 °C for 1 h. The reaction solution was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 40 - 100% EtOAc/ hexane) to give the title compound (125 mg). MS: $[M+H]^+$ = 316, 318.

[0522] Preparation 65: 6-Bromo-7-chloro-2,3-dihydro-1,3-benzothiazole-2-thione

[0523] [Chem.99]

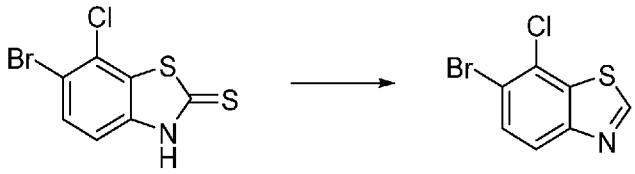


[0524] A mixture of 4-bromo-2,3-dichloroaniline (10.0 g, 41.5 mmol) and potassium ethyl xanthate (15.0 g, 93.4 mmol) in DMF (100 mL) was stirred at 120 °C for 18 h. The mixture was quenched with 2 M aq. HCl (80 ml) and water (400 mL). The mixture was filtered and washed with water to give the title compound (1.13 g). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 14.10 (1H, s), 7.78 (1H, d), 7.19 (1H, d).

[0525] Preparation 66: 6-Bromo-7-chloro-1,3-benzothiazole

[0526]

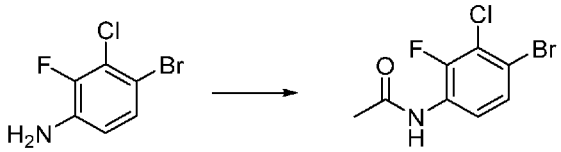
[Chem.100]



[0527] A round bottomed flask charged with 6-bromo-7-chloro-2,3-dihydro-1,3-benzothiazole-2-thione (1.13 g, 40.3 mmol), iron powder (12.4 g, 221.5 mmol) and acetic acid (200 mL) at RT was stirred (with mechanical stirrer) at 120 °C for 2 h. Further iron powder (24.8 g, 443.0 mmol) was added and the mixture was stirred at 120 °C for 2 h. Additional iron powder (12.4 g, 221.5 mmol) was added and the reaction was stirred at 120 °C for 15 h. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc and then by column chromatography on silica gel (10% EtOAc/petrol) to give the title compound (0.27 g). MS: $[M+H]^+ = 248$.

[0528] Preparation 67: N-(4-Bromo-3-chloro-2-fluorophenyl)acetamide

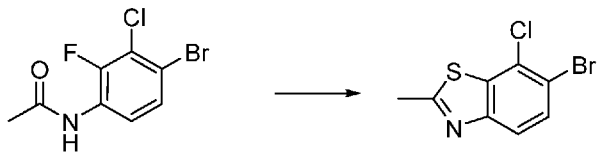
[0529] [Chem.101]



[0530] To a solution of 4-bromo-3-chloro-2-fluoroaniline (25 g, 111 mmol) and DIPEA (48.5 ml, 278 mmol) in DCM (250 mL) cooled in an ice bath was added acetic anhydride (11.05 ml, 117 mmol) over 1.5 h. The reaction was warmed to RT and stirred for 24 h. The reaction was washed with HCl (1 M, 250 mL), $NaHCO_3$ (150 mL) and water (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (gradient elution, 0-40% EtOAc/petrol) to give the title compound (23.8 g). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.97 (s, 1H), 7.95 - 7.77 (m, 1H), 7.56 (dd, 1H), 2.10 (s, 3H).

[0531] Preparation 68: 6-Bromo-7-chloro-2-methyl-1,3-benzothiazole

[0532] [Chem.102]

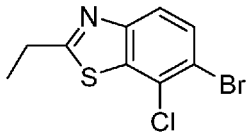


[0533] To a solution of N-(4-bromo-3-chloro-2-fluorophenyl)acetamide (1.0 g, 3.77 mmol)

in xylene (9.86 mL) was added Lawesson's Reagent (1.53 g, 2.26 mmol). The reaction was heated to 110 °C for 18 h. Cesium carbonate (4.11 g, 7.55 mmol) was added and the mixture was stirred at 110 °C for 18 h. The reaction was cooled to RT and the reaction was diluted with water (500 mL) and ethyl acetate. The organic layer was separated and washed with sat. brine solution, then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (gradient elution, 0-20% EtOAc/petrol), to give the title compound (0.97 g). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.85 (2H, d), 2.83 (3H, s).

[0534] Preparation 69: 6-Bromo-7-chloro-2-ethylbenzo[d]thiazole

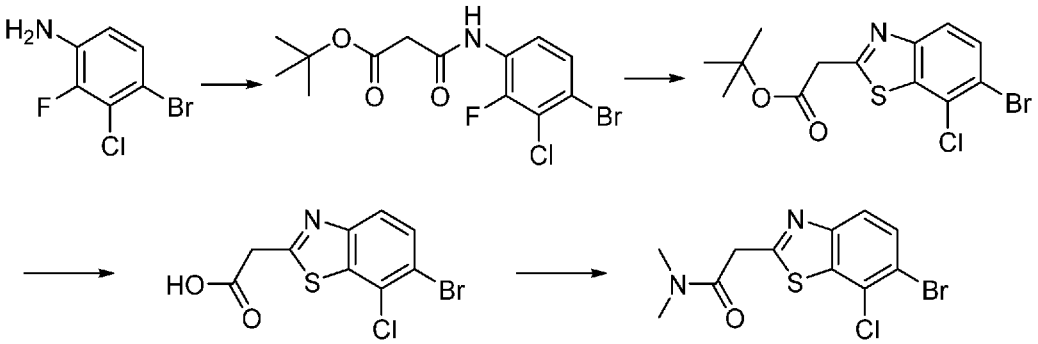
[0535] [Chem.103]



[0536] Prepared from propionyl chloride using similar procedure for the preparation of 6-bromo-7-chloro-2-methyl-1,3-benzothiazole, to give the title compound. MS: $[M+H]^+$ = 211, 213.

[0537] Preparation 70: 2-(6-Bromo-7-chlorobenzo[d]thiazol-2-yl)-N,N-dimethylacetamide

[0538] [Chem.104]



[0539] Step 1

To a solution of 4-bromo-3-chloro-2-fluoro-aniline (3 g, 13.4 mmol) and HATU (10.2 g, 26.7 mmol) in DMA (30 mL) was added TEA (5.58 mL, 40.1 mmol) and 3-tert-butoxy-3-oxopropanoic acid (3.09 mL, 20.0 mmol) at RT. The mixture was stirred at 50 °C for 1 h, diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 30 - 70% EtOAc/hexane) to give tert-butyl 3-(4-bromo-3-chloro-2-fluoro-anilino)-3-oxo-propanoate (3.35 g).

[0540] Step 2

To a suspension of tert-butyl

3-(4-bromo-3-chloro-2-fluoro-anilino)-3-oxo-propanoate (2 g, 5.47 mmol) in toluene (20 mL) was added LAWESSON'S REAGENT (1.32 g, 3.27 mmol) at RT. The mixture was stirred at 110°C for 3 h. Cs_2CO_3 (3.56 g, 10.9 mmol) was added. The mixture was stirred at 110°C for 19 h, cooled to RT, and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 20% EtOAc/$CHCl_3$) to give tert-butyl 2-(6-bromo-7-chlorobenzo[d]thiazol-2-yl)acetate (983 mg).

[0541] Step 3

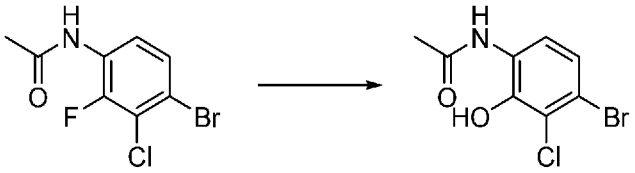
To a solution of tert-butyl 2-(6-bromo-7-chlorobenzo[d]thiazol-2-yl)acetate (500 mg, 1.38 mmol) in $CHCl_3$ (5 mL) was added TFA (2.5 mL, 32 mmol) at RT. The mixture was stirred at 60 °C for 1 h. The reaction solution was concentrated in vacuo, and the residue was suspended with hexane. The precipitate was collected, washed with hexane, and dried at 60 °C for 3 h under reduced pressure to give 2-(6-bromo-7-chlorobenzo[d]thiazol-2-yl)acetic acid (200 mg). MS: $[M+H]^+$ = 306, 308.

[0542] Step 4

To a solution of 2-(6-bromo-7-chlorobenzo[d]thiazol-2-yl)acetic acid (200 mg, 0.65 mmol) in THF (4 mL) was added TEA (0.45 mL, 3.26 mmol), propylphosphonic anhydride (1.6 M in THF, 0.82 mL, 1.30 mmol), and dimethylamine (2.0 M in THF, 0.65 mL, 1.30 mmol) at RT. The mixture was stirred at RT for 10 min. The reaction solution was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 80 - 100% EtOAc/hexane) to give the title compound (168 mg). MS: $[M+H]^+$ = 333, 335.

[0543] Preparation 71: N-(4-Bromo-3-chloro-2-hydroxyphenyl)acetamide

[0544] [Chem.105]

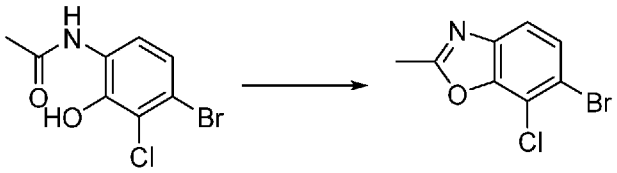


[0545] The suspension of N-(4-bromo-3-chloro-2-fluoro-phenyl)acetamide (1.0 g, 3.8 mmol), cesium carbonate (2.0 equiv., 7.5 mmol) in NMP (6.0 mL) was irradiated by microwave (Initiator, Biotage) at 150 °C for 5 h. To the mixture was added NMP (15 mL) and the mixture was again irradiated at 150 °C by microwave for 5 h. The reaction mixture was diluted by EtOAc and water and acidified with 5 N HCl aq. to adjust its pH to 1 - 2. The mixture was extracted with EtOAc (X3), and the organic extracts were washed with brine and dried over Na_2SO_4. Concentration gave the crude mixture (1.20 g, a brown oil), which was subjected to column chromatography purification (gradient

elution, 5 - 70% EtOAc/hexane) to give the title compound (425 mg, 1.61 mmol, 43% Yield) as a yellow solid. MS: $[M+H]^+$ = 264, 266.

[0546] Preparation 72: 6-Bromo-7-chloro-2-methylbenzo[d]oxazole

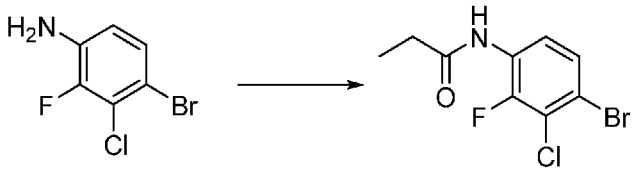
[0547] [Chem.106]



[0548] To the solution of N-(4-bromo-3-chloro-2-hydroxyphenyl)acetamide (1.09 g, 4.12 mmol), triphenylphosphine (1.62 g, 6.18 mmol) in THF (30 mL) was added di-isopropyl azodicarboxylate (1.21 mL, 6.18 mmol) and the mixture was heated in an oil bath at 50 °C for 2 h 45 min. The reaction mixture was concentrated to give the crude oil (4.30 g, a brown oil), which was subjected to column chromatography purification (gradient elution, 5 - 70% EtOAc/hexane), successively suspended in hexane and collected by filteration to give the title compound (908 mg, 3.68 mmol, 89% Yield) as a colorless solid. MS: $[M+H]^+$ = 246, 248.

[0549] Preparation 73: N-(4-Bromo-3-chloro-2-fluorophenyl)propionamide

[0550] [Chem.107]

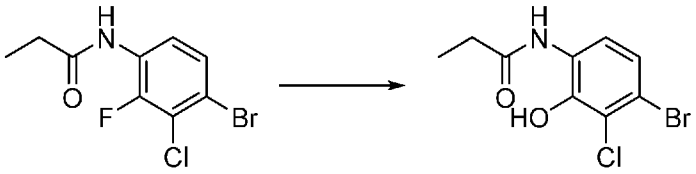


[0551] To the solution of 4-bromo-3-chloro-2-fluoroaniline (5.00 g, 22.3 mmol) in DCM (40 mL) were added TEA (2.0 equiv., 44.6 mmol) and propionyl chloride (2.34 mL, 26.7 mmol) at 0 °C. The ice water bath was removed and the mixture was stirred at RT for 17 h. Propionyl chloride (0.779 mL, 8.92 mmol) was added to the mixture at RT. After 45 min stirring at RT, water was added to the mixture. The mixture was extracted with EtOAc (X2) and the organic extracts were washed with water, dil. NH_4Cl aq., $NaHCO_3$ aq. , and brine and dried over Na_2SO_4. The concentrated crude mixture was suspended in hexane - EtOAc (4/1) and collected by a Kiriyama-roshi (No.4) to give the title compound (4.22 g, 15.0 mmol, 67% Yield) as a colorless needle. The filterate (an orange solid, 2.23 g) was subjected to column chromatography purification (gradient elution, 5 - 40% EtOAc/hexane) to give the title compound (1.33 g, 4.74 mmol, 21% Yield) as a colorless needle. MS: $[M+H]^+$ = 280, 282.

[0552] Preparation 74: N-(4-Bromo-3-chloro-2-hydroxyphenyl)propionamide

[0553]

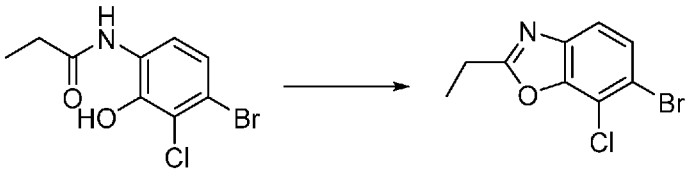
[Chem.108]



[0554] The suspension of N-(4-bromo-3-chloro-2-fluoro-phenyl)propanamide (2.50 g, 8.91 mmol), cesium carbonate (5.80 g, 17.8 mmol) in NMP (15 mL) was irradiated by microwave (Initiator, Biotage) at 150 °C for 5 h. To the mixture was added NMP (15 mL) and the mixture was again irradiated at 150 °C by microwave for 5 h. The reaction mixture was diluted by EtOAc and water and acidified with 5 N HCl aq. to adjust its pH to 1 - 2. The mixture was extracted with EtOAc (X3), and the organic extracts were washed with brine and dried over Na_2SO_4. Concentration gave the crude mixture (5.90 g, a brown oil), which was subjected to column chromatography purification (gradient elution, 5 - 100% EtOAc/hexane) to give the title compound (1.27 g, 4.56 mmol, 51% Yield). MS: $[M+H]^+$ = 278, 280.

[0555] Preparation 75: 6-Bromo-7-chloro-2-ethylbenzo[d]oxazole

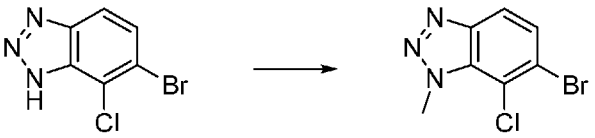
[0556] [Chem.109]



[0557] To the solution of N-(4-bromo-3-chloro-2-hydroxyphenyl)propanamide (607 mg, 2.18 mmol), triphenylphosphine (857 mg, 3.27 mmo) in THF (10 mL) was added di-isopropyl azodicarboxylate (0.642 mL, 3.27 mmol) and the mixture was heated in an oil bath at 50 °C for 1 h 45 min. The reaction mixture was concentrated to give the crude oil (2.38 g, a brown oil), which was subjected to column chromatography purification (gradient elution, 5 - 50% EtOAc/hexane) to give the title compound (525 mg, 2.02 mmol, 92% Yield) as a pale yellow solid. MS: $[M+H]^+$ = 260, 262.

[0558] Preparation 76: 6-Bromo-7-chloro-1-methyl-1H-benzo[d][1,2,3]triazole

[0559] [Chem.110]

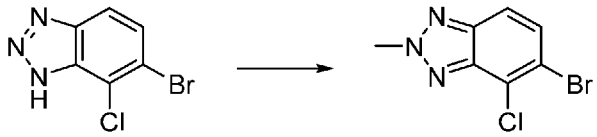


[0560] To a solution of 6-bromo-7-chloro-1H-benzo[d][1,2,3]triazole (400 mg, 1.72 mmol) in THF (8 mL) was added triphenylphosphine (542 mg, 2.06 mmol), MeOH (0.084

mL, 2.06 mmol) and DMEAD (484 mg, 2.06 mmol) at RT. The mixture was stirred at RT for 2 h. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 10 - 40% EtOAc/ hexane). The fractions containing target product were collected, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 20% EtOAc/hexane) to give the title compound (152 mg). ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, d, J = 8.8 Hz), 7.58 (1H, d, J = 8.8 Hz), 4.57 (3H, s). MS: $[M+H]^+$ = 246, 248.

[0561] Preparation 77: 5-Bromo-4-chloro-2-methyl-2H-benzo[d][1,2,3]triazole

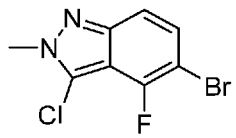
[0562] [Chem.111]



[0563] To a solution of 6-bromo-7-chloro-1H-benzo[d][1,2,3]triazole (400 mg, 1.72 mmol) in THF (8 mL) was added triphenylphosphine (542 mg, 2.06 mmol), MeOH (0.084 mL, 2.06 mmol) and DMEAD (484 mg, 2.06 mmol) at RT. The mixture was stirred at RT for 2 h. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 10 - 40% EtOAc/ hexane). The fractions containing target product were collected, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 20% EtOAc/hexane) to give the title compound (160 mg). ^{1}H-NMR ($CDCl_3$) δ: 7.66 (1H, d, J = 9.0 Hz), 7.57 (1H, d, J = 9.0 Hz), 4.54 (3H, s). MS: $[M+H]^+$ = 246, 248.

[0564] Preparation 78: 5-Bromo-3-chloro-4-fluoro-2-methyl-2H-indazole

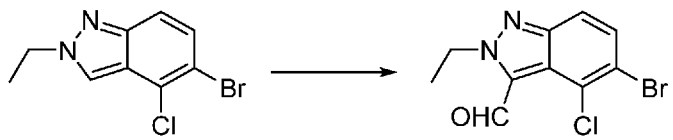
[0565] [Chem.112]



[0566] Prepared from 5-bromo-4-fluoro-2-methyl-2H-indazole using similar procedure for the preparation of 5-bromo-3,4-dichloro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+$ = 263, 265.

[0567] Preparation 79: 5-Bromo-4-chloro-2-ethyl-2H-indazole-3-carbaldehyde

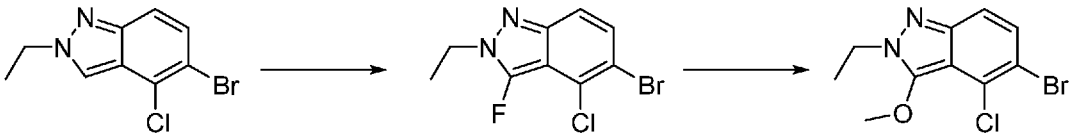
[0568] [Chem.113]



[0569] To a solution of 5-bromo-4-chloro-2-ethyl-2H-indazole (1.1 g, 4.1 mmol) in THF (8.3 mL) was added LDA (1.08 M in hexane-THF, 5.8 mL, 6.3 mmol) at -78 °C. The mixture was stirred at 0 °C for 30 min. N,N-dimethylformamide (0.61 g, 8.3 mmol) was added at 0 °C. The mixture was stirred at RT overnight, quenched with sat. NH_4Cl aq., and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 40% EtOAc/hexane) to give the title compound (772 mg). MS: $[M+H]^+$ = 287, 289.

[0570] Preparation 80: 5-Bromo-4-chloro-2-ethyl-3-methoxy-2H-indazole

[0571] [Chem.114]

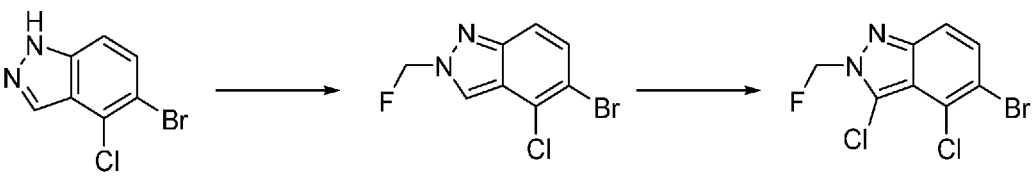


[0572] To a solution of 5-bromo-4-chloro-2-ethyl-2H-indazole (500 mg, 1.92 mmol) in THF (10 mL) was added LDA (1.08 M in THF, 2.14 mL, 2.31 mmol) at -78 °C. The mixture was stirred at 0 °C for 30 min. N-Fluorobenzenesulfonimide (850 mg, 2.69 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h, quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give 5-bromo-4-chloro-2-ethyl-3-fluoro-2H-indazole (185 mg). MS: $[M+H]^+$ = 277, 279.

To a solution of 5-bromo-4-chloro-2-ethyl-3-fluoro-2H-indazole (183 mg, 0.659 mmol) in THF (3 mL) was added NaOMe (28% in MeOH, 0.472 mL, 1.97 mmol) at RT. The mixture was stirred at 60 °C for 4 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give the title compound (166 mg). MS: $[M+H]^+$ = 289, 291.

[0573] Preparation 81: 5-Bromo-3,4-dichloro-2-(fluoromethyl)-2H-indazole

[0574] [Chem.115]



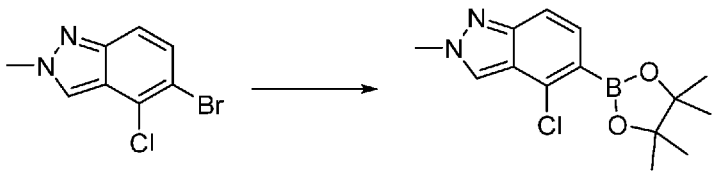
[0575] The mixture of 5-bromo-4-chloro-1H-indazole (1.00 g, 4.32 mmol), fluoromethyl p-toluenesulfonate (0.970 g, 4.75 mmol), Cs_2CO_3 (1.68 g, 5.18 mmol) and NMP (10 mL) was stirred at 60 °C for 11 h, cooled to RT, poured into water, and extracted with

EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give 5-bromo-4-chloro-2-(fluoromethyl)-2H-indazole (346 mg). MS: $[M+H]^+$ = 263, 265.

[0576] To a solution of 5-bromo-4-chloro-2-(fluoromethyl)-2H-indazole (378 mg, 1.43 mmol) in DMF (4 mL) was added NCS (210 mg, 1.57 mmol) at 0 °C. The mixture was stirred at RT for 44 h. NCS (40 mg, 0.299 mmol) was added at RT. The mixture was stirred at RT for 24 h, poured into water, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 10 - 35% EtOAc/hexane) to give the title compound (401 mg). MS: $[M+H]^+$ = 297, 299.

[0577] Preparation 82:
4-Chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

[0578] [Chem.116]



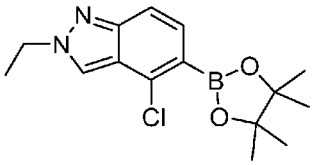
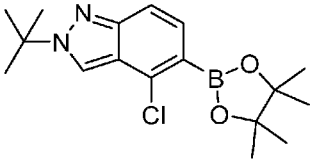
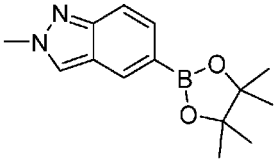
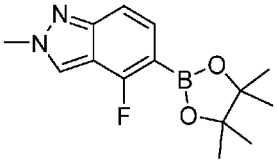
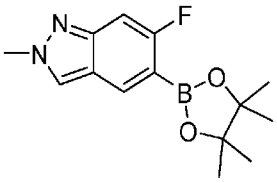
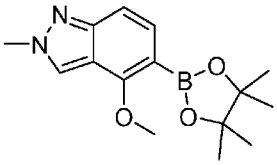
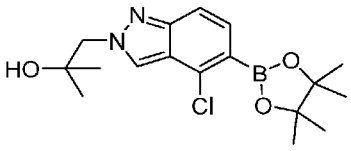
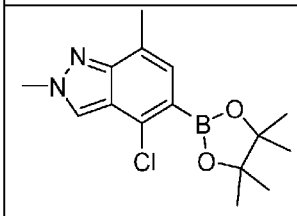
[0579] The mixture of 5-bromo-4-chloro-2-methyl-2H-indazole (12.14 g, 49.45 mmol), bis(pinacolato)diboron (18.83 g, 74.18 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (4.038 g, 4.945 mmol) and potassium acetate (9.706 g, 98.90 mmol) in 1,4-dioxane (120 mL) was degassed, purged with nitrogen, and stirred at 120 °C for 5 h. The reaction was cooled to RT, filtered through a pad of Celite, and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 70% EtOAc/hexane) to give the title compound (14.36 g). MS: $[M+H]^+$ = 293, 295.

[0580] Compounds of Table 1 below were prepared using procedures analogous to that described in preparation 82, starting from the appropriate substituted aryl halide (synthesised as described above with any significant variations indicated below).

[0581]

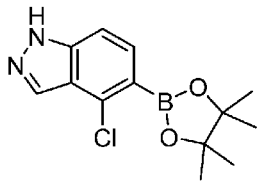
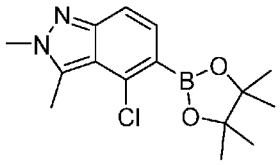
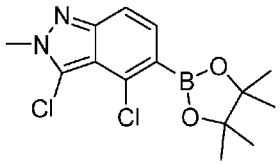
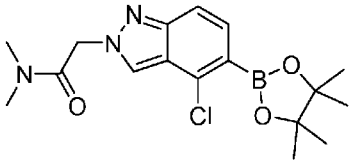
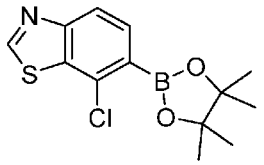
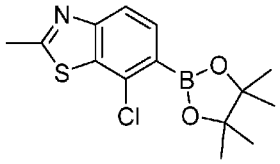
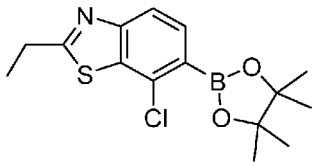
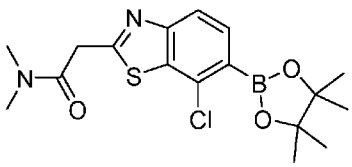
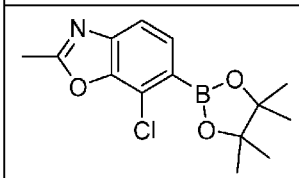
[Table 1-1]

TABLE 1

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	4-Chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	307, 309	Prepared as preparation 82 above using 5-bromo-4-chloro-2-ethyl-2*H*-indazole
	2-(*tert*-Butyl)-4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	335, 337	Prepared as preparation 82 above using 5-bromo-2-(*tert*-butyl)-4-chloro-2*H*-indazole
	2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	259	Prepared as preparation 82 above using 5-bromo-2-methyl-2*H*-indazole
	4-Fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	277	Prepared as preparation 82 above using 5-bromo-4-fluoro-2-methyl-2*H*-indazole
	6-Fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	277	Prepared as preparation 82 above using 5-bromo-6-fluoro-2-methyl-2*H*-indazole
	4-Methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	289	Prepared as preparation 82 above using 5-bromo-4-methoxy-2-methyl-2*H*-indazole
	1-(4-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-2-methylpropan-2-ol	351, 353	Prepared as preparation 82 above using 1-(5-bromo-4-chloro-2*H*-indazol-2-yl)-2-methylpropan-2-ol
	4-Chloro-2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	307, 309	Prepared as preparation 82 above using 5-bromo-4-chloro-2,7-dimethyl-2*H*-indazole

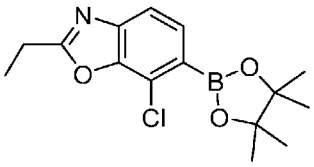
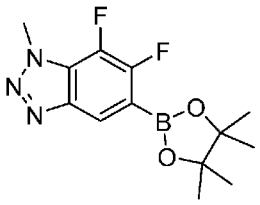
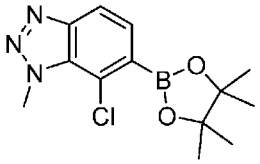
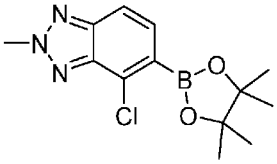
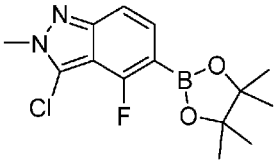
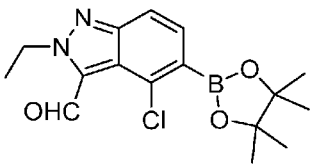
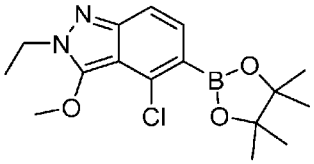
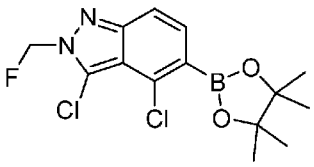
[0582]

[Table 1-2]

	4-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole	279, 281	Prepared as preparation 82 above using 5-bromo-4-chloro-1*H*-indazole
	4-Chloro-2,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	307, 309	Prepared as preparation 82 above using 5-bromo-4-chloro-2,3-dimethyl-2*H*-indazole
	3,4-Dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	327, 329	Prepared as preparation 82 above using 5-bromo-3,4-dichloro-2-methyl-2*H*-indazole
	2-(4-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide	364, 366	Prepared as preparation 82 above using 2-(5-bromo-4-chloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide
	7-Chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole	296, 298	Prepared as preparation 82 above using 6-bromo-7-chlorobenzo[*d*]thiazole
	7-Chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole	310, 312	Prepared as preparation 82 above using 6-bromo-7-chloro-2-methylbenzo[*d*]thiazole
	7-Chloro-2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole	324, 326	Prepared as preparation 82 above using 6-bromo-7-chloro-2-ethylbenzo[*d*]thiazole
	2-(7-Chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylacetamide	381, 383	Prepared as preparation 82 above using 2-(6-bromo-7-chlorobenzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylacetamide
	7-Chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole	294, 296	Prepared as preparation 82 above using 6-bromo-7-chloro-2-methylbenzo[*d*]oxazole

[0583]

[Table 1-3]

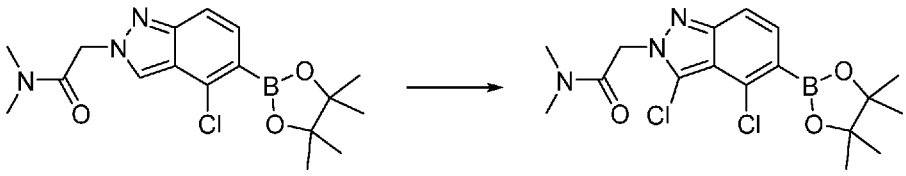
	7-Chloro-2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole	308, 310	Prepared as preparation 82 above using 6-bromo-7-chloro-2-ethylbenzo[*d*]oxazole
	6,7-Difluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole	296	Prepared as preparation 82 above using 5-bromo-6,7-difluoro-1-methyl-1*H*-benzo[*d*][1,2,3]triazole
	7-Chloro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole	294, 296	Prepared as preparation 82 above using 6-bromo-7-chloro-1-methyl-1*H*-benzo[*d*][1,2,3]triazole
	4-Chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*d*][1,2,3]triazole	294, 296	Prepared as preparation 82 above using 5-bromo-4-chloro-2-methyl-2*H*-benzo[*d*][1,2,3]triazole
	3-Chloro-4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	311, 313	Prepared as preparation 82 above using 5-bromo-3-chloro-4-fluoro-2-methyl-2*H*-indazole
	4-Chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole-3-carbaldehyde	335, 337	Prepared as preparation 82 above using 5-bromo-4-chloro-2-ethyl-2*H*-indazole-3-carbaldehyde
	4-Chloro-2-ethyl-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	337, 339	Prepared as preparation 82 above using 5-bromo-4-chloro-2-ethyl-3-methoxy-2*H*-indazole
	3,4-Dichloro-2-(fluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole	345, 347	Prepared as preparation 82 above using 5-bromo-3,4-dichloro-2-(fluoromethyl)-2*H*-indazole

[0584] Preparation 83:

2-(3,4-Dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)-N,N-dimethylacetamide

[0585]

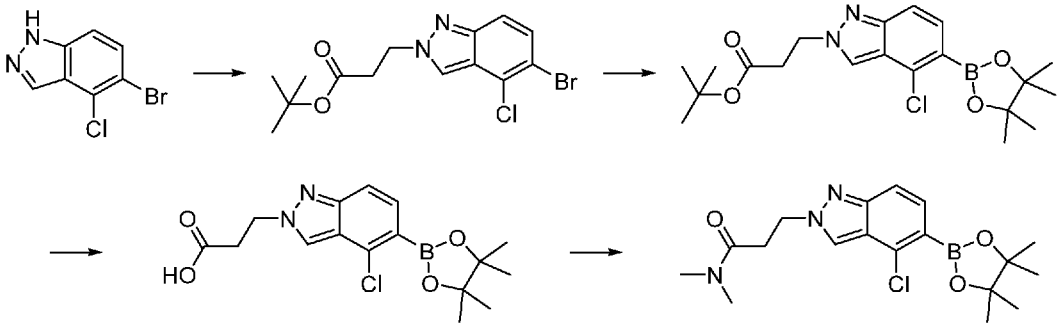
[Chem.117]



[0586] To a solution of 2-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)-N,N-dimethylacetamide (109 mg, 0.30 mmol) in MeCN (2.18 mL) was added NCS (48 mg, 0.36 mmol) at RT. The mixture was stirred at 50 °C for 18 h. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 0 - 20% MeOH/$CHCl_3$) to give the title compound (71 mg). MS: $[M+H]^+$ = 398, 400.

[0587] Preparation 84:
3-(4-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)-N,N-dimethylpropanamide

[0588] [Chem.118]



[0589] Step 1
To a solution of 5-bromo-4-chloro-1H-indazole (1 g, 4.32 mmol) in DMF (10 mL) was added K_2CO_3 (1.19 g, 8.64 mmol) and tert-butyl 3-bromopropanoate (1.44 mL, 8.64 mmol) at RT. The mixture was stirred at 100 °C for 2 h, diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 5 - 30% EtOAc/hexane) to give tert-butyl 3-(5-bromo-4-chloro-2H-indazol-2-yl)propanoate (599 mg). MS: $[M+H]^+$ = 361, 363.

[0590] Step 2
The mixture of tert-butyl 3-(5-bromo-4-chloro-2H-indazol-2-yl)propanoate (599 mg, 1.67 mmol), bis(pinacolato)diboron (634 mg, 2.50 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (109 mg, 0.133 mmol) and potassium acetate (327 g, 3.33 mmol) in

1,4-dioxane (6 mL) was degassed, purged with nitrogen, and stirred at 120 °C for 5 h. The reaction was cooled to RT, filtered through a pad of Celite, and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 10 - 30% EtOAc/hexane) to give tert-butyl 3-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)propanoate (553 g). MS: $[M+H]^+$ = 406, 408.

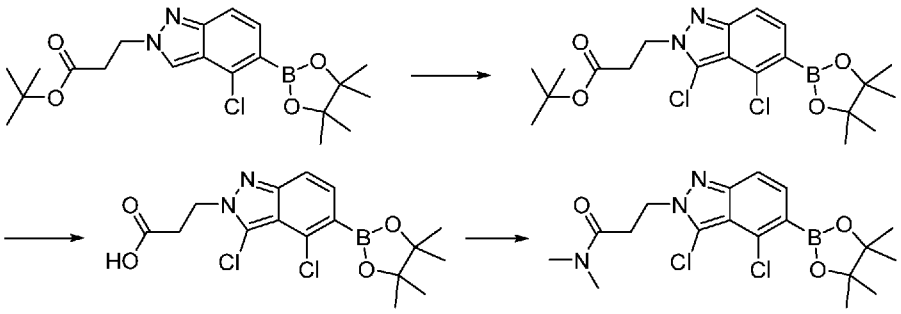
[0591] Step 3

To a solution of tert-butyl 3-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)propanoate (200 mg, 0.492 mmol) in $CHCl_3$ (2 mL) was added TFA (1 mL, 13.0 mmol) at RT . The mixture was stirred at 60 °C for 1 h, diluted with water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was diluted with THF (4 mL). The mixture was added TEA (0.685 mL, 4.92 mmol), propylphosphonic anhydride (1.6 M in THF, 0.92 mL, 1.48 mmol), and dimethylamine (2.0 M in THF, 0.98 mL, 1.97 mmol) at RT. The mixture was stirred at RT for 30 min. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (116 mg). MS: $[M+H]^+$ = 378, 380.

[0592] Preparation 85:

3,4-Dichloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

[0593] [Chem.119]



[0594] Step 1

To a solution of tert-butyl 3-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)propanoate (250 mg, 0.615 mmol) in MeCN (5 mL) was added NCS (99 mg, 0.738 mmol) at RT. The mixture was stirred at 60 °C for 12 h. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 10 - 20% EtOAc/hexane) to give tert-butyl

3-(3,4-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)propanoate (164 mg). MS: $[M+H]^+$ = 441, 443.

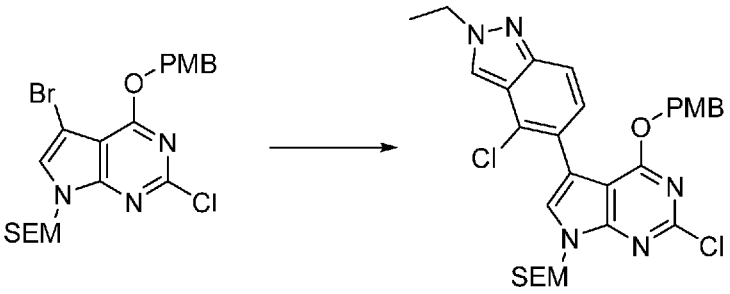
[0595] Step 2

To a solution of tert-butyl 3-(3,4-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazol-2-yl)propanoate (164 mg, 0.372 mmol) in $CHCl_3$ (1 mL) was added TFA (1 mL, 13.0 mmol) at RT . The mixture was stirred at 70 °C for 10 min, diluted with water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was diluted with THF (2.58 mL). The mixture was added TEA (0.233 mL, 1.68 mmol), propylphosphonic anhydride (1.6 M in THF, 0.420 mL, 0.670 mmol), and dimethylamine (2.0 M in THF, 0.34 mL, 0.670 mmol) at RT. The mixture was stirred at RT for 30 min. The reaction solution was then concentrated in vacuo, and the residue was purified by column chromatography on silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (128 mg). MS: $[M+H]^+$ = 412, 414.

[0596] Preparation 86:

2-Chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

[0597] [Chem.120]

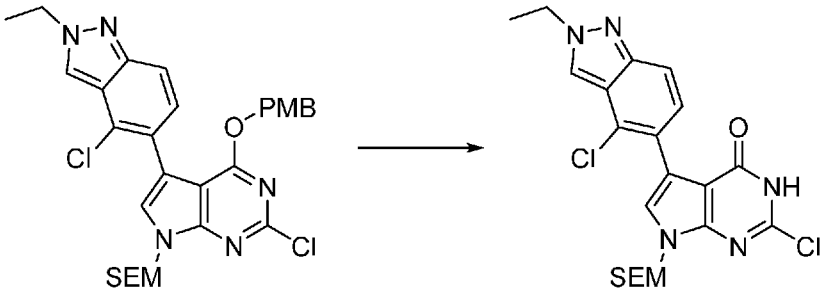


[0598] The mixture of 5-bromo-2-chloro-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (2.68 g, 5.37 mmol), 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (2.47 g, 6.45 mmol), K_3PO_4 (2.28 g, 10.7 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.439 g, 0.537 mmol), 1,4-dioxane (53.6 mL) and water (5.36 mL) was stirred at 120 °C for 1 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title

compound (1.7 g). MS: $[M+H]^+$ = 598, 600.

[0599] Preparation 87:
2-Chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

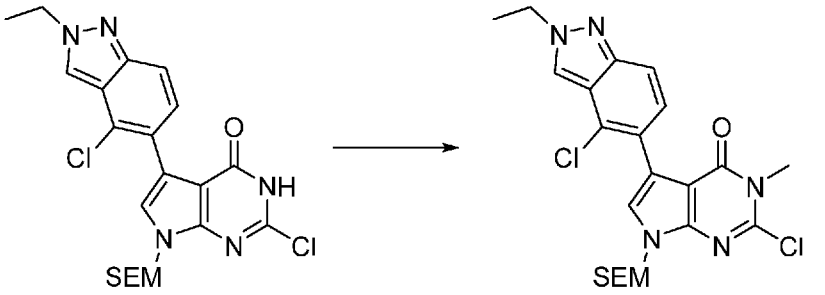
[0600] [Chem.121]



[0601] To a solution of
2-chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (1.7 g, 2.84 mmol) in DCM (32.3 mL) were added 2,3-dichloro-5,6-dicyano-p-benzoquinone (1.93 g, 8.52 mmol) and water (1.7 mL) at RT. The mixture was stirred at RT overnight. $CHCl_3$ and sat. $NaHCO_3$ were added at RT. The mixture was filtered through a pad of Celite, and washed with $CHCl_3$ and water. The filtrate was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (0.713 g). MS: $[M+H]^+$ = 478, 480.

[0602] Preparation 88:
2-Chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0603] [Chem.122]



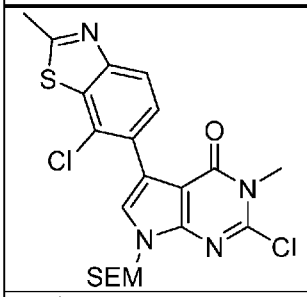
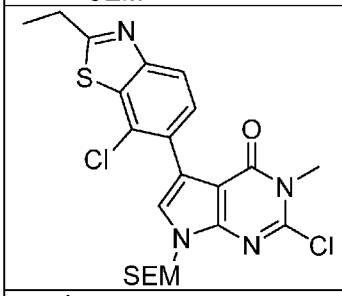
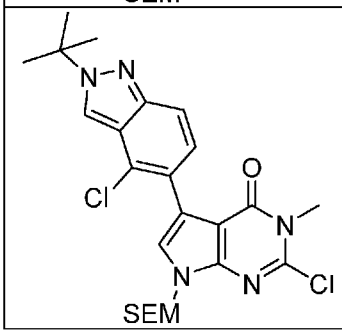
[0604] To a solution of
2-chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (0.713 g, 1.49 mmol) in DMF (7.13 mL)

were added K_2CO_3 (0.412 g, 2.98 mmol) and iodomethane (0.186 mL, 2.98 mmol) at RT. The mixture was stirred at RT for 30 min, poured into water, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (0.717 g). MS: $[M+H]^+$ = 492, 494.

[0605] Compounds of Table 2 below were prepared using procedures analogous to that described in preparation 86 - 88, starting from the appropriate substituted aryl boronate (synthesised as described above with any significant variations indicated below).

[0606] [Table 2]

TABLE 2

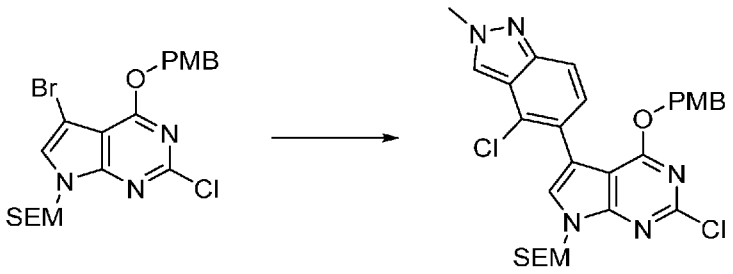
Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	2-Chloro-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	495, 497	Prepared as preparation 86 above using 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	2-Chloro-5-(7-chloro-2-ethylbenzo[*d*]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	509, 511	Prepared as preparation 86 above using 7-chloro-2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	5-(2-(*tert*-Butyl)-4-chloro-2*H*-indazol-5-yl)-2-chloro-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	520, 522	Prepared as preparation 86 above using 2-(*tert*-butyl)-4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

[0607] Preparation 89:

2-Chloro-5-(4-chloro-2-methyl-2H-indazol-5-yl)-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

[0608]

[Chem.123]

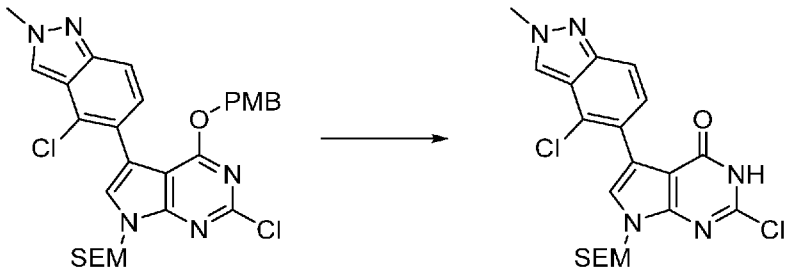


[0609] Prepared from 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole using similar procedure for the preparation of 2-chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine, to give the title compound. MS: $[M+H]^+$ = 584, 586.

[0610] Preparation 90:

2-Chloro-5-(4-chloro-2-methyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0611] [Chem.124]



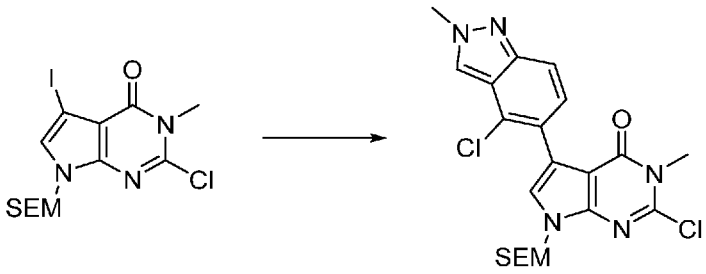
[0612] Prepared from 2-chloro-5-(4-chloro-2-methyl-2H-indazol-5-yl)-4-((4-methoxybenzyl)oxy)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine using similar procedure for the preparation of 2-chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one, to give the title compound. MS: $[M+H]^+$ = 464, 466.

[0613] Preparation 91:

2-Chloro-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0614]

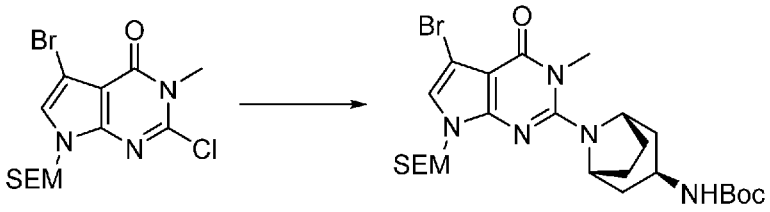
[Chem.125]



[0615] The mixture of 2-chloro-5-iodo-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (150 mg, 0.341 mmol), 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (171 mg, 0.409 mmol), K_2CO_3 (110 mg, 0.798 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (27.8 mg, 0.0341 mmol), 1,4-dioxane (2.5 mL) and water (0.5 mL) was stirred at 70 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (90 mg). MS: $[M+H]^+$ = 478, 480.

[0616] Preparation 92: tert-Butyl (endo-8-(5-bromo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate

[0617] [Chem.126]

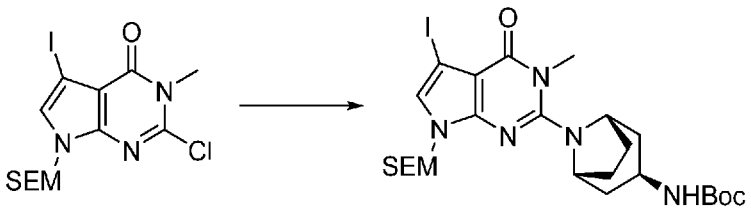


[0618] The mixture of 5-bromo-2-chloro-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (0.700 g, 1.78 mmol), tert-butyl endo-(8-azabicyclo[3.2.1]octan-3-yl)carbamate (1.21 g, 5.34 mmol), DIPEA (3.10 mL, 17.8 mmol) and NMP (1 mL) was stirred at 120 °C for 30 min, and cooled to RT. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient

elution, 0 - 100% EtOAc/hexane) to give the title compound. MS: $[M+H]^+$ = 581, 583.

[0619] Preparation 93: tert-Butyl (endo-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate

[0620] [Chem.127]



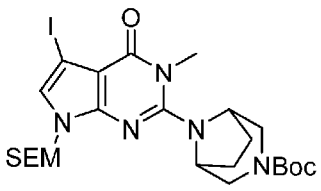
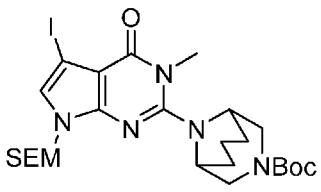
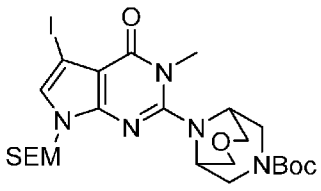
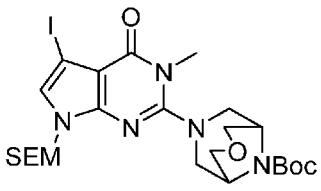
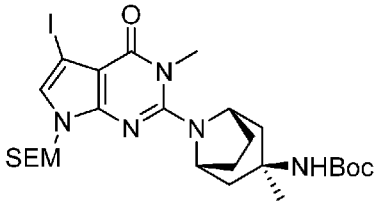
[0621] The mixture of 5-iodo-2-chloro-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (2.00 g, 4.55 mmol), tert-butyl endo-(8-azabicyclo[3.2.1]octan-3-yl)carbamate (1.24 g, 5.46 mmol), DIPEA (1.58 mL, 9.10 mmol) and NMP (10 mL) was stirred at 120 °C for 8 h, and cooled to RT. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 80% EtOAc/hexane) to give the title compound (2.41 g). MS: $[M+H]^+$ = 630.

[0622] Compounds of Table 3 below were prepared using procedures analogous to that described in preparation 93, starting from the appropriate substituted amine (synthesised as described above with any significant variations indicated below).

[0623]

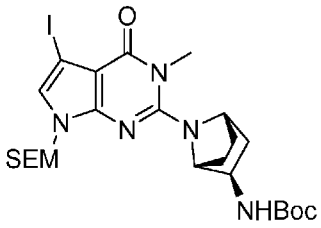
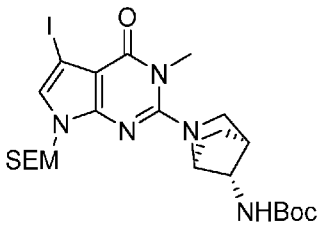
[Table 3-1]

TABLE 3

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-Butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	616	Prepared as preparation 93 above using *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate
	*tert*-Butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	630	Prepared as preparation 93 above using *tert*-butyl 3,9-diazabicyclo[3.3.1]nonane-3-carboxylate
	*tert*-Butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate	632	Prepared as preparation 93 above using *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate
	*tert*-Butyl 7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	632	Prepared as preparation 93 above using *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate
	*tert*-Butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	644	Prepared as preparation 93 above using *tert*-butyl (*endo*-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate

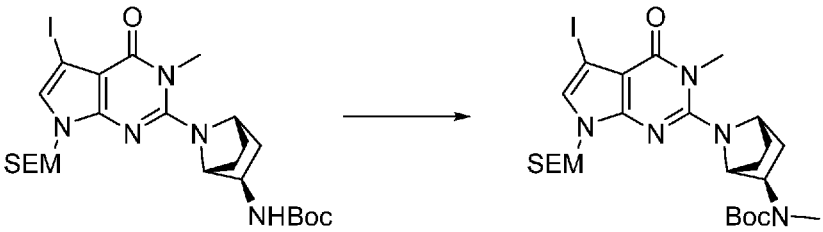
[0624]

[Table 3-2]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	616	Prepared as preparation 93 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	*rac-tert*-butyl ((1S,4S,7S)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	616	Prepared as preparation 93 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

[0625] Preparation 94: tert-Butyl ((1R,2R,4S)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate

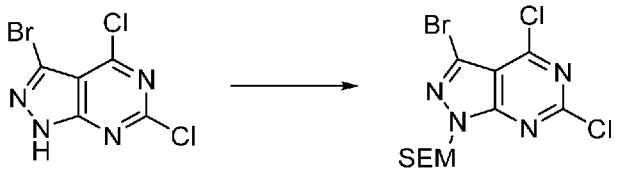
[0626] [Chem.128]



[0627] To a solution of tert-butyl ((1R,2R,4S)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (500 mg, 0.812 mmol) in THF (15 mL) was added NaH (60% in mineral oil, 64.9 mg, 1.62 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min. Iodomethane (0.101 mL, 1.62 mmol) was added at 0 °C. The mixture was stirred at RT overnight, poured into sat. NH_4Cl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 30 - 50% EtOAc/hexane) to give the title compound (493 mg). MS: $[M+H]^+ = 630$.

[0628] Preparation 95: 3-Bromo-4,6-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine

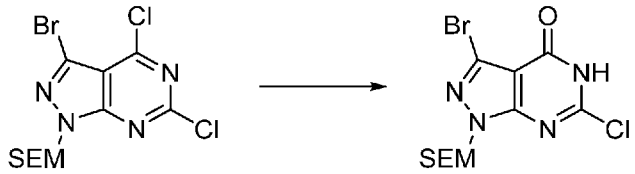
[0629] [Chem.129]



[0630] To a mixture of 3-bromo-4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine (1.00 g, 3.73 mmol) and DIPEA (1.95 mL, 11.2 mmol) in DCM (10 mL) was added SEMCl (0.794 mL, 4.47 mmol) at RT. The mixture was stirred at RT for 1 h and purified by column chromatography on silica gel (gradient elution, 0 - 15% EtOAc/hexane) to give the title compound (1.12 g). MS: $[M+H]^+$ = 397, 399.

[0631] Preparation 96:
3-Bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

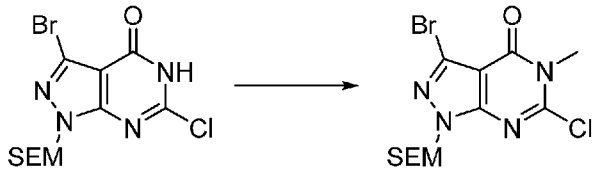
[0632] [Chem.130]



[0633] To a solution of 3-bromo-4,6-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine (1.12 g, 2.81 mmol) in THF (10 mL) was added 5 M NaOH (5.06 mL, 25.3 mmol) at RT. The mixture was stirred at RT for 7 h, diluted with 2-methyltetrahydrofuran, acidified with 6 M HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (1.05 g). MS: $[M+H]^+$ = 379, 381.

[0634] Preparation 97:
3-Bromo-6-chloro-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0635] [Chem.131]

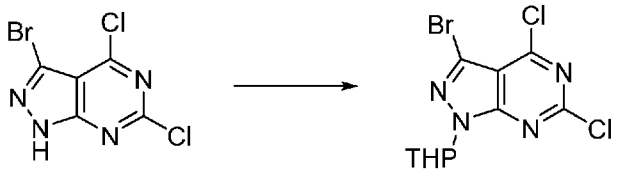


[0636] To a mixture of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[3,4-d

]pyrimidin-4-one (1.05 g, 2.77 mmol) and K_2CO_3 (0.764 g, 5.53 mmol) in DMF (10 mL) was added iodomethane (0.344 mL, 5.53 mmol) at RT. The mixture was stirred at RT for 30 min, diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 50% EtOAc/hexane) to give the title compound (0.780 g). MS: $[M+H]^+$ = 393, 395.

[0637] Preparation 98:
3-Bromo-4,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine

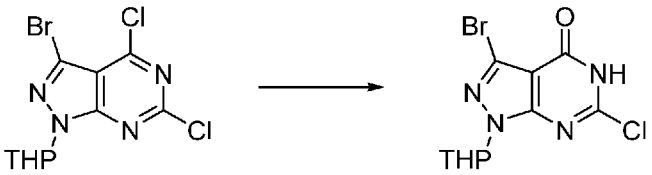
[0638] [Chem.132]



[0639] 3-Bromo-4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine (4.55 g, 17.0 mmol), 3,4-dihydro-2H-pyran (4.62 mL, 51.0 mmol) and p-toluenesulfonic acid monohydrate (0.646 g, 3.40 mmol) were dissolved in THF (74 mL) and heated at 70 °C for 2 h. The solvent was removed under vacuum and the solid residue triturated in Et_2O (30 mL) at 40 °C for 2 h. The resulting suspension was allowed to slowly cool down to RT. The solid was collected by filtration and washed with Et_2O. This wet solid was dried in a vacuum oven at 50 °C to give the title compound (4.8 g). MS: $[M+H]^+$ = 353, 355.

[0640] Preparation 99:
3-Bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

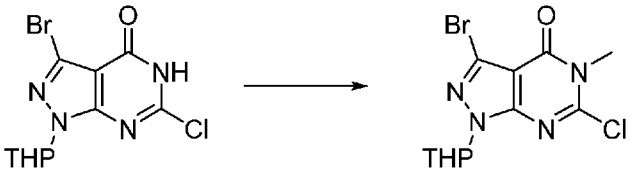
[0641] [Chem.133]



[0642] To a solution of
3-bromo-4,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (5.42 g, 15.4mmol) in THF (54 mL) was added 5 M NaOH (27 mL) at 0 °C. The mixture was stirred at RT overnight. The mixture was diluted with 2-methyltetrahydrofuran, acidified with 6 M HCl, and extracted with 2-methyltetrahydrofuran. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the the title compound (5.14 g). MS: $[M+H]^+$ = 333, 335.

[0643] Preparation 100: 3-Bromo-6-chloro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

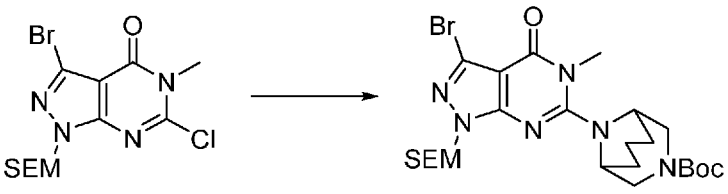
[0644] [Chem.134]



[0645] To a mixture of 3-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (12.8 g, 38.4 mmol) and K_2CO_3 (10.6 g, 76.7 mmol) in NMP (256 mL) was added iodomethane (4.78 mL, 76.7 mmol) at RT. The mixutre was stirredat RT for 1 h, diluted with EtOAc, washed with water (x2) and brine, dried over Na_2SO_4, filtered and then concentrated in vacuo to give the title compound (9.08 g). MS: $[M+H]^+$ = 347, 349.

[0646] Preparation 101: tert-Butyl 9-(3-bromo-5-methyl-4-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate

[0647] [Chem.135]

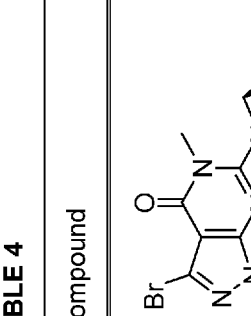


[0648] The mixture of 3- bromo-6-chloro-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (780 mg, 1.981 mmol), tert-butyl 3,9-diazabicyclo[3.3.1]nonane-3-carboxylate (0.89 g, 3.9620 mmol), DIPEA (1.72 mL, 9.90 mmol) and NMP (8 mL) was stirred at 120 °C for 5 h, cooled to RT, poured in to water, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/ hexane) to give the title compound (1.10 g). MS: $[M+H]^+$ = 583, 585.

[0649] Compounds of Table 4 below were prepared using procedures analogous to that described in preparation 101, starting from the appropriate substituted amine (synthesised as described above with any significant variations indicated below).

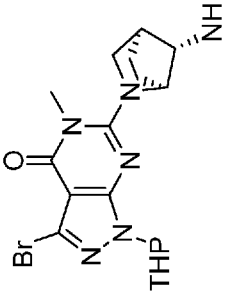
[0650] [Table 4-1]

TABLE 4

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	523, 525	Prepared as preparation 101 above using 3-bromo-6-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	tert-Butyl (*endo*-8-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	551, 553	Prepared as preparation 101 above using 3-bromo-6-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	tert-Butyl 9-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	537, 539	Prepared as preparation 101 above using 3-bromo-6-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl 3,9-diazabicyclo[3.3.1]nonane-3-carboxylate

[0651]

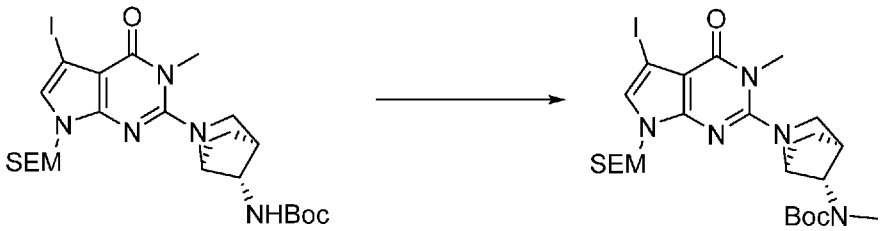
[Table 4-2]

	*rac-tert*-Butyl ((1*S*,4*S*,7*S*)-2-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	523, 525	Prepared as preparation 101 above using 3-bromo-6-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

[0652] Preparation 102: rac-tert-butyl ((1S,4S,7S)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)(methyl)carbamate

[0653]

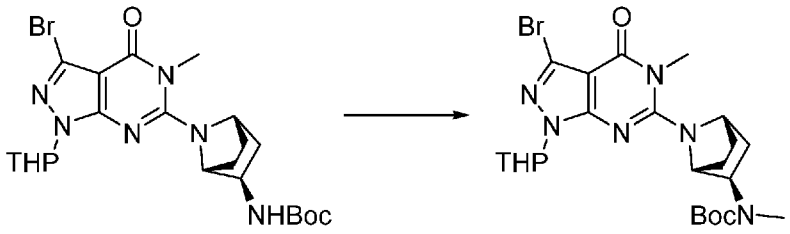
[Chem.136]



[0654] rac-tert-Butyl ((1S,4S,7S)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)(methyl)carbamate was prepared from rac-tert-butyl ((1S,4S,7S)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate using procedures analogous to that described in Preparation 94. MS: $[M+H]^+$ = 630.

[0655] Preparation 103: tert-Butyl ((1R,2R,4S)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate

[0656] [Chem.137]

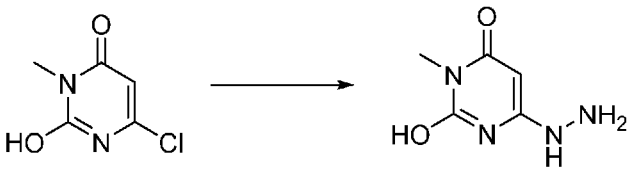


[0657] To a solution of tert-butyl ((1R,2R,4S)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (1.5 g, 2.90 mmol) in THF (30 mL) was added NaH (60% in mineral oil, 230 mg, 5.70 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min. Iodomethane (0.360 mL, 5.70 mmol) was added at 0 °C. The mixture was stirred at RT overnight, poured into sat. NH_4Cl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 20 - 50% EtOAc/hexane) to give the title compound (1.37 g). MS: $[M+H]^+$ = 537, 539.

[0658] Preparation 104: 6-Hydrazinyl-2-hydroxy-3-methyl-3,4-dihydropyrimidin-4-one

[0659]

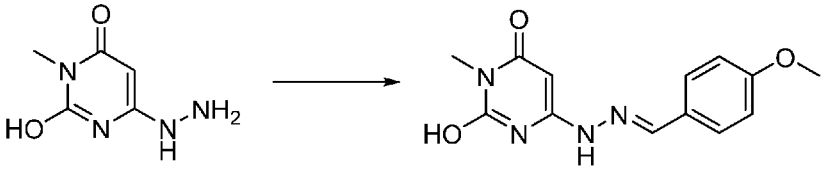
[Chem.138]



[0660] To a suspension of 6-chloro-2-hydroxy-3-methylpyrimidin-4(3H)-one (27.15 g, 169 mmol) in EtOH (250 mL), was added hydrazine-H_2O (49.7 mL, 507 mmol) at room temperature. The resulting suspension was allowed to stir at 80 °C for 18 h. The reaction was allowed to cool to room temperature and then at 0 °C in an ice bath for 1 h. The off-white precipitate was collected and washed with cold EtOH (2 x 100 mL). MS: $[M+H]^+ = 157$.

[0661] Preparation 105: 2-Hydroxy-6-[(E)-2-[(4-methoxyphenyl)methylidene]hydrazin-1-yl]-3-methyl-3,4-dihydropyrimidin-4-one

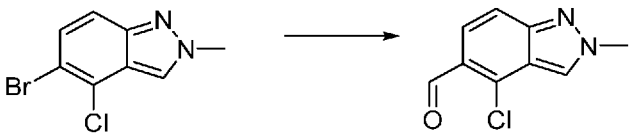
[0662] [Chem.139]



[0663] 4-Methoxybenzaldehyde (11.68 mL, 96 mmol) was added slowly to a suspension of 6-hydrazinyl-2-hydroxy-3-methyl-3,4-dihydropyrimidin-4-one (10 g, 64.0 mmol) in methanol (250 mL) and the mixture was stirred for 3 hours before being filtered. The precipitate was washed with MeOH (3 x 100 mL) before being transferred to a flask and stirred with 3:1 DCM/EtOAc (400 mL) overnight. The precipitate was filtered and dried on a sinter to give the title compound (9.56 g, 31.7 mmol, 49.5 % yield) as a colourless solid. MS: $[M+H]^+ = 275$.

[0664] Preparation 106: 4-Chloro-2-methyl-2H-indazole-5-carbaldehyde

[0665] [Chem.140]

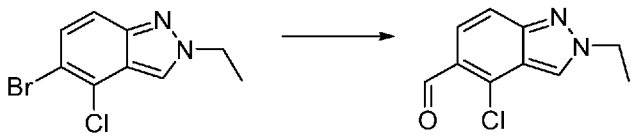


[0666] A solution of 5-bromo-4-chloro-2-methyl-2H-indazole (8.78 g, 35.8 mmol) in THF (60 mL) was added slowly over 10 minutes to a three-necked flask containing i-PrMgCl · LiCl (55 mL, 71.5 mmol) under nitrogen. The reaction was stirred at 30 °C for 4 hours before DMF (13.84 mL, 179 mmol) was added slowly. The reaction was

stirred at 30 °C for 1 hour before MeOH (40 mL) was added over 10 minutes. The mixture was allowed to stand at room temperature overnight. The mixture was concentrated under vacuum and the residue taken up in a mixture of EtOAc (150 mL), DCM (10 mL), and MeOH (10 mL). This solution was washed with water (100 mL) and brine (100 mL). The organic phase was isolated and the aqueous phase was further extracted with EtOAc (100 mL). The combined organic phases were then washed with water (2 x 100 mL) then dried (MgSO4), filtered, and concentrated to give the crude material. This was triturated with 4:1 isohexane/EtOAc (4 x 25 mL) and the solids filtered. They were then further triturated with 4:1 isohexane/EtOAc (2 x 25 mL) to give 4-chloro-2-methyl-2H-indazole-5-carbaldehyde (1.17 g, 5.89 mmol, 16.48 % yield) as a pale brown solid. MS: $[M+H]^+ = 195$.

[0667] Preparation 107: 4-Chloro-2-ethyl-2H-indazole-5-carbaldehyde

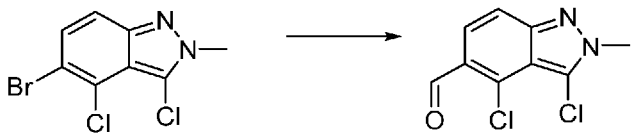
[0668] [Chem.141]



[0669] 4-Chloro-2-ethyl-2H-indazole-5-carbaldehyde was prepared from 5-bromo-4-chloro-2-ethyl-2H-indazole using procedures analogous to that described in preparation 106. MS: $[M+H]^+ = 209$.

[0670] Preparation 108: 3,4-Dichloro-2-methyl-2H-indazole-5-carbaldehyde

[0671] [Chem.142]

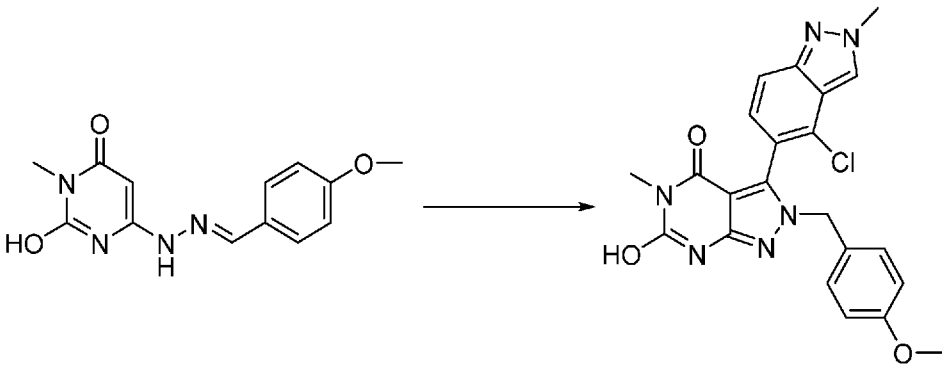


[0672] 3,4-Dichloro-2-methyl-2H-indazole-5-carbaldehyde was prepared from 5-bromo-3,4-dichloro-2-methyl-2H-indazole using procedures analogous to that described in preparation 106. MS: $[M+H]^+ = 229$.

[0673] Preparation 109: 3-(4-Chloro-2-methyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0674]

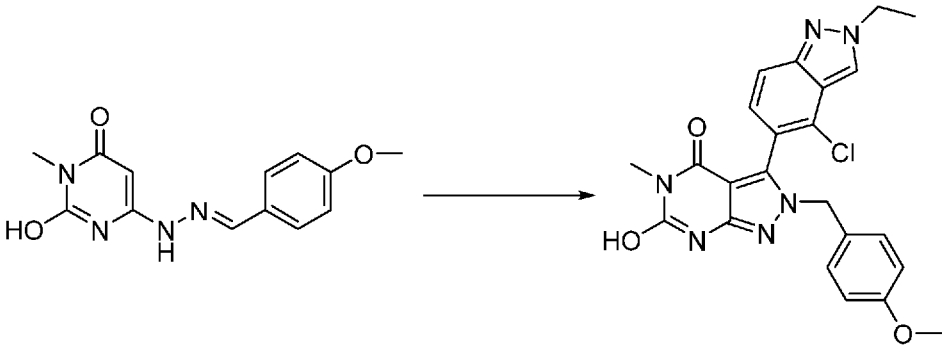
[Chem.143]



[0675] A suspension of 2-hydroxy-6-[(E)-2-[(4-methoxyphenyl)methylidene]hydrazin-1-yl]-3-methyl-3,4-dihydropyrimidin-4-one (2.013 g, 7.34 mmol) and 4-chloro-2-methyl-2H-indazole-5-carbaldehyde (1.5 g, 7.71 mmol) was stirred in DMF/IPA (2:1, 55 mL) at room temperature. Piperidine (0.763 mL, 7.71 mmol) was added in one portion and the reaction was stirred at 35 °C overnight. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (2 x 100 mL) and 10% MeOH in DCM (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. The crude product was purified by chromatography on silica gel (80 g cartridge, 0-3% MeOH/DCM) to afford the title compound (932 mg, 2.0 mmol, 27.3 % yield) as a pale orange solid. MS: $[M+H]^+$ = 451. ^1H NMR (500 MHz, DMSO-d_6) δ: 11.74 (s, 1H), 8.65 (s, 1H), 7.70 (dd, J = 8.8, 1.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.08 (d, J = 15.1 Hz, 1H), 4.99 (d, J = 15.1 Hz, 1H), 4.25 (s, 3H), 3.69 (s, 3H), 3.10 (s, 3H).

[0676] Preparation 110:
3-(4-Chloro-2-ethyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0677] [Chem.144]

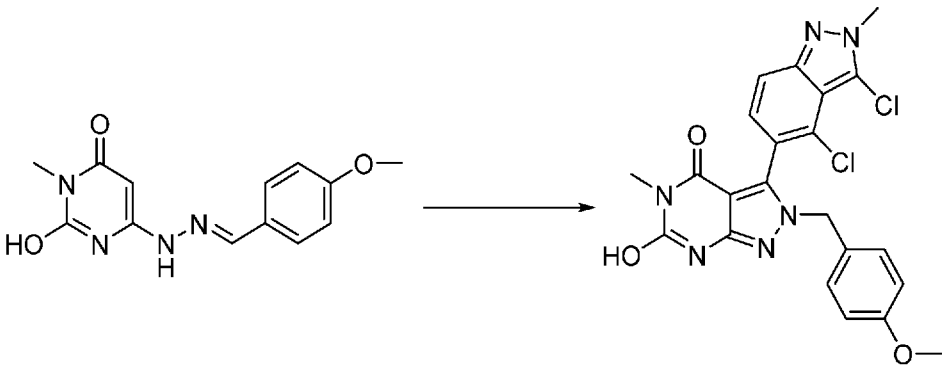


[0678] 3-(4-Chloro-2-ethyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-me

thyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one was prepared using procedures analogous to that described in preparation 109, starting from 2-hydroxy-6-[(E)-2-[(4-methoxyphenyl)methylidene]hydrazin-1-yl]-3-methyl-3,4-dihydropyrimidin-4-one and 4-chloro-2-ethyl-2H-indazole-5-carbaldehyde. MS: $[M+H]^+$ = 465. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.73 (s, 1H), 8.70 (s, 1H), 7.71 (dd, J = 8.8, 0.7 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.09 (d, J = 15.1 Hz, 1H), 5.00 (d, J = 15.1 Hz, 1H), 4.54 (q, J = 7.3 Hz, 2H), 3.69 (s, 3H), 3.10 (s, 3H), 1.55 (t, J = 7.3 Hz, 3H).

[0679] Preparation 111: 3-(3,4-Dichloro-2-methyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0680] [Chem.145]



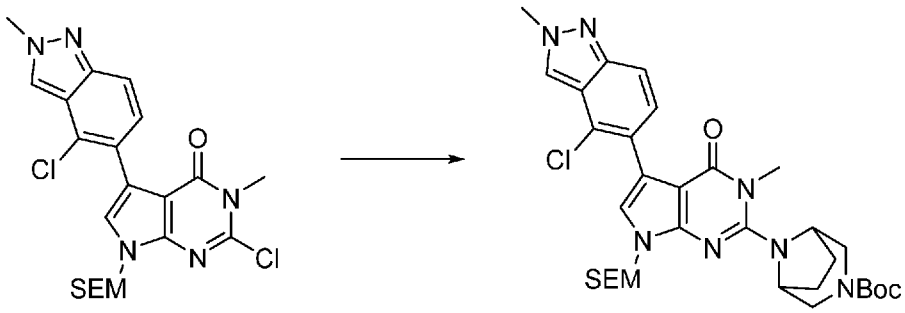
[0681] 3-(3,4-Dichloro-2-methyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one was prepared using procedures analogous to that described in preparation 109, starting from 2-hydroxy-6-[(E)-2-[(4-methoxyphenyl)methylidene]hydrazin-1-yl]-3-methyl-3,4-dihydropyrimidin-4-one and 3,4-dichloro-2-methyl-2H-indazole-5-carbaldehyde. MS: $[M+H]^+$ = 485.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.76 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.08 (d, J = 15.1 Hz, 1H), 5.01 (d, J = 15.1 Hz, 1H), 4.19 (s, 3H), 3.69 (s, 3H), 3.10 (s, 3H).

[0682] General procedure 1: tert-Butyl 8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[0683]

[Chem.146]



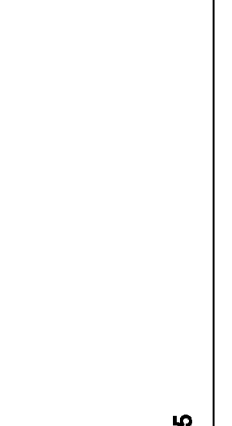
[0684] The mixture of 2-chloro-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (100 mg, 0.209 mmol), tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (88.7 mg, 0.418 mmol), DIPEA (0.109 mL, 0.627 mmol) and NMP (2 mL) was stirred at 120 °C for 8 h, cooled to RT, diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (140 mg). MS: $[M+H]^+$ = 654, 656.

[0685] Compounds of Table 5 below were prepared using procedures analogous to that described in general procedure 1 starting from the appropriate substituted protected pyrrolopyrimidinone and varying the amine(synthesised as described above with any significant variations indicated below).

[0686]

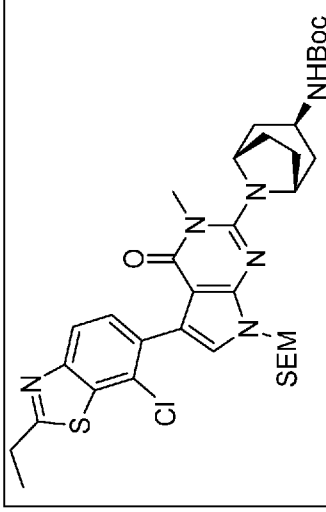
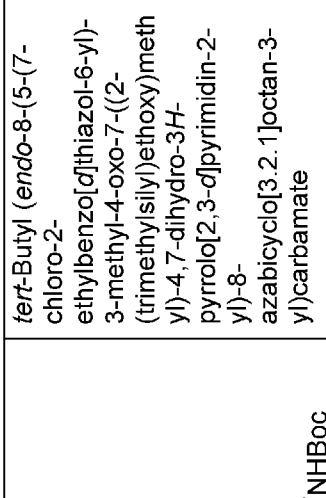
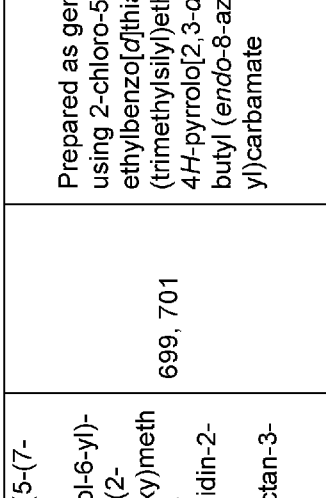
[Table 5-1]

TABLE 5

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-Butyl ((1-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate	684, 686	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((4-methylpiperidin-4-yl)methyl)carbamate
	tert-Butyl (1-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-methylpiperidin-4-yl)carbamate	670, 672	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (4-methylpiperidin-4-yl)carbamate
	tert-Butyl (*endo*-8-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate

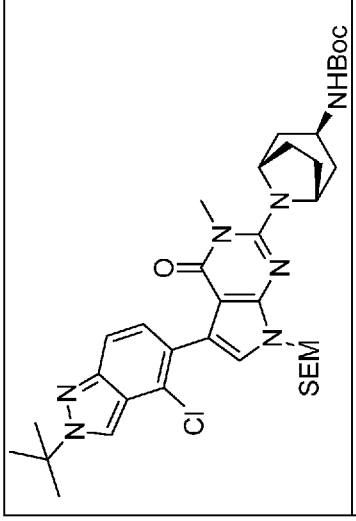
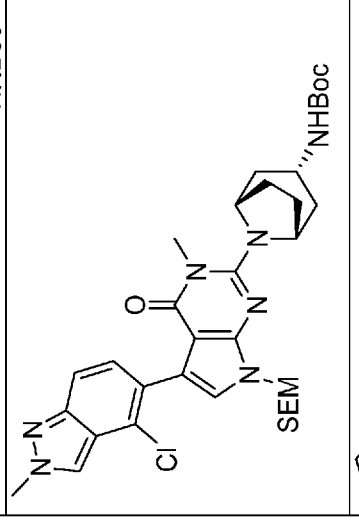
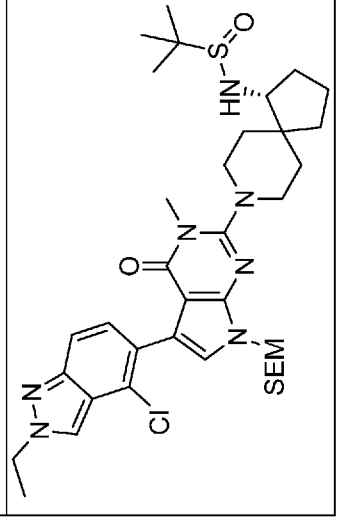
[0687]

[Table 5-2]

	*tert*-Butyl (*endo*-8-(5-(7-chloro-2-ethylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	699, 701	Prepared as general procedure 1 above using 2-chloro-5-(7-chloro-2-ethylbenzo[*d*]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-Butyl (*endo*-8-(5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	685, 687	Prepared as general procedure 1 above using 2-chloro-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate

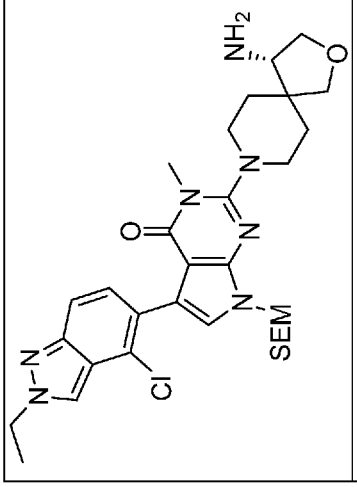
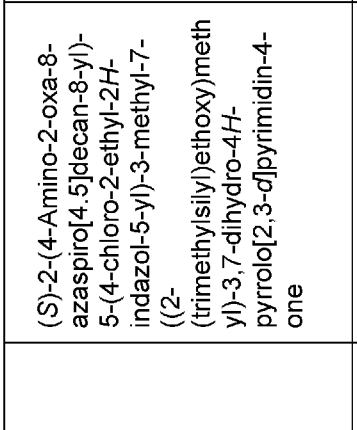
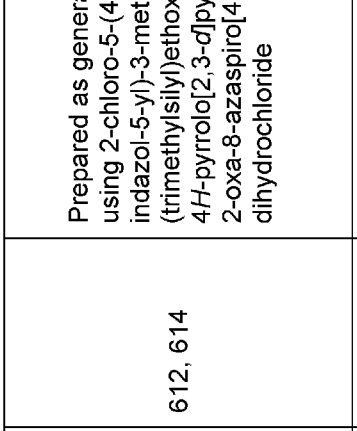
[0688]

[Table 5-3]

	*tert*-Butyl (*endo*-8-(5-(2-(*tert*-butyl)-4-chloro-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	710, 712	Prepared as general procedure 1 above using 5-(2-(*tert*-butyl)-4-chloro-2*H*-indazol-5-yl)-2-chloro-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-Butyl (*exo*-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*exo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*N*-((*R*)-8-(5-(4-Chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azaspiro[4.5]decan-1-yl)-2-methylpropane-2-sulfinamide	714, 716	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and 2-methyl-*N*-((*R*)-8-azaspiro[4.5]decan-1-yl)propane-2-sulfinamide

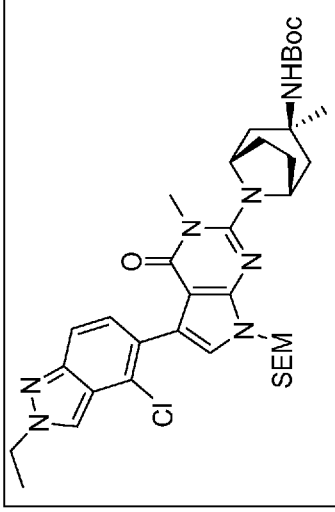
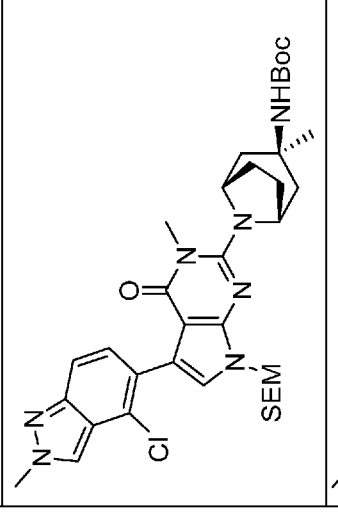
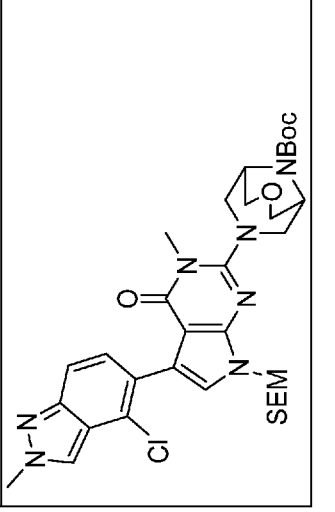
[0689]

[Table 5-4]

	(S)-2-(4-Amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	612, 614	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and (*S*)-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride
	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)carbamate	696, 698	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)(methyl)carbamate
	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)carbamate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)(methyl)carbamate

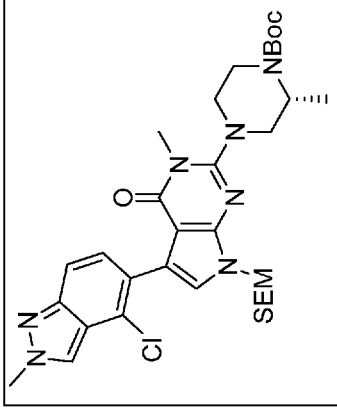
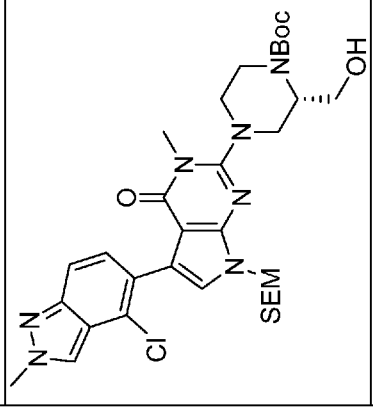
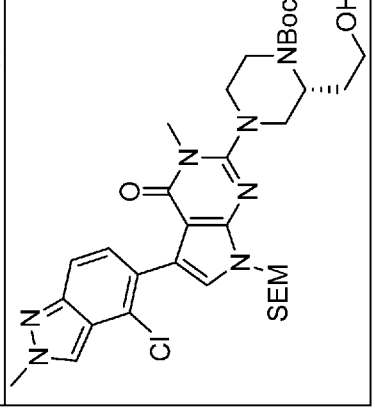
[0690]

[Table 5-5]

	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	696, 698	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-Butyl 7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	670, 672	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate

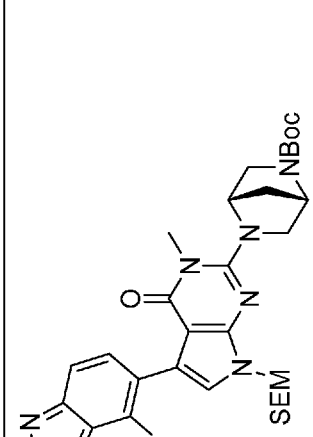
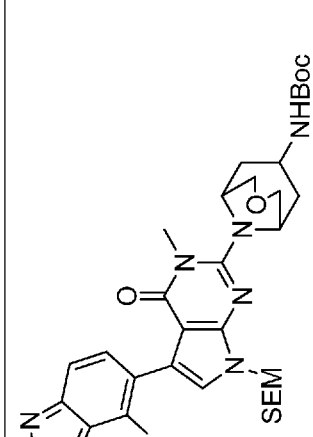
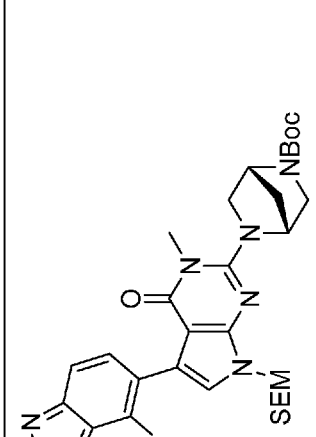
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[Table 5-6]

	*tert*-Butyl (*R*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-2-methylpiperazine-1-carboxylate.
	*tert*-Butyl (*S*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate	658, 660	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-2-(hydroxymethyl)piperazine-1-carboxylate.
	*tert*-Butyl (*R*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-(2-hydroxyethyl)piperazine-1-carboxylate	672, 674	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-2-(2-hydroxyethyl)piperazine-1-carboxylate.

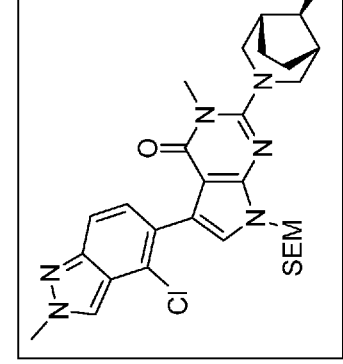
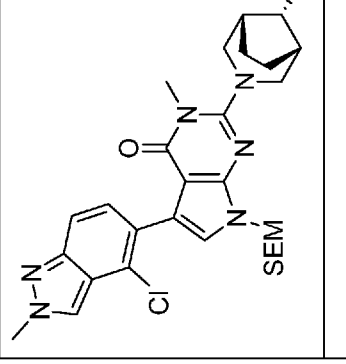
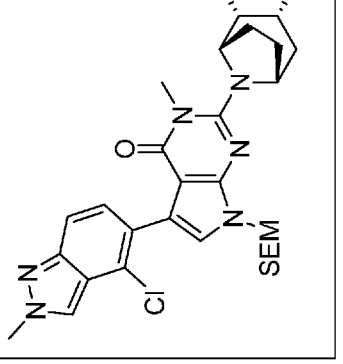
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[Table 5-7]

	*tert*-Butyl (1*S*,4*S*)-5-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate
	*tert*-Butyl (9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)carbamate	684, 686	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)carbamate
	*tert*-Butyl (1*R*,4*R*)-5-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

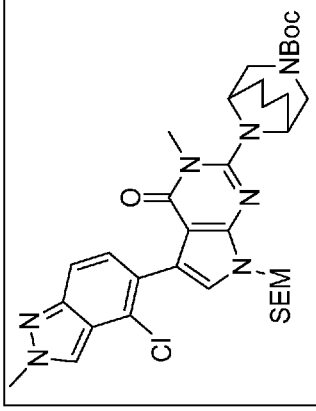
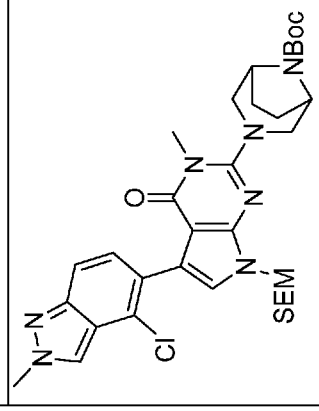
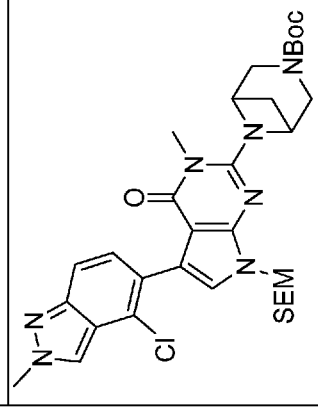
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[Table 5-8]

	*tert*-Butyl (*exo*-3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.2.1]octan-8-yl)carbamate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*exo*-3-azabicyclo[3.2.1]octan-8-yl)carbamate
	*tert*-Butyl (*endo*-3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.2.1]octan-8-yl)carbamate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-3-azabicyclo[3.2.1]octan-8-yl)carbamate
	*rac*-Benzyl ((1*S*,2*R*,3*R*,5*R*)-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac*-benzyl ((1*S*,2*S*,3*R*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate hydrochloride

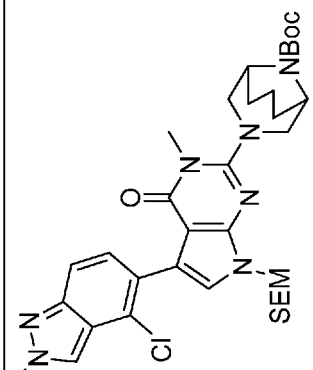
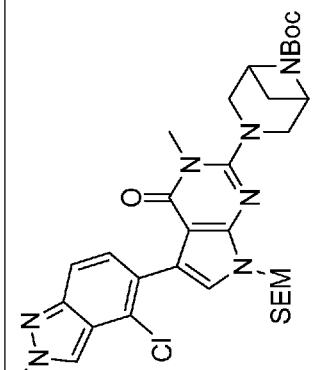
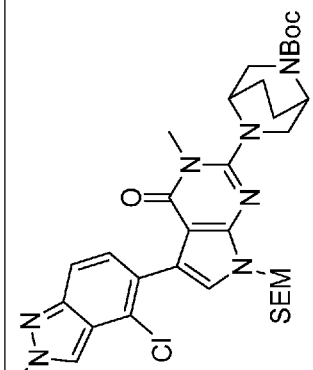
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[Table 5-9]

	*tert*-Butyl 9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,9-diazabicyclo[3.3.1]nonane-3-carboxylate
	*tert*-Butyl 3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate
	*tert*-Butyl 6-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate

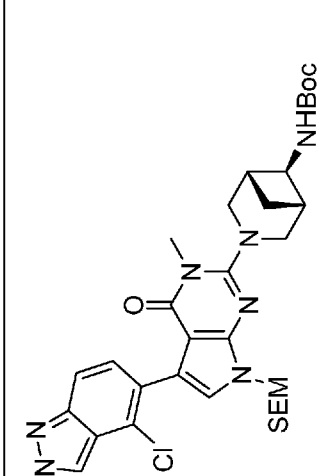
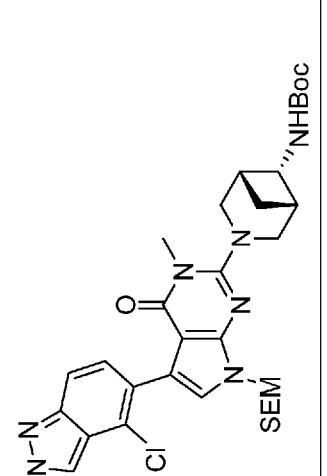
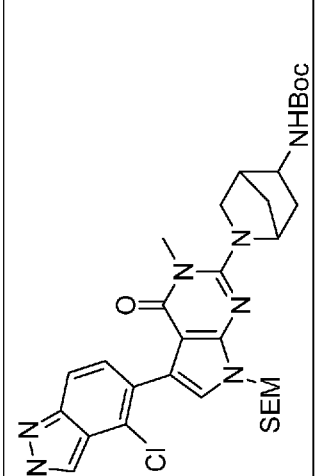
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[Table 5-10]

	*tert*-Butyl 3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,9-diazabicyclo[3.3.1]nonane-9-carboxylate
	*tert*-Butyl 3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate
	*tert*-Butyl 5-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2,5-diazabicyclo[2.2.2]octane-2-carboxylate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 2,5-diazabicyclo[2.2.2]octane-2-carboxylate

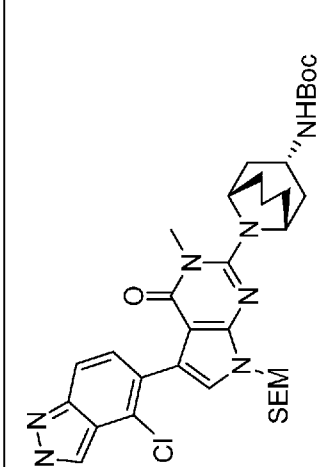
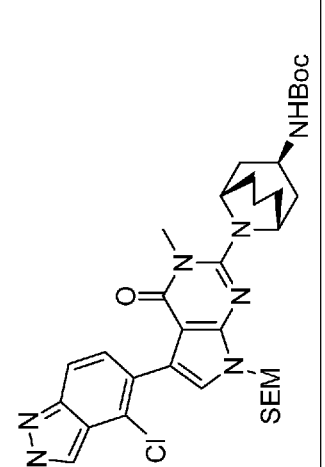
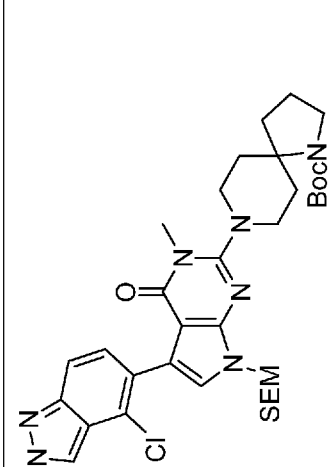
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[Table 5-11]

	*tert*-Butyl (*exo*-3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.1.1]heptan-6-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*exo*-3-azabicyclo[3.1.1]heptan-6-yl)carbamate.
	*tert*-Butyl (*endo*-3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.1.1]heptan-6-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-3-azabicyclo[3.1.1]heptan-6-yl)carbamate
	*tert*-Butyl (2-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-5-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (2-azabicyclo[2.2.1]heptan-5-yl)carbamate

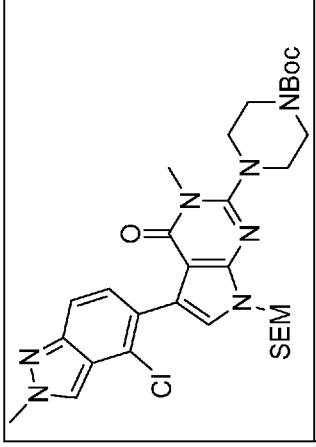
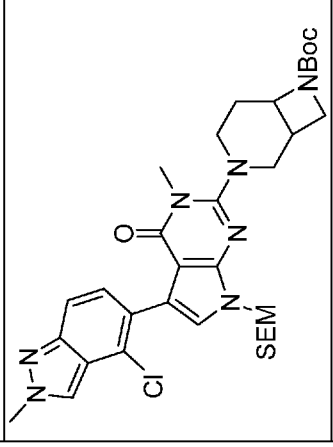
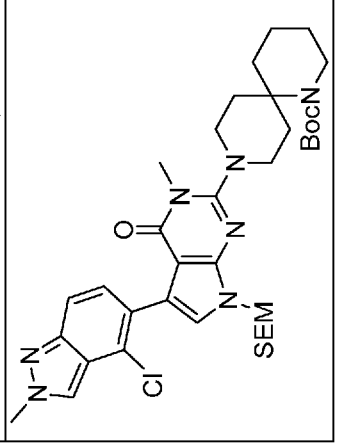
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[Table 5-12]

	*tert*-Butyl (*exo*-9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-9-azabicyclo[3.3.1]nonan-3-yl)carbamate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*exo*-9-azabicyclo[3.3.1]nonan-3-yl)carbamate.
	*tert*-Butyl (*endo*-9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-9-azabicyclo[3.3.1]nonan-3-yl)carbamate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-9-azabicyclo[3.3.1]nonan-3-yl)carbamate.
	*tert*-Butyl 8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-1,8-diazaspiro[4.5]decane-1-carboxylate	682, 684	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 1,8-diazaspiro[4.5]decane-1-carboxylate.

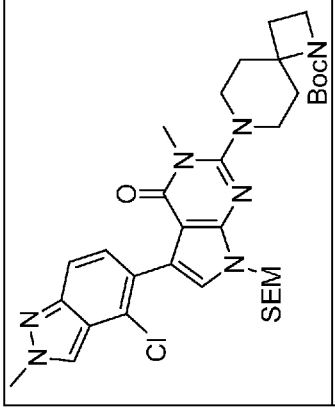
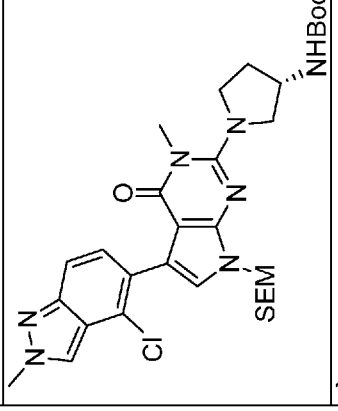
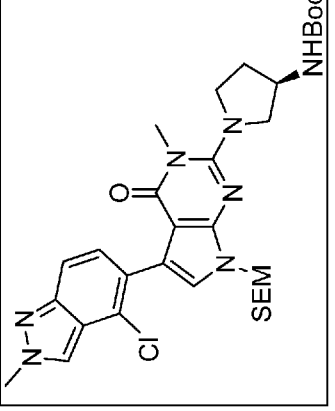
[0698]

[Table 5-13]

	*tert*-Butyl 4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)piperazine-1-carboxylate	628, 630	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl piperazine-1-carboxylate
	*tert*-Butyl 3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,7-diazabicyclo[4.2.0]octane-7-carboxylate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 3,7-diazabicyclo[4.2.0]octane-7-carboxylate
	*tert*-Butyl 9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-1,9-diazaspiro[5.5]undecane-1-carboxylate	696, 698	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 1,9-diazaspiro[5.5]undecane-1-carboxylate

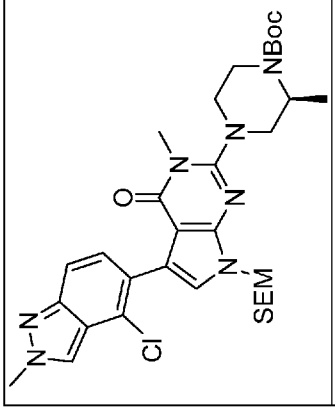
[0699]

[Table 5-14]

	*tert*-Butyl 7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-1,7-diazaspiro[3.5]nonane-1-carboxylate	668, 670	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 1,7-diazaspiro[3.5]nonane-1-carboxylate
	*tert*-Butyl (*S*)-(1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)carbamate	628, 630	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-pyrrolidin-3-ylcarbamate
	*tert*-Butyl (*R*)-(1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)carbamate	628, 630	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate

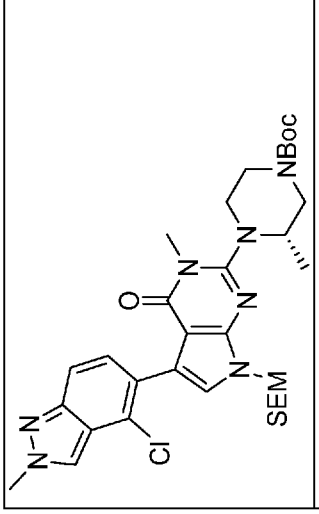
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[Table 5-15]

	*tert*-Butyl (*S*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-2-methylpiperazine-1-carboxylate
	tert-Butyl ((1*S*,2*S*,4*R*)-7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((1*S*,2*S*,4*R*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	tert-Butyl (*R*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate

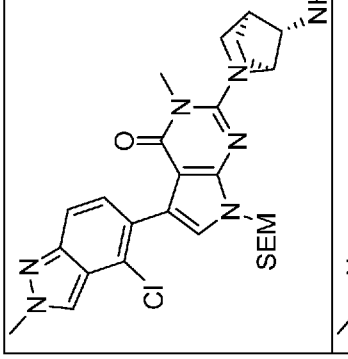
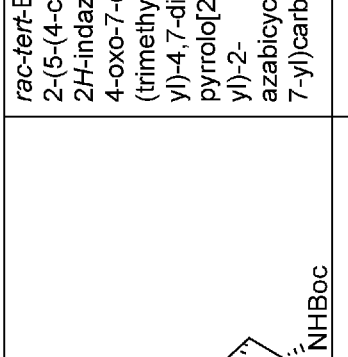
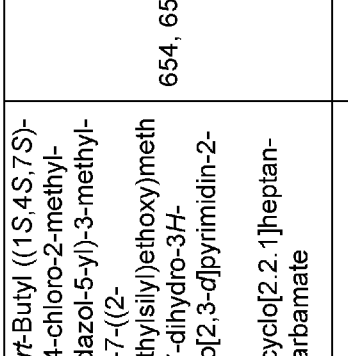
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[Table 5-16]

	*tert*-Butyl (*S*)-4-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	tert-Butyl ((3*R*,4*S*)-1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-fluoropyrrolidin-3-yl)carbamate	646, 648	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((3*R*,4*S*)-4-fluoropyrrolidin-3-yl)carbamate

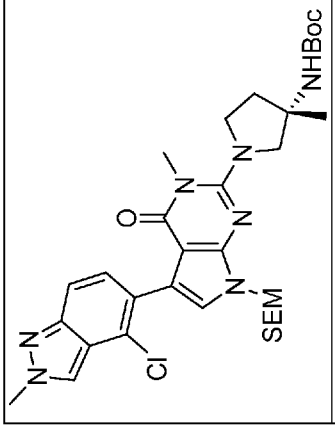
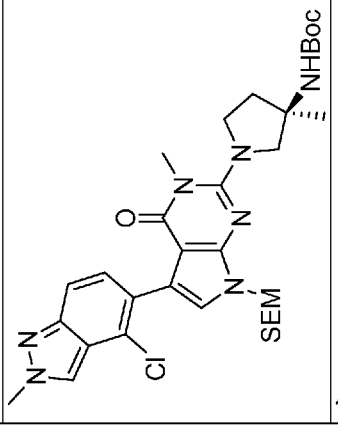
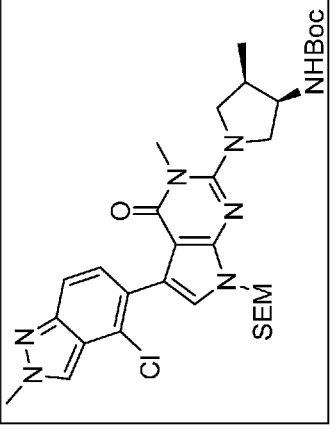
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[Table 5-17]

	*rac-tert*-Butyl ((1*S*,4*S*,7*S*)-2-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate
	*tert*-Butyl ((3*S*,4*S*)-1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-fluoropyrrolidin-3-yl)carbamate	646, 648	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((3*S*,4*S*)-4-fluoropyrrolidin-3-yl)carbamate
	*tert*-Butyl (1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4,4-difluoropyrrolidin-3-yl)carbamate	664, 666	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (4,4-difluoropyrrolidin-3-yl)carbamate

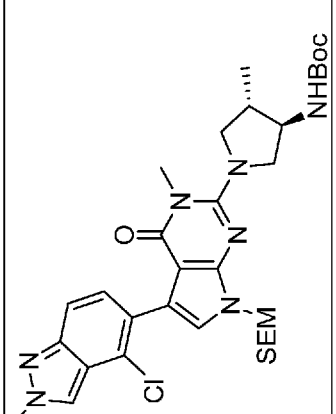
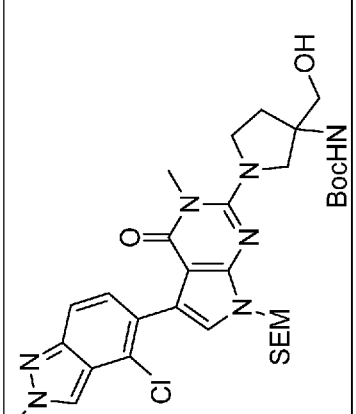
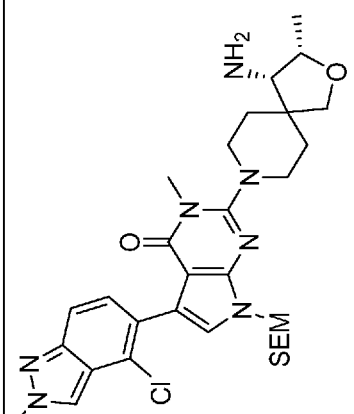
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[Table 5-18]

	*tert*-Butyl (*S*)-(1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methylpyrrolidin-3-yl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-(3-methylpyrrolidin-3-yl)carbamate
	*tert*-Butyl (*R*)-(1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methylpyrrolidin-3-yl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-(3-methylpyrrolidin-3-yl)carbamate
	*tert*-Butyl ((3*R*,4*R*)-1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-methylpyrrolidin-3-yl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((3*R*,4*R*)-4-methylpyrrolidin-3-yl)carbamate

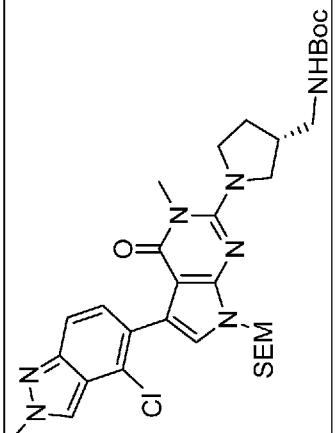
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[Table 5-19]

	*tert*-Butyl ((3*R*,4*S*)-1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-methylpyrrolidin-3-yl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((3*R*,4*S*)-4-methylpyrrolidin-3-yl)carbamate
	*tert*-Butyl (1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-(hydroxymethyl)pyrrolidin-3-yl)carbamate	658, 660	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (3-(hydroxymethyl)pyrrolidin-3-yl)carbamate
	2-((3*S*,4*S*)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	612, 614	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and (3*S*,4*S*)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride

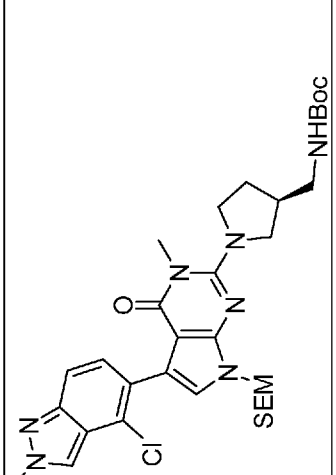
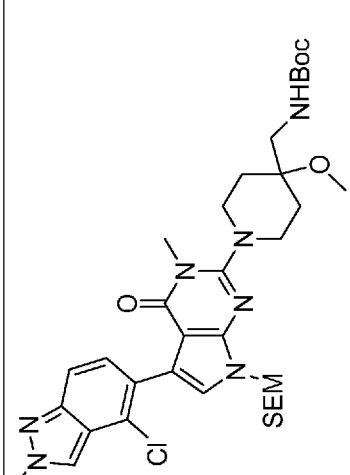
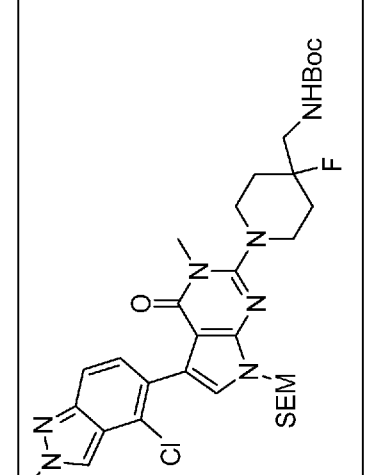
[0705]

[Table 5-20]

	*tert*-Butyl (*R*)-((1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)methyl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*S*)-(pyrrolidin-3-ylmethyl)carbamate
	tert-Butyl (3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (3-azabicyclo[3.1.0]hexan-1-yl)carbamate
	tert-Butyl (3-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)carbamate	640, 642	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (3-azabicyclo[3.1.0]hexan-6-yl)carbamate

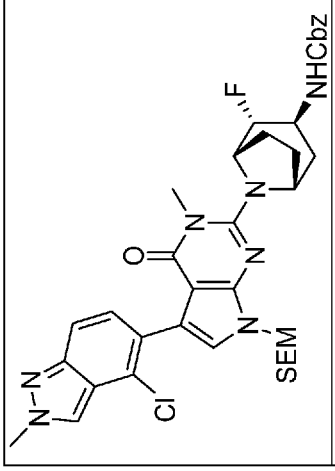
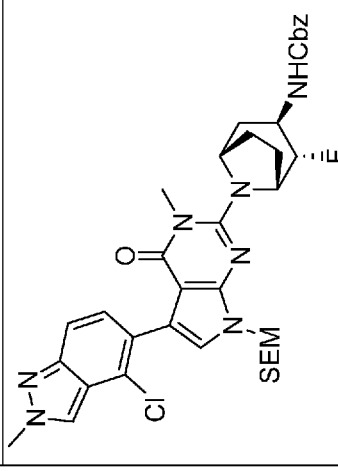
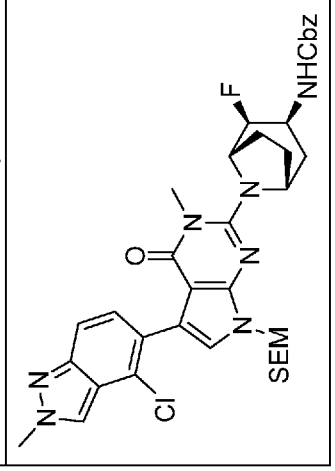
[0706]

[Table 5-21]

	*tert*-Butyl (*S*)-((1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)methyl)carbamate	642, 644	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl (*R*)-(pyrrolidin-3-ylmethyl)carbamate
	*tert*-Butyl ((1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-methoxypiperidin-4-yl)methyl)carbamate	686, 688	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((4-methoxypiperidin-4-yl)methyl)carbamate
	*tert*-Butyl ((1-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-4-fluoropiperidin-4-yl)methyl)carbamate	674, 676	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((4-fluoropiperidin-4-yl)methyl)carbamate

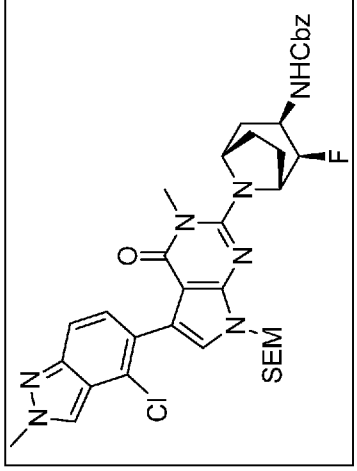
[0707]

[Table 5-22]

	Benzyl ((1*S*,2*R*,3*S*,5*R*)-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and benzyl ((1*S*,2*S*,3*S*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	Benzyl ((1*R*,2*S*,3*R*,5*S*)-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and benzyl ((1*R*,2*R*,3*R*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	Benzyl ((1*S*,2*S*,3*S*,5*R*)-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and benzyl ((1*S*,2*R*,3*S*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate

[0708]

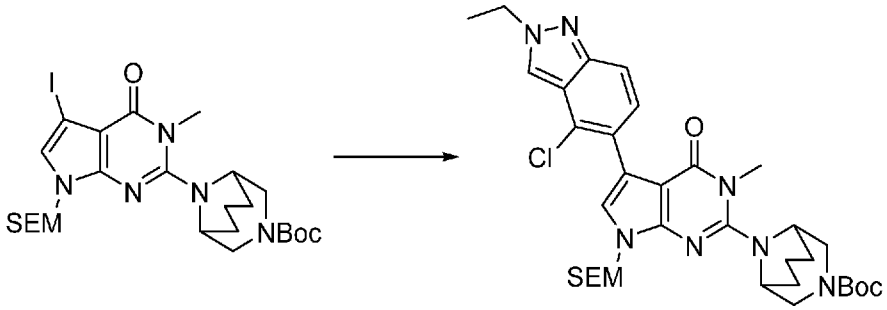
[Table 5-23]

	Benzyl ((1*R*,2*R*,3*R*,5*S*)-8-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and benzyl ((1*R*,2*S*,3*R*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate

[0709] General procedure 2: tert-Butyl 9-(5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)

methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate

[0710] [Chem.147]



[0711] The mixture of tert-butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate (500 mg, 0.794 mmol), 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (365 mg, 1.19 mmol), K_3PO_4 (337 mg, 1.58 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (64.8 mg, 0.0794 mmol), 1,4-dioxane (8 mL) and water (2 mL) was stirred at 70 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (375 mg). MS: $[M+H]^+$ = 682, 684.

[0712] Compounds of Table 6 below were prepared using procedures analogous to that described in general procedure 2 starting from the appropriate substituted protected pyrrolopyrimidinone and varying the boronate or boronic acid (synthesised as described above with any significant variations indicated below).

[0713]

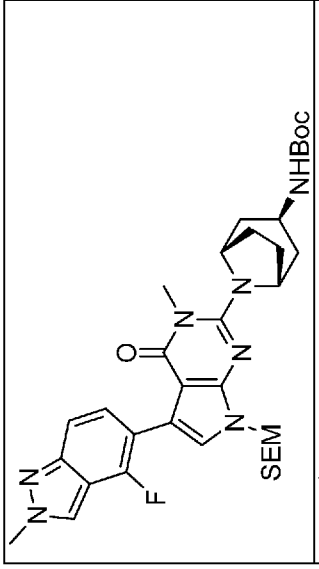
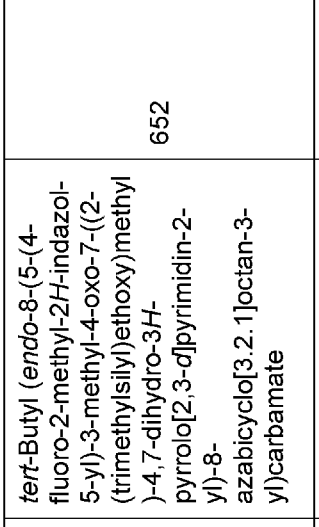
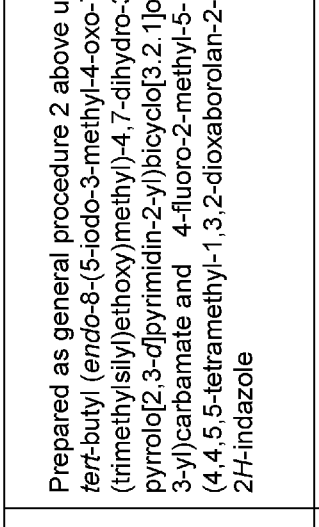
[Table 6-1]

TABLE 6

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	tert-Butyl (*endo*-8-(3-methyl-5-(2-methyl-2*H*-indazol-5-yl)-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	634	Prepared as general procedure 2 above using *tert*-Butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl (*endo*-8-[5-(7-chloro-2-methylbenzo[*d*]oxazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)pyrrolo[2,3-*d*]pyrimidin-2-yl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate	669, 671	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole
	tert-Butyl (*endo*-8-(5-(7-chloro-2-ethylbenzo[*d*]oxazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	683, 685	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-bromo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 7-chloro-2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole

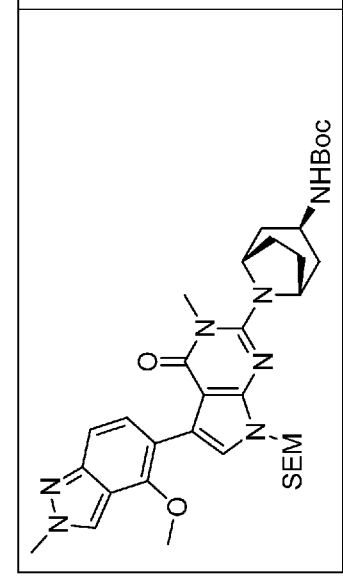
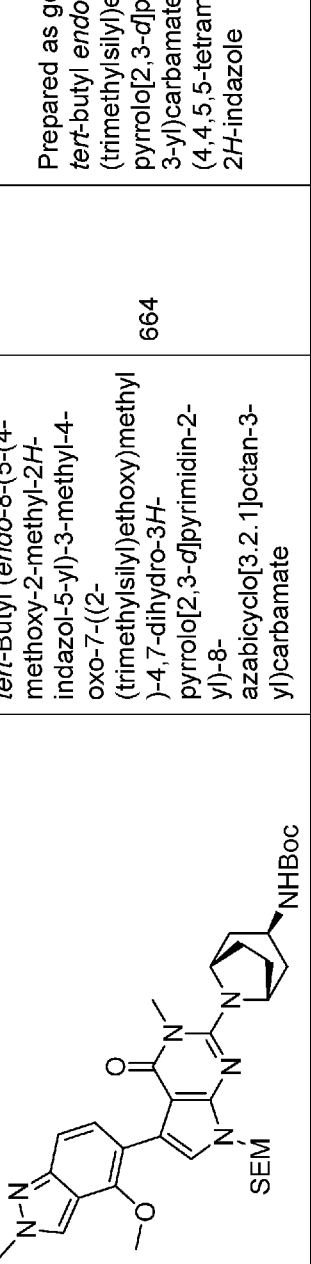
[0714]

[Table 6-2]

	*tert*-Butyl (*endo*-8-(5-(4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	652	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl (*endo*-8-(5-(6,7-difluoro-1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	671	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 6,7-difluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole
	*tert*-Butyl (*endo*-8-(5-(6-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	652	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 6-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

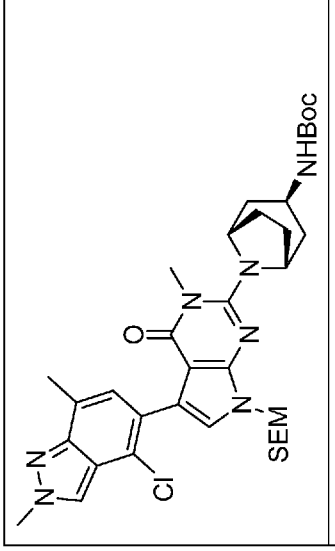
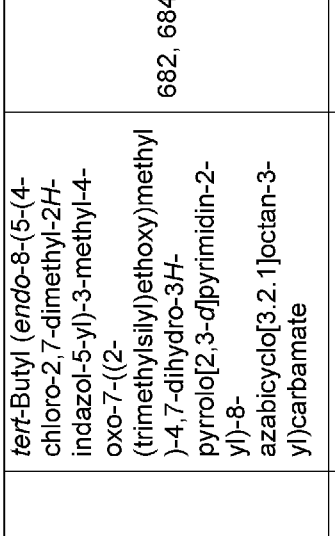
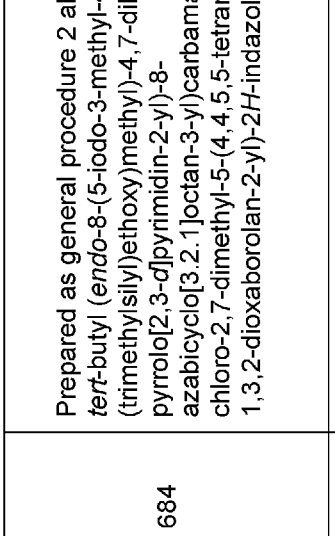
[0715]

[Table 6-3]

	*tert*-Butyl (*endo*-8-(5-(4-methoxy-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	664	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 4-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl (*endo*-8-(5-(7-chloro-1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	669, 671	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 7-chloro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole
	*tert*-Butyl (*endo*-8-(5-(4-chloro-2-(2-hydroxy-2-methylpropyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	726, 728	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 1-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-2-methylpropan-2-ol

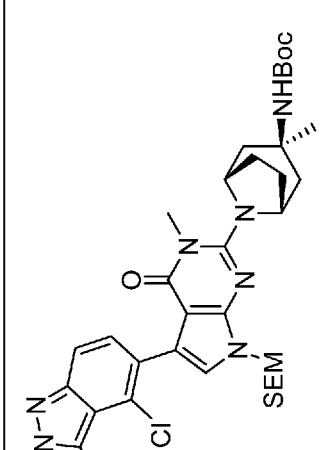
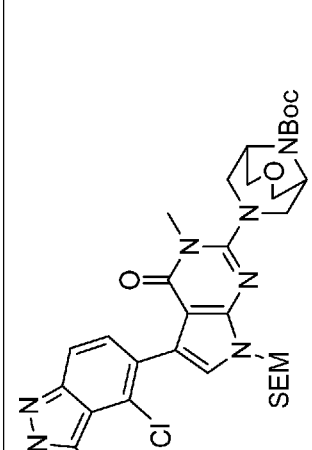
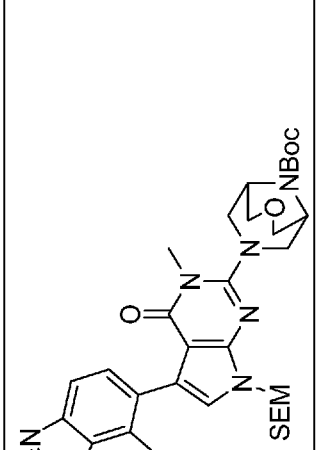
[0716]

[Table 6-4]

	*tert*-Butyl (*endo*-8-(5-(4-chloro-2,7-dimethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	682, 684	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 4-chloro-2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl (*endo*-8-(5-(4-chloro-1*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	654, 656	Prepared as general procedure 2 above using *tert*-butyl *endo*-(8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)bicyclo[3.2.1]octan-3-yl)carbamate and 4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole
	*tert*-Butyl (*endo*-8-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	702, 704	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

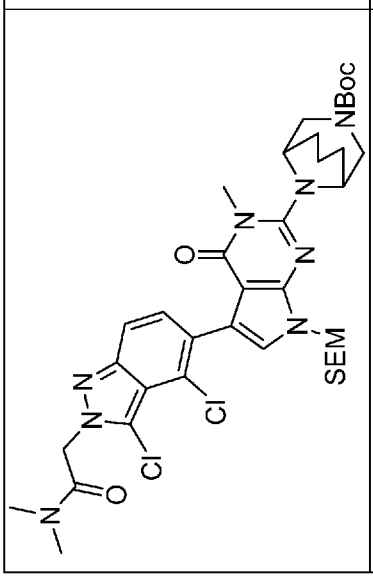
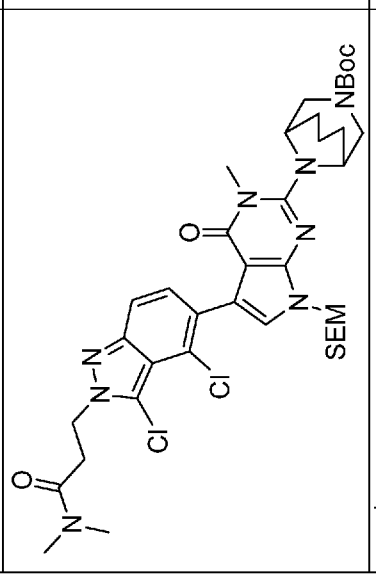
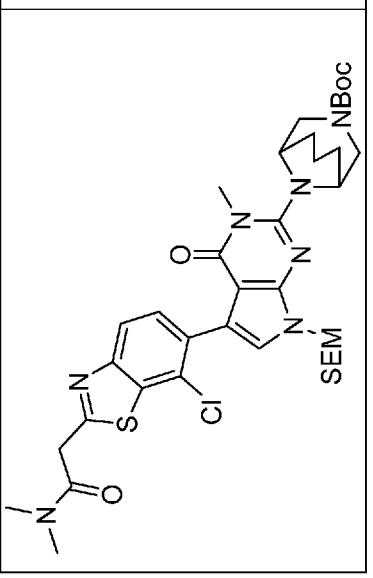
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[Table 6-5]

	*tert*-Butyl (*endo*-8-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	716, 718	Prepared as general procedure 2 above using *tert*-butyl (*endo*-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl 7-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-d]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	704, 706	Prepared as general procedure 2 above using *tert*-butyl 7-[5-iodo-3-methyl-4-oxo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*d*]pyrimidin-2-yl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl 7-(5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	687, 689	Prepared as general procedure 2 above using *tert*-butyl 7-[5-iodo-3-methyl-4-oxo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*d*]pyrimidin-2-yl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazole

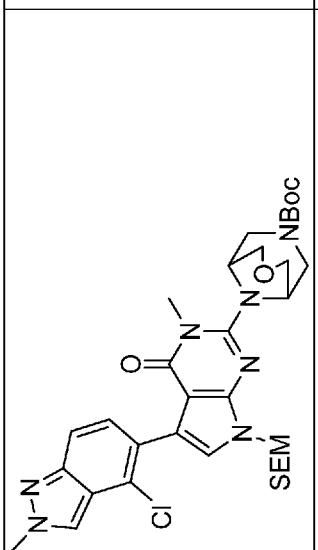
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[Table 6-6]

	*tert*-Butyl 9-(5-(3,4-dichloro-2-(2-(dimethylamino)-2-oxoethyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	773, 775	Prepared as general procedure 2 above using 2-(3,4-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide
	*tert*-Butyl 9-(5-(3,4-dichloro-2-(3-(dimethylamino)-3-oxopropyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	787, 789	Prepared as general procedure 2 above using 3-(3,4-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide
	*tert*-Butyl 9-(5-(7-chloro-2-(2-(dimethylamino)-2-oxoethyl)benzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	756, 758	Prepared as general procedure 2 above using 2-(7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylacetamide

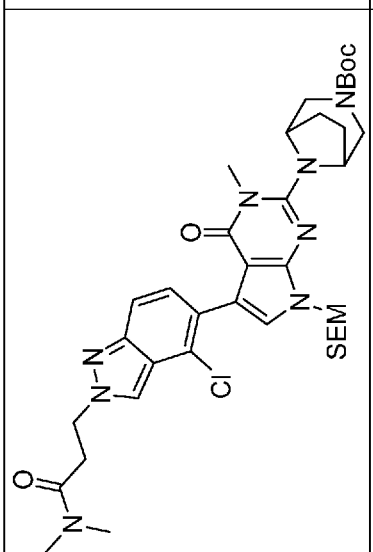
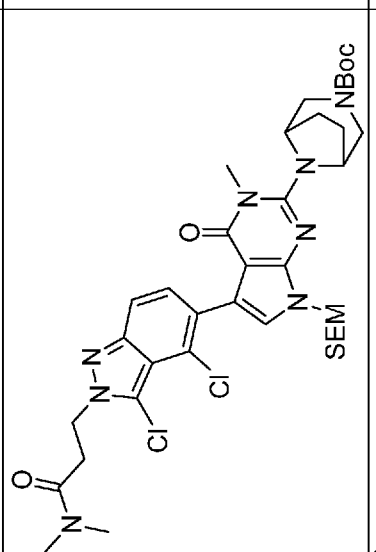
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[Table 6-7]

	*tert*-Butyl 9-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate	670, 672	Prepared as general procedure 2 above using *tert*-butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl 8-(5-(4-chloro-2-(2-(dimethylamino)-2-oxoethyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	725, 727	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 2-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide
	tert-Butyl 8-(5-(4-chloro-2-methyl-2*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	655, 657	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*d*][1,2,3]triazole

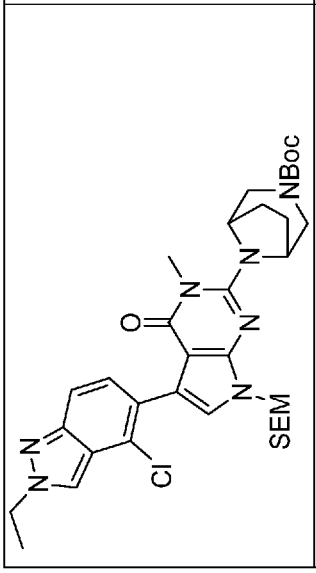
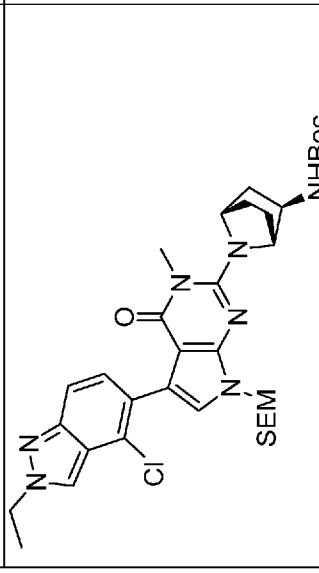
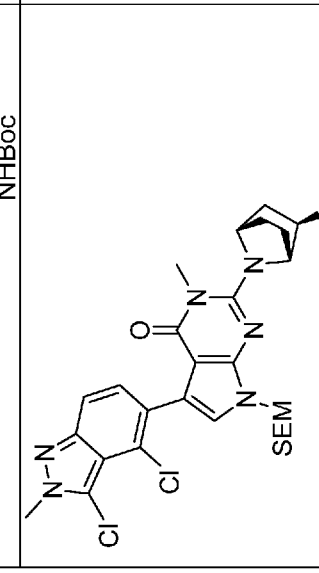
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[Table 6-8]

	*tert*-Butyl 8-(5-(4-chloro-2-(3-(dimethylamino)-3-oxopropyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	739, 741	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 3-(4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide
	*tert*-Butyl 8-(5-(3,4-dichloro-2-(3-(dimethylamino)-3-oxopropyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	773, 775	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 3-(3,4-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide
	*tert*-Butyl 8-(5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	671, 673	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole

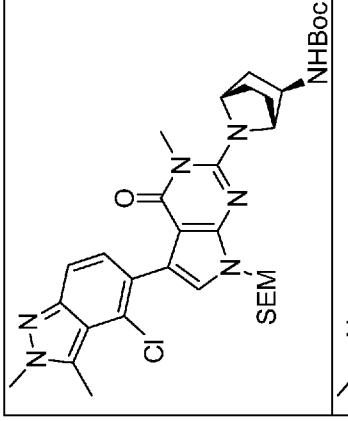
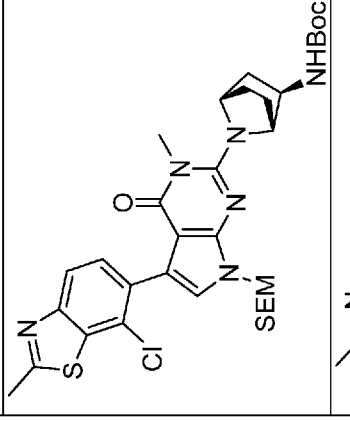
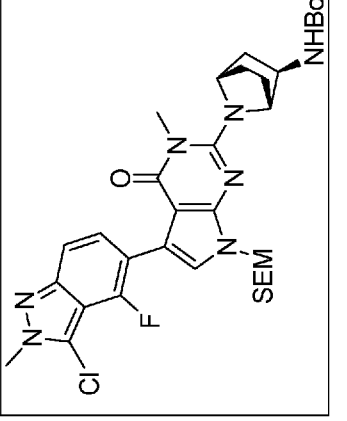
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[Table 6-9]

	*tert*-Butyl 8-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	668, 670	Prepared as general procedure 2 above using *tert*-butyl 8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	668, 670	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	688, 690	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

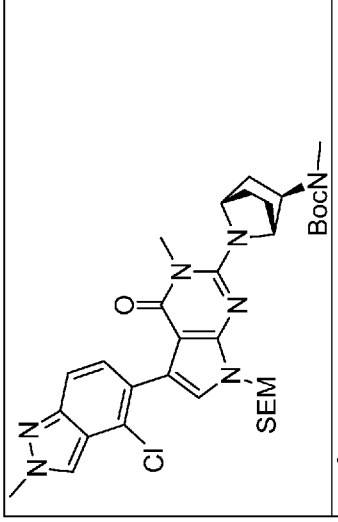
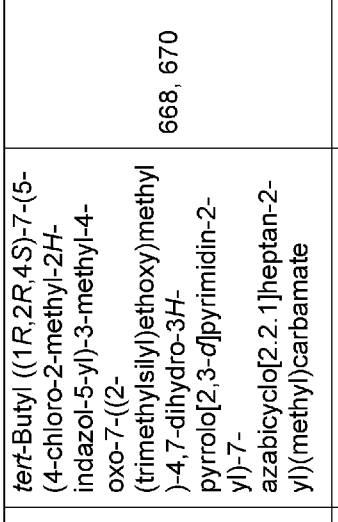
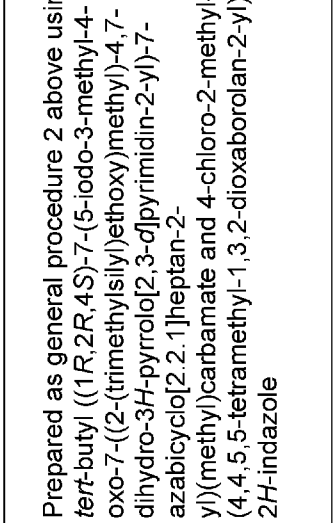
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[Table 6-10]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2,3-dimethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	668, 670	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 4-chloro-2,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	671, 673	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	672, 674	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 3-chloro-4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

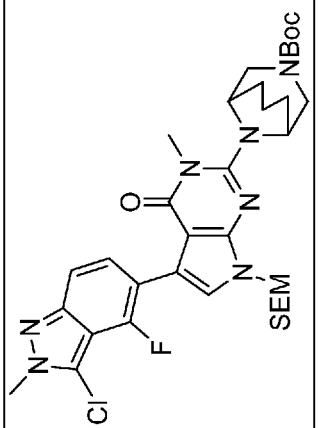
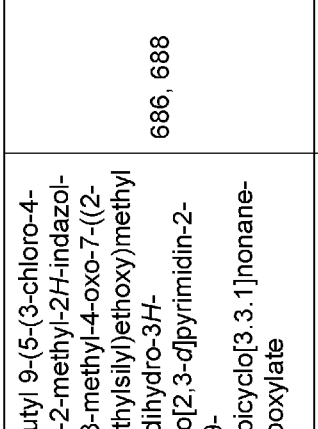
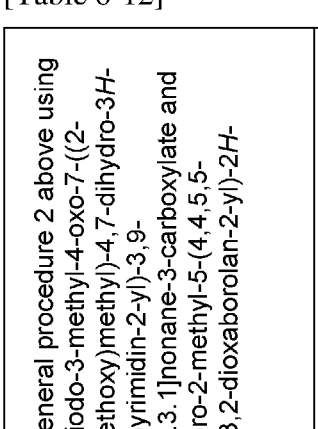
[0723]

[Table 6-11]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	668, 670	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	682, 684	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate
	*tert*-Butyl 9-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	702, 704	Prepared as general procedure 2 above using *tert*-butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

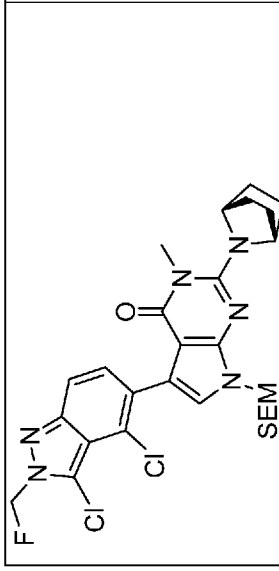
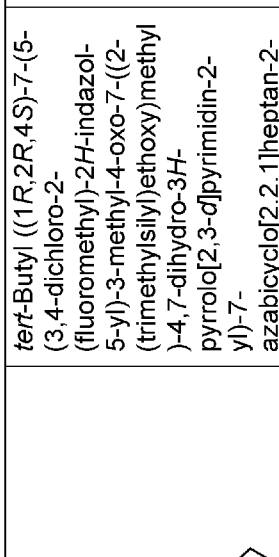
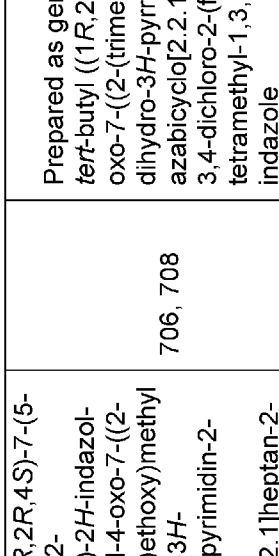
[0724]

[Table 6-12]

	*tert*-Butyl 9-(5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	686, 688	Prepared as general procedure 2 above using *tert*-butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 3-chloro-4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	657, 659	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-ethyl-3-methoxy-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	698, 700	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 4-chloro-2-ethyl-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

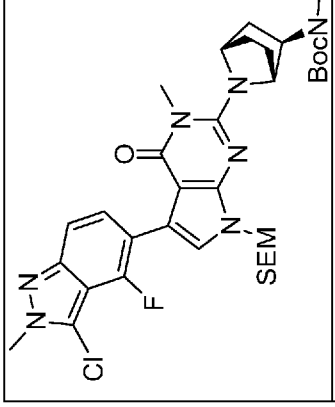
[0725]

[Table 6-13]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(3,4-dichloro-2-(fluoromethyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	706, 708	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 3,4-dichloro-2-(fluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	702, 704	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	671, 673	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole

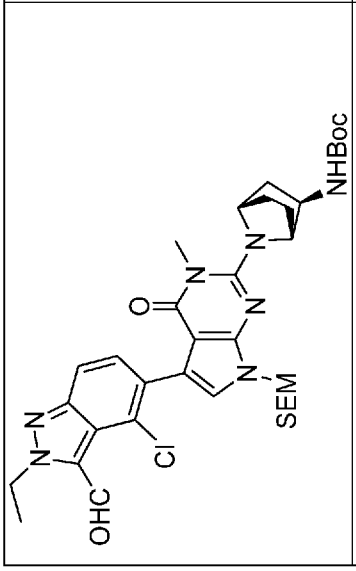
[0726]

[Table 6-14]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	686, 688	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 3-chloro-4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	685, 687	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	tert-Butyl 9-(5-(benzo[*d*]thiazol-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	685, 687	Prepared as general procedure 2 above using *tert*-butyl 9-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole

[0727]

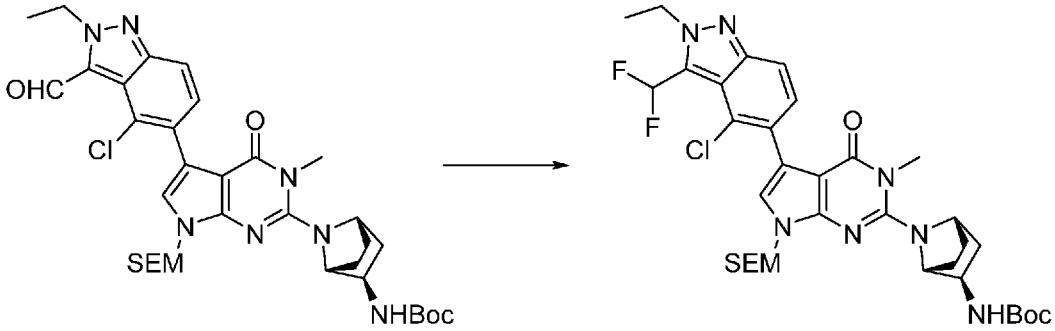
[Table 6-15]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-ethyl-3-formyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	696, 698	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole-3-carbaldehyde
	rac-tert-Butyl ((1*S*,4*S*,7*S*)-2-(5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	668, 670	Prepared as general procedure 2 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	rac-tert-butyl ((1*S*,4*S*,7*S*)-2-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)(methyl)carbamate	668, 670	Prepared as general procedure 2 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)(methyl)carbamate and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

[0728] Preparation 112: tert-Butyl

((1R,2R,4S)-7-(5-(4-chloro-3-(difluoromethyl)-2-ethyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

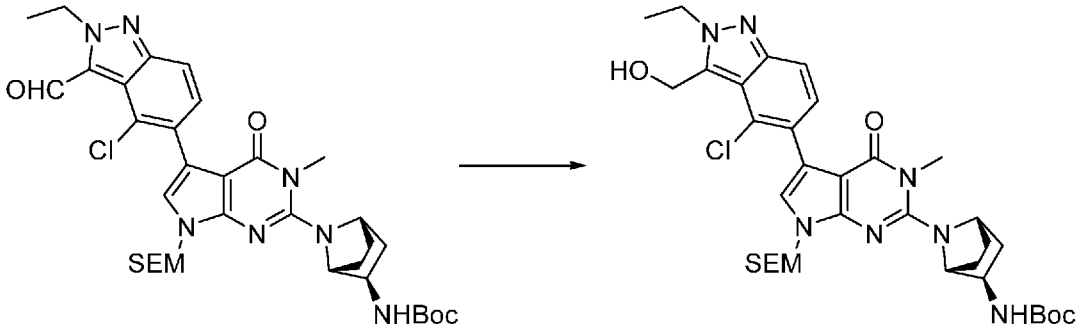
[0729] [Chem.148]



[0730] To a solution of tert-butyl ((1R,2R,4S)-7-(5-(4-chloro-2-ethyl-3-formyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (220 mg, 0.32 mmol) in 1,2-dichloroethane (1.3 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (290 mg, 1.3 mmol). The mixture was stirred at 50 °C overnight. The mixture was quenched with sat. $NaHCO_3$, and extracted with EtOAc. The organic layer was concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 80% EtOAc/hexane) to give the title compound (54 mg). MS: $[M+H]^+$ = 718, 720.

[0731] Preparation 113: tert-Butyl ((1R,2R,4S)-7-(5-(4-chloro-2-ethyl-3-(hydroxymethyl)-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0732] [Chem.149]

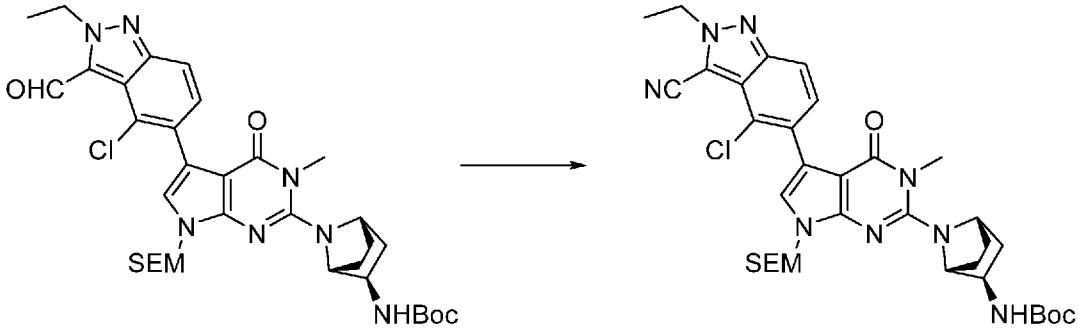


[0733] To a solution of tert-butyl ((1R,2R,4S)-7-(5-(4-chloro-2-ethyl-3-formyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (240 mg, 0.34 mmol) in methanol (3.0 mL) was added sodium borohydride (21 mg, 0.56 mmol). The mixture was stirred at RT for 1 h. The

mixture was quenched with sat. NH_4Cl aq., extracted with EtOAc. The organic layer was washed with water and brine, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (215 mg). MS: $[M+H]^+$ = 698, 700.

[0734] Preparation 114: tert-butyl ((1R,2R,4S)-7-(5-(4-chloro-3-cyano-2-ethyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0735] [Chem.150]

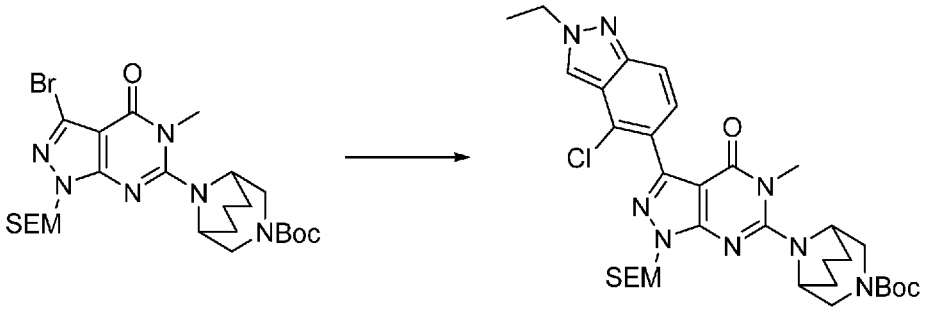


[0736] To a mixture of tert-butyl ((1R,2R,4S)-7-(5-(4-chloro-2-ethyl-3-formyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (314 mg, 0.45 mmol) and sodium carbonate (75 mg, 0.71 mmol) in ethanol (0.9 mL) was added hydroxylamine hydrochloride (49 mg, 0.71 mmol). The mixture was stirred at RT overnight. The mixture was diluted with EtOAc, washed with water and brine, and concentrated in vacuo. To the residue was added acetonitrile (2.4 ml) and copper(II) acetate (8.1 mg, 0.045 mmol). The mixture was stirred at 80 °C for 5 h, and then concentrated in vacuo. The residue was purified by column chromatography on NH-silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (245 mg). MS: $[M+H]^+$ = 693, 695.

[0737] General procedure 3: tert-Butyl 9-(3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate

[0738]

[Chem.151]



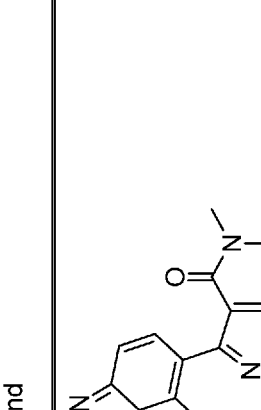
[0739] The mixture of tert-butyl 9-(3-bromo-5-methyl-4-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate (300 mg, 0.475 mmol), 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (315 mg, 1.02 mmol), K_3PO_4 (327 mg, 1.54 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (41.9 mg, 0.0514 mmol), 1,4-dioxane (6 mL) and water (1.5 mL) was stirred at 90 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (200 mg). MS: $[M+H]^+$ = 683, 685.

[0740] Compounds of Table 7 below were prepared using procedures analogous to that described in general procedure 3 starting from the appropriate the appropriate substituted protected pyrazolopyrimidinone and varying the boronate or boronic acid (synthesised as described above with any significant variations indicated below).

[0741]

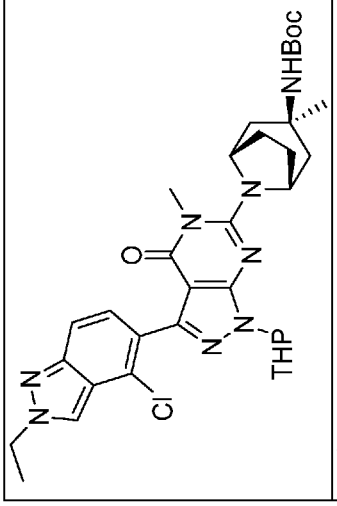
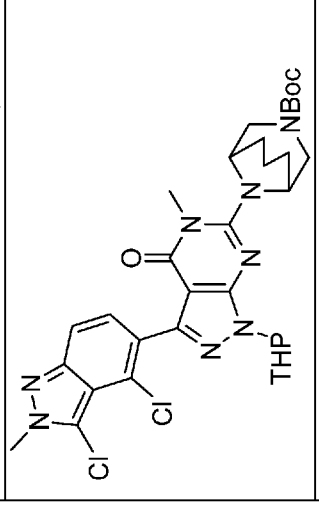
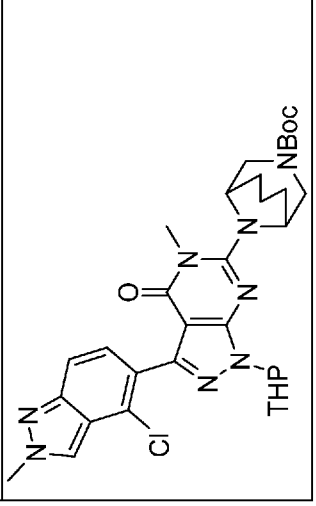
[Table 7-1]

TABLE 7

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	623, 625	Prepared as general procedure 3 above using *tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	626, 628	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	643, 645	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

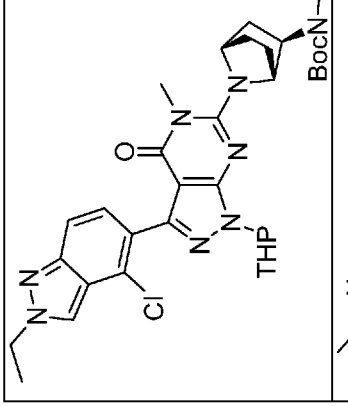
[0742]

[Table 7-2]

	*tert*-Butyl (*endo*-8-(3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	651, 653	Prepared as general procedure 3 above using *tert*-butyl (*endo*-8-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole.
	*tert*-Butyl 9-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	657, 659	Prepared as general procedure 3 above using *tert*-butyl 9-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*tert*-Butyl 9-(3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	623, 625	Prepared as general procedure 3 above using *tert*-butyl 9-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole.

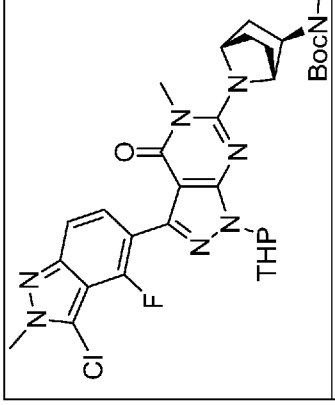
[0743]

[Table 7-3]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	637, 639	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	657, 659	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	623, 625	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

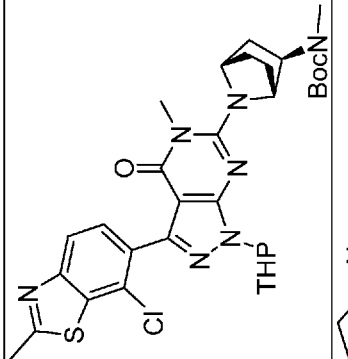
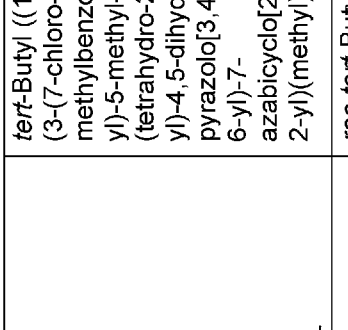
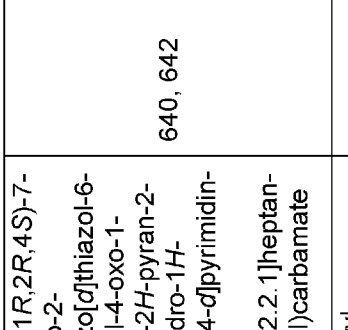
[0744]

[Table 7-4]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	642, 644	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 3-chloro-4-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	tert-Butyl 9-(3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate	626, 628	Prepared as general procedure 3 above using *tert*-butyl 9-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	tert-Butyl ((1*R*,2*R*,4*S*)-7-(3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	626, 628	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole

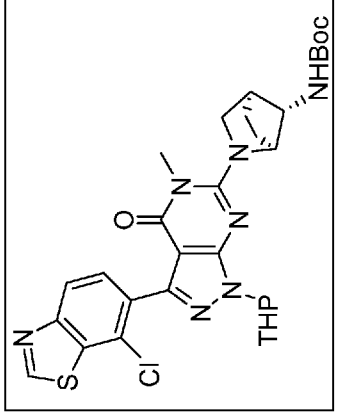
[0745]

[Table 7-5]

	*tert*-Butyl ((1*R*,2*R*,4*S*)-7-(3-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate	640, 642	Prepared as general procedure 3 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole
	*rac-tert*-Butyl ((1*S*,4*S*,7*S*)-2-(3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	623, 625	Prepared as general procedure 3 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate and 4-chloro-2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole
	*rac-tert*-Butyl ((1*S*,4*S*,7*S*)-2-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	643, 645	Prepared as general procedure 3 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate and 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

[0746]

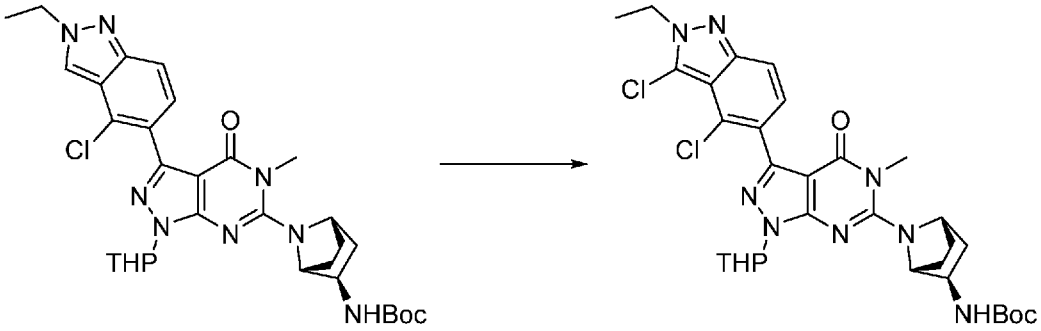
[Table 7-6]

	*rac-tert*-Butyl ((1*S*,4*S*,7*S*)-2-(3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-4-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	612, 614	Prepared as general procedure 3 above using *rac-tert*-butyl ((1*S*,4*S*,7*S*)-2-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate and 7-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole

[0747] Preparation 115: tert-Butyl

((1R,2R,4S)-7-(3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

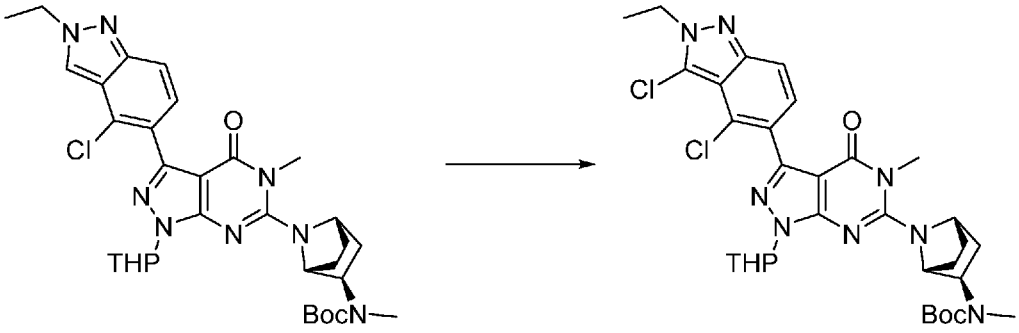
[0748] [Chem.152]



[0749] To a solution of tert-butyl ((1R,2R,4S)-7-(3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (140 mg, 0.225 mmol) in DMF (1.4 mL) was added NCS (36 mg, 0.270 mmol) at RT . The mixture was stirred at 60 °C for 5 h. The reaction mixture was cooled to RT and treated with NCS (15 mg, 0.112 mmol) at RT. The mixture was stirred at 60 °C for 1 h, diluted with water, and extracted with EtOAc. The organic layer was washed with water (x3) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 50 - 80% EtOAc/hexane) to give the title compound (81 mg). MS: $[M+H]^+$ = 657, 659.

[0750] Preparation 116: tert-Butyl ((1R,2R,4S)-7-(3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate

[0751] [Chem.153]

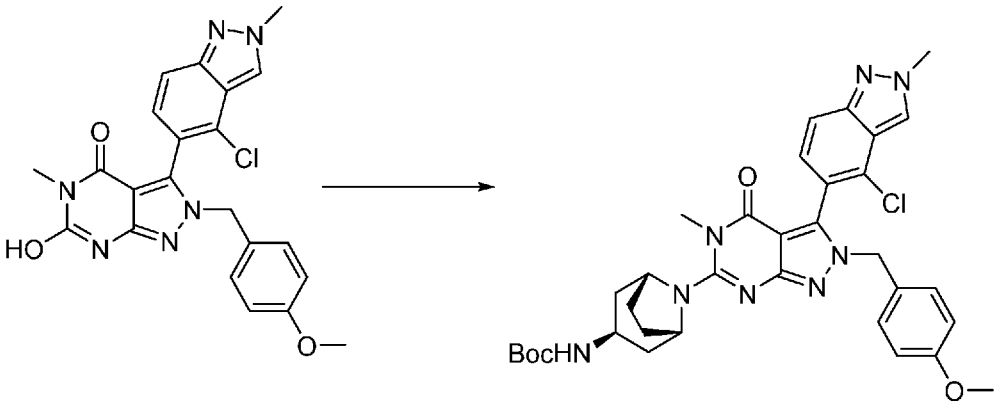


[0752] To a solution of tert-butyl ((1R,2R,4S)-7-(3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]hepta

n-2-yl)(methyl)carbamate (177 mg, 0.278 mmol) in DMF (1.4 mL) was added NCS (55.6 mg, 0.417 mmol) at RT . The mixture was stirred at 60 °C for 30 min, diluted with water, and extracted with EtOAc. The organic layer was washed with water (x3) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 40 - 80% EtOAc/hexane) to give the title compound (115 mg). MS: $[M+H]^+$ = 671, 673.

[0753] General Procedure 4: tert-Butyl N-[endo-8-[3-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate

[0754] [Chem.154]



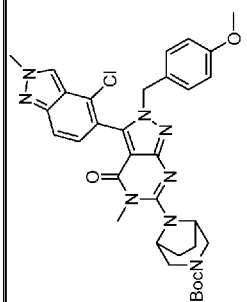
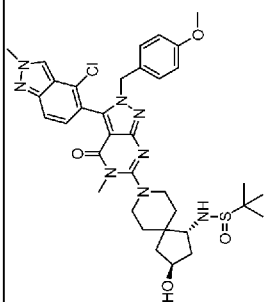
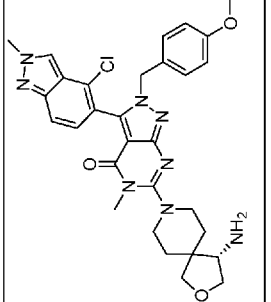
[0755] DBU (0.0677 mL, 0.45 mmol) was added dropwise at ambient temperature to 3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one (135 mg, 0.3 mmol) and PyBOP(172 mg, 0.33 mmol) in DMF (2.5 mL). The mixture was stirred for 10 minutes, then treated with tert-butyl N-(endo-8-azabicyclo[3.2.1]octan-3-yl)carbamate (102 mg, 0.45 mmol). The mixture was left to stirring overnight for 20 hours - some starting material remaining. The mixture was treated with water (40 mL). The fine precipitate was then extracted into EtOAc (50 mL), then the organic layer was washed with water (2 x 20 mL), dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-100% EtOAc/isohexane) to afford the title compound (128 mg, 0.19 mmol, 65 % yield) as a clear colourless glass. MS: $[M+H]^+$ = 659.

[0756] Compounds of Table 8 below were prepared using procedures analogous to that described in general Procedure 4, starting from the appropriate substituted protected pyrazolopyrimidinone and varying the amine (synthesised as described above with any significant variations indicated below).

[0757]

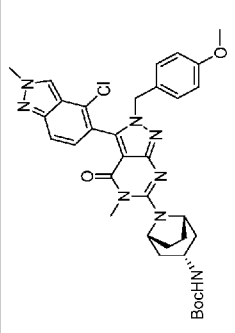
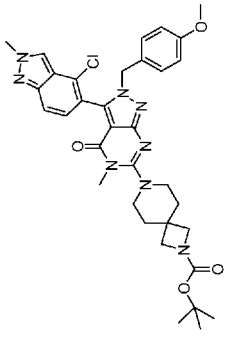
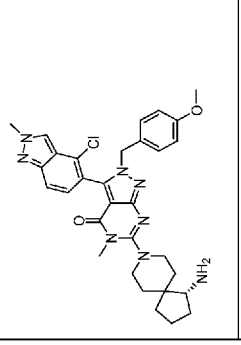
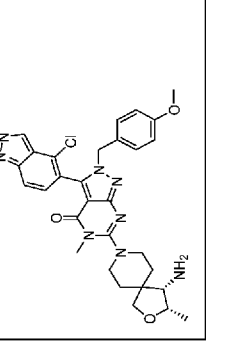
[Table 8-1]

TABLE 8

Compound	Compound Name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-Butyl 8-[3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	645	Prepared as general procedure 4 using 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate, stirring for 48 h.
	*N*-[(1*R*,3*S*)-8-[3-(4-Chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-hydroxy-8-azaspiro[4.5]decan-1-yl]-2-methylpropane-2-sulfinamide	707	Prepared as general procedure 4 using 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *N*-((1*R*,3*S*)-3-hydroxy-8-azaspiro[4.5]decan-1-yl)-2-methylpropane-2-sulfinamide, stirring for 24 h at room temperature, 24 h at 40 °C and 24 h at 50 °C.
	6-[(4*S*)-4-Amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	589	Prepared as general procedure 4 from 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (*S*)-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride using 3.5 eq. of DBU and stirring for 2 h.

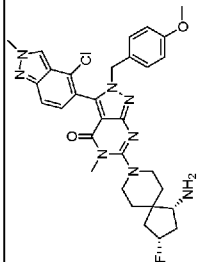
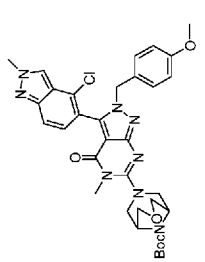
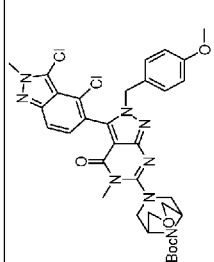
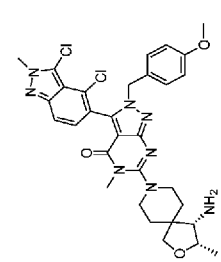
[0758]

[Table 8-2]

	*tert*-Butyl *N*-[*exo*-8-[3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate	659	Prepared as general procedure 4 using 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl *N*-(*exo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate.
	*tert*-Butyl 7-[3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate	659	Prepared as general procedure 4 using 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate, stirring for 48 h.
	6-[(1*R*)-1-Amino-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	587	Prepared as general procedure 4 from 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (*R*)-8-azaspiro[4.5]decan-1-amine dihydrochloride using 3.5 eq. DBU.
	6-[(3*S*,4*S*)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	603	Prepared as general procedure 4 from 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (3*S*,4*S*)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride using 4.5 eq. DBU.

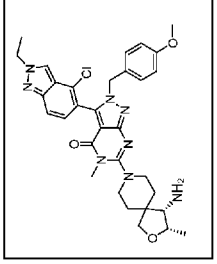
[0759]

[Table 8-3]

	6-[(1*R*,3*R*)-1-Amino-3-fluoro-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	605	Prepared as general procedure 4 from 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (1*R*,3*R*)-3-fluoro-8-azaspiro[4.5]decan-1-amine dihydrochloride using 4.5 eq. DBU.
	*tert*-Butyl 7-[3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	661	Prepared as general procedure 4 from 3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate.
	*tert*-Butyl 7-[3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate	695	Prepared as general procedure 4 from 3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate.
	6-[(3*S*,4*S*)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	637	Prepared as general procedure 4 from 3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (3*S*,4*S*)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride using 4.5 eq. DBU.

[0760]

[Table 8-4]

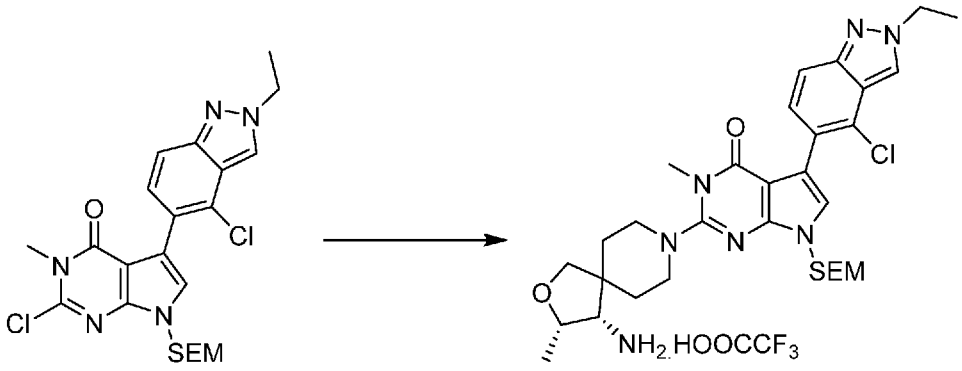
	6-[(3*S*,4*S*)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	617	Prepared as general procedure 4 from 3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-6-hydroxy-2-[(4-methoxyphenyl)methyl]-5-methyl-2*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and (3*S*,4*S*)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride using 4.5 eq. DBU.

[0761] General Procedure 5:

2-[(3S,4S)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2

H-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

[0762] [Chem.155]



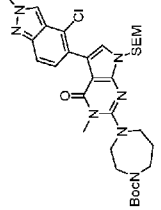
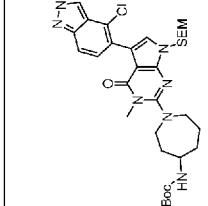
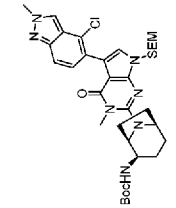
[0763] A mixture of 2-chloro-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one (250 mg, 0.51 mmol), (3S,4S)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine dihydrochloride (148 mg, 0.61 mmol) and triethylamine (0.21 mL, 1.52 mmol) in NMP (1 mL) was heated to 100 °C for 2 h. Cooled to ambient temperature and partitioned between EtOAc and water, phases separated and aq. phase extracted with EtOAc. Combined organic phases washed with 50% sat. brine, then brine, dried ($MgSO_4$ + hydrophobic frit) and concentrated. The residue was purified by reverse phase chromatography on C18 silica, eluted with 5-100% MeCN/H_2O with 0.1% TFA added to afford the title compound as the TFA salt (256 mg, 0.346 mmol, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.48 (1H, s), 7.98 (3H, s), 7.54 (1H, dd), 7.31 (1H, d), 7.25 (1H, s), 5.48 (2H, s), 4.50 (2H, q), 4.29-4.18 (1H, m), 3.70-3.66 (1H, m), 3.62 (2H, t), 3.53-3.33 (7H, m), 3.03-2.73 (2H, m), 1.98-1.86 (2H, m), 1.82-1.77 (1H, m), 1.66 (1H, d), 1.53 (3H, t), 1.24 (3H, d), 0.93-0.82 (2H, m), 0.02-0.08 (9H, m). MS: $[M+H]^+$ = 626.

[0764] Compounds of Table 9 below were prepared using procedures analogous to that described in general Procedure 5, starting from the appropriate substituted protected pyrrolopyrimidinone and varying the amine (synthesised as described above with any significant variations indicated below).

[0765]

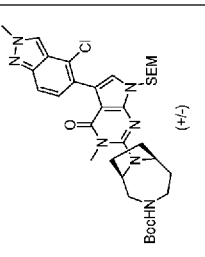
[Table 9-1]

TABLE 9

Compound	Compound Name	MS: [M+H]+ m/z	Procedure
	*tert*-Butyl 4-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-1,4-diazepane-1-carboxylate	656	Prepared as general procedure 5 using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl 1,4-diazepane-1-carboxylate, purified by normal phase chromatography on silica gel.
	*tert*-Butyl *N*-{1-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]azepan-4-yl}carbamate	670	Prepared as general procedure 5 using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *N*-(azepan-4-yl)carbamate, purified by normal phase chromatography on silica gel.
	*rac-tert*-Butyl *N*-[(1*R*,2*R*,5*R*)-8-[5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-8-azabicyclo[3.2.1]octan-2-yl]carbamate	668	Prepared as general procedure 5 from 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-{[(trimethylsilyl) ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl *N*-[(1*R*,2*R*,5*S*)-8-azabicyclo[3.2.1]octan-2-yl]carbamate using DIPEA and heating for 16h. The crude product was purified by normal phase chromatography on silica gel.

[0766]

[Table 9-2]

	*rac-tert*-Butyl (1*R*,6S)-9-[5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-3,9-diazabicyclo[4.2.1]nonane-3-carboxylate	668	Prepared as general procedure 5 from 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-{[(trimethylsilyl)methoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl (1*R*,6S)-3,9-diazabicyclo[4.2.1]nonane-3-carboxylate using DIPEA and heating for 16h. The crude product was purified by normal phase chromatography on silica gel.

[0767] General procedures for preparations of compounds of Formula (I)

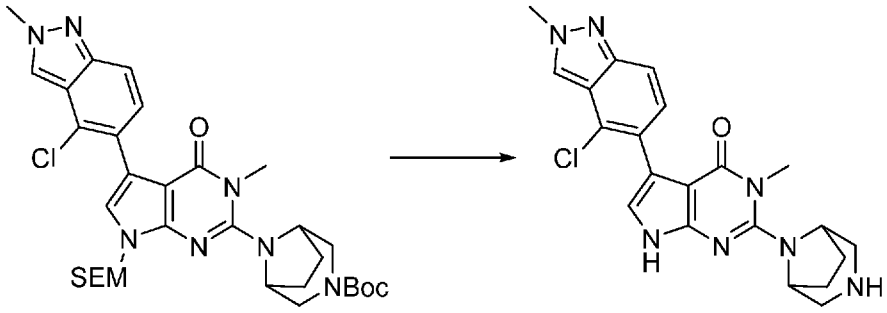
The following procedures are illustrative for general methods used in the preparation

of Examples 1-135 listed in Table 10 below.

[0768] Method 1:

2-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0769] [Chem.156]

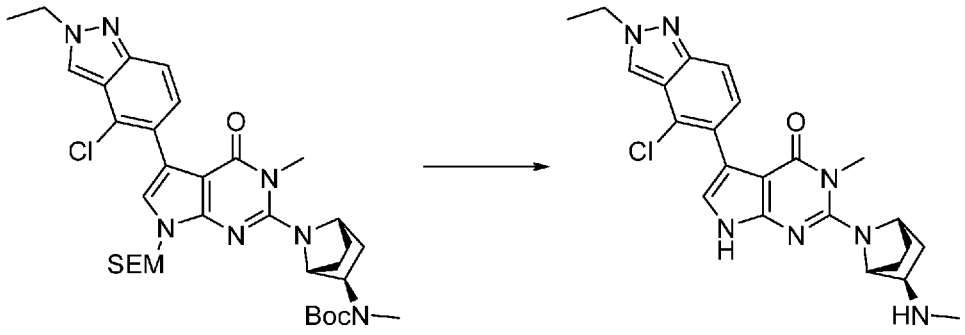


[0770] To a solution of tert-butyl 8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (140 mg, 0.214 mmol) in $CHCl_3$ (2 mL) was added TFA (2 mL) at RT. The mixture was stirred at RT for 3 h, and concentrated in vacuo. The residue was dissolved in MeOH (4 mL). 4 M NaOH (1 mL) was added at RT. The mixture was stirred at RT for 1 h, poured into water, and extracted with $CHCl_3$ - MeOH. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$). The fraction was concentrated in vacuo, and purified by r-HPLC. The fraction was basified with sat. $NaHCO_3$, and extracted with $CHCl_3$ - MeOH. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (24 mg).

[0771] Method 2:

5-(4-Chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0772] [Chem.157]

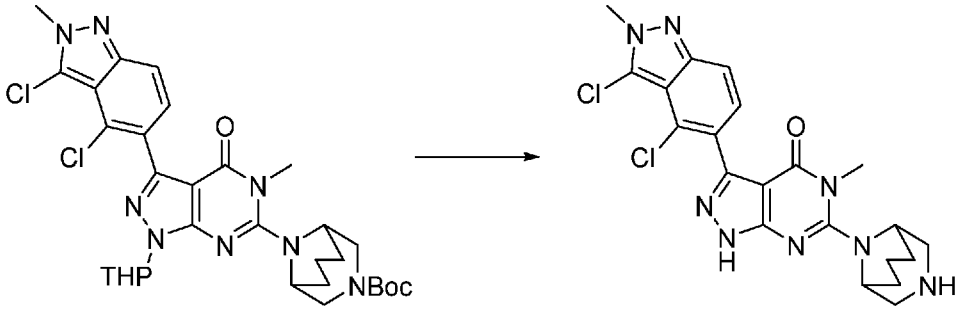


[0773] The mixture of tert-butyl

((1R,2R,4S)-7-(5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate (150 mg, 0.219 mmol) and TFA (3 mL) was stirred at RT for 2 h, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 15% MeOH/$CHCl_3$). The residue was dissolved in MeOH (3 mL). Ethylenediamine (0.2 mL, 2.99 mmol) was added at RT. The mixture was stirred at RT for 2 h, and concentrated in vacuo. After concentration, the residue was purified by r-HPLC. The obtained fractions were passed through Vari-Pure, and concentrated in vacuo. The obtained solid was suspended in EtOAc - hexane. The precipitate was collected and dried at 60 °C under reduced pressure to give the title compound (48 mg).

[0774] Method 3:
6-(3,9-Diazabicyclo[3.3.1]nonan-9-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0775] [Chem.158]

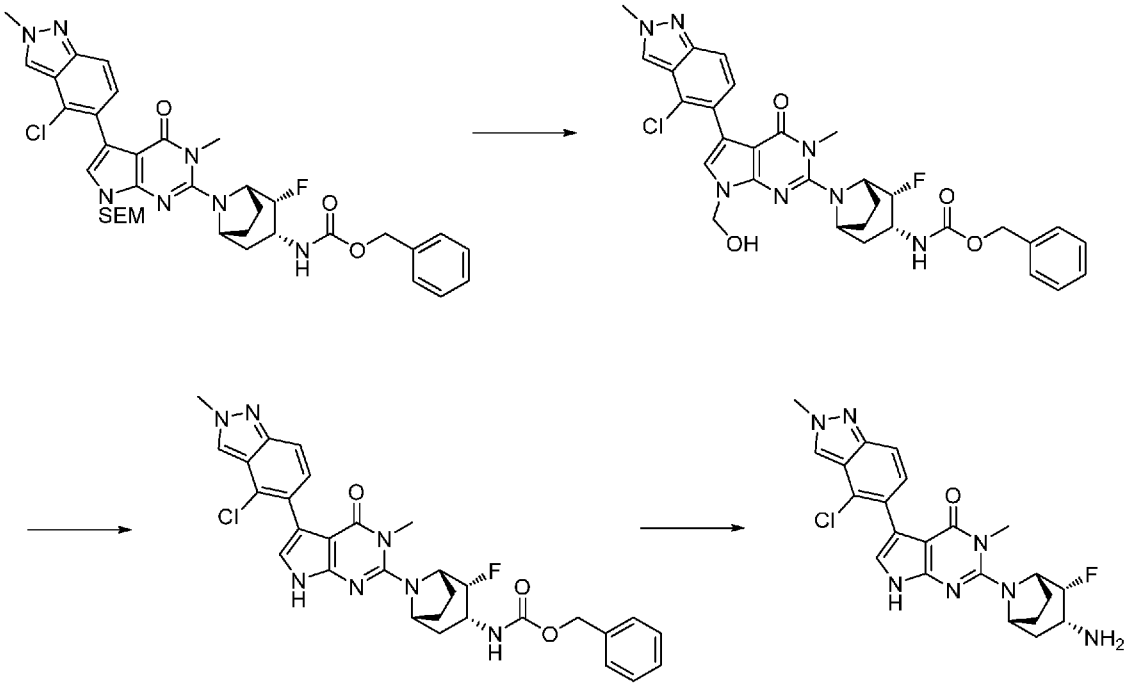


[0776] To a mixture of tert-butyl 9-(3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-3,9-diazabicyclo[3.3.1]nonane-3-carboxylate (120 mg, 0.182 mmol) in MeOH (1 mL) was added 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) at RT. The mixture was stirred at RT for 2 h, and concentrated in vacuo. The residue was purified by r-HPLC. The obtained fractions were passed through Vari-Pure, and concentrated in vacuo. The obtained solid was suspended in EtOAc - hexane. The precipitate was collected and dried at 60 °C under reduced pressure to give the title compound (38 mg).

[0777] Method 4: rac-
2-((1S,2R,3R,5R)-3-Amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0778]

[Chem.159]



[0779] To a solution of rac-benzyl ((1S,2R,3R,5R)-8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate (129 mg, 0.179 mmol) in $CHCl_3$ (0.5 mL) was added TFA (0.5 mL) at RT. The mixture was stirred at RT for 6 h, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$). The fraction was concentrated in vacuo to give rac-benzyl ((1S,2R,3R,5R)-8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-7-(hydroxymethyl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate (106 mg, 0.17 mmol, 95% Yield).

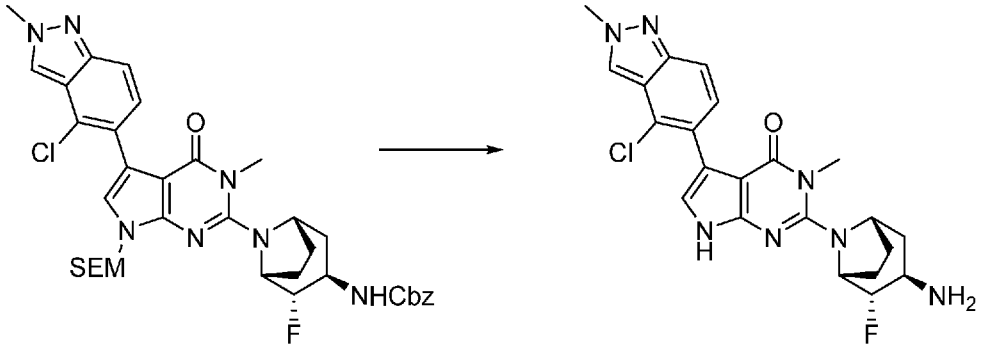
[0780] The residue (106 mg, 0.17 mmol) was dissolved in MeOH (0.40 mL) and THF (0.40 mL). Ethylenediamine (0.2 mL, 2.99 mmol) was added at RT. The mixture was stirred at RT for 1 h, and concentrated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$). The fraction was concentrated in vacuo to give rac-benzyl ((1S,2R,3R,5R)-8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate (97 mg, 0.16 mmol, 96% Yield).

[0781] To the suspension of the residue (97 mg, 0.16 mmol), triethylsilane (0.42 mL, 2.6 mmol), triethylamine (0.073 mL, 0.52 mmol) in CH_2Cl_2 (2.0 mL) was added

Palladium(II) acetate (18 mg, 0.082 mmol) at RT under N_2 atmosphere and the suspension was stirred at RT for 2.5h. The solid was removed by filteration using a pad of celite. The filterate was concentrated to give the crude oil-solid, which was purified by column chromatography on NH silica gel (gradient elution, 0 - 15% MeOH/$CHCl_3$) to give the crude solid-oil. The crude oil-solid was purified by r-HPLC. The obtained fractions were concentrated and almost concentrated residue was basified with 1N NaOH and extracted with $CHCl_3$ to give the title compound (27 mg, 0.059 mmol, 36% Yield).

[0782] Method 5:
2-((1R,2S,3R,5S)-3-Amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0783] [Chem.160]

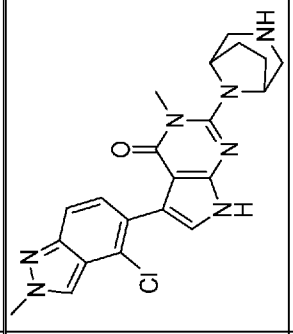
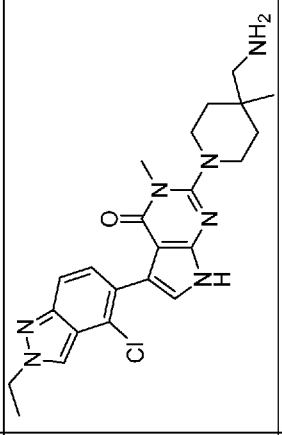
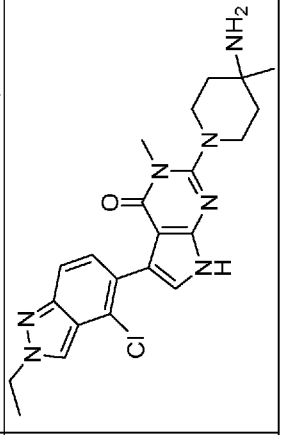


[0784] Benzyl ((1R,2S,3R,5S)-8-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate (61 mg, 0.085 mmol) was dissolved in methanesulfonic acid (1.0 mL) and stirred for 3 h at RT. The mixture was poured into saturated $NaHCO_3$ aq. at 0 °C, and extracted with $CHCl_3$. The organic layer was concentrated in vacuo. The residue was dissolved in THF (1 mL). To the mixture was added 5 M NaOH aq. (0.085 mL, 0.43 mmol) at 0 °C, and stirred for 1 h at RT. The mixture was evaporated in vacuo. The residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (35 mg).

[0785]

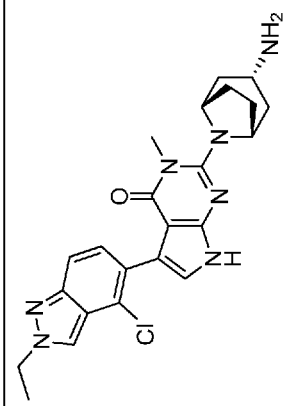
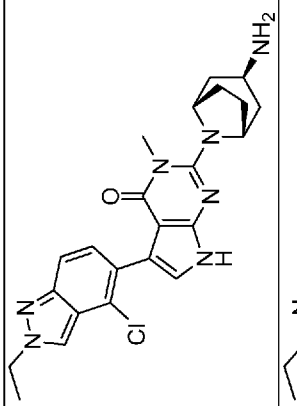
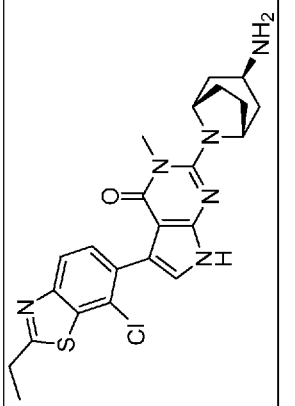
[Table 10-1]

TABLE 10: Examples 1 - 135

Example	Structure	Name	NMR data	MS: $[M+H]^+$ m/z	Method
1		2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.96 (1H, d, *J* = 2.2 Hz), 4.19 (3H, s), 3.98 (2H, br s), 3.46 (3H, s), 2.99-2.96 (2H, m), 2.66-2.63 (2H, m), 1.97-1.80 (4H, m).	424, 426	1
2		2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.52 (1H, s), 7.57 (1H, d, *J* = 8.8 Hz), 7.37 (1H, d, *J* = 8.8 Hz), 7.06 (1H, s), 4.54 (2H, q, *J* = 7.3 Hz), 3.43 (3H, s), 3.24-3.17 (2H, m), 3.08-2.99 (2H, m), 1.66-1.56 (5H, m), 1.46-1.39 (2H, m), 1.09 (2H, d, *J* = 6.1 Hz), 0.98 (3H, s).	454, 456	2
3		2-(4-amino-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.75 (1H, br s), 8.45 (1H, s), 7.50 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.00 (1H, s), 4.48 (2H, q, *J* = 7.3 Hz), 3.37 (3H, s), 3.21-3.16 (2H, m), 3.11-3.05 (2H, m), 1.63-1.43 (7H, m), 1.11 (3H, s).	440, 442	2

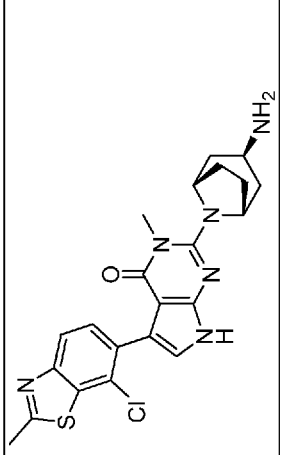
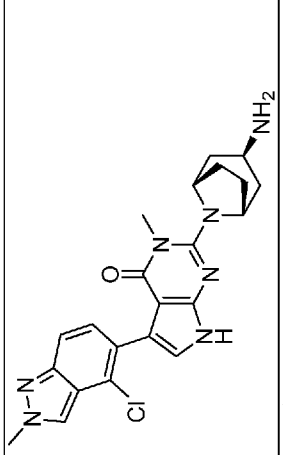
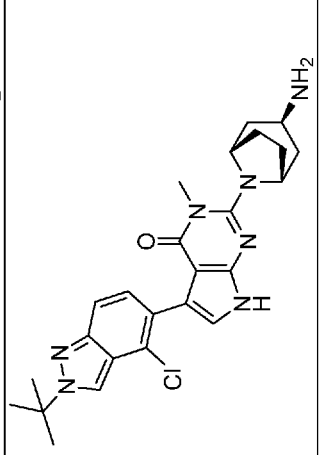
[0786]

[Table 10-2]

4		2-(*exo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.45 (1H, s), 7.49 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.94 (1H, s), 4.48 (2H, q, *J* = 7.2 Hz), 4.11 (2H, br s), 3.43 (3H, s), 3.06-2.94 (1H, m), 2.04-1.92 (2H, m), 1.85-1.78 (2H, m), 1.71-1.63 (2H, m), 1.56-1.46 (6H, m).	452, 454	1
5		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.94 (1H, s), 4.48 (2H, q, *J* = 7.3 Hz), 4.12-4.05 (2H, m), 3.41 (3H, s), 2.27-2.22 (2H, m), 2.17-2.09 (2H, m), 2.00-1.92 (2H, m), 1.59-1.50 (7H, m).	452, 454	1
6		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, s), 7.82 (1H, d, *J* = 8.4 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 6.98 (1H, s), 4.06 (2H, br s), 3.38 (3H, s), 3.13 (2H, q, *J* = 7.6 Hz), 2.24-2.19 (2H, m), 2.13-2.08 (2H, m), 1.93-1.92 (3H, m), 1.56-1.52 (3H, m), 1.37 (3H, t, *J* = 7.6 Hz).	469, 471	1

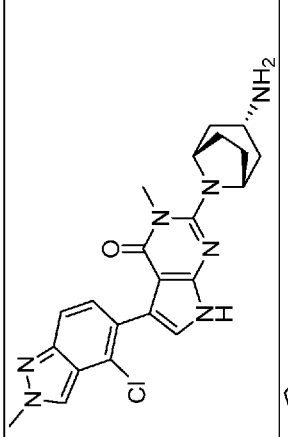
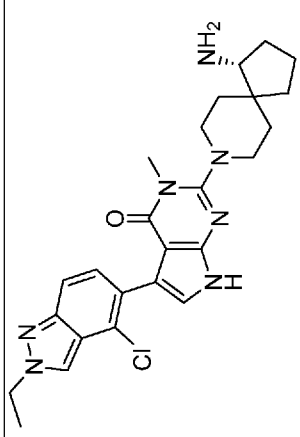
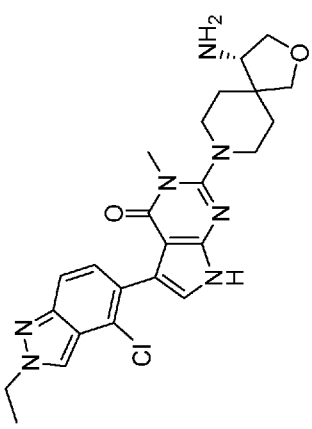
[0787]

[Table 10-3]

7		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.81 (1H, d, *J* = 8.2 Hz), 7.56 (1H, d, *J* = 8.4 Hz), 6.99 (1H, s), 4.16-4.03 (1H, m), 3.42-3.32 (5H, m), 2.82 (3H, s), 2.29-2.19 (1H, m), 2.18-2.07 (2H, m), 2.02-1.89 (2H, m), 1.65-1.50 (2H, m).	455, 457	1
8		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.96 (1H, s), 4.19 (3H, s), 4.08-4.00 (2H, br s), 3.41 (3H, s), 2.24-2.19 (2H, m), 2.15-2.06 (2H, m), 2.05-1.97 (3H, m), 1.61-1.55 (3H, m).	438, 440	1
9		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(2-(*tert*-butyl)-4-chloro-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($CDCl_3$) δ: 8.58 (1H, br s), 8.09 (1H, s), 7.64 (1H, d, *J* = 8.8 Hz), 7.45 (1H, d, *J* = 8.8 Hz), 6.89 (1H, br s), 4.09 (2H, br s), 3.54 (3H, s), 3.44 (1H, br s), 2.40-2.25 (2H, m), 2.20-2.06 (4H, m), 1.73 (9H, s), 1.62 (2H, br d, *J* = 13.9 Hz).	480, 482	1

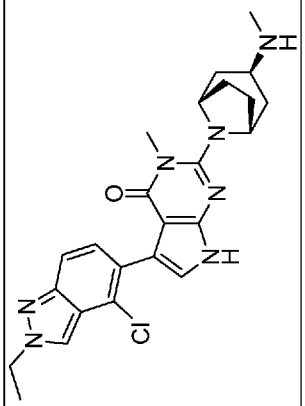
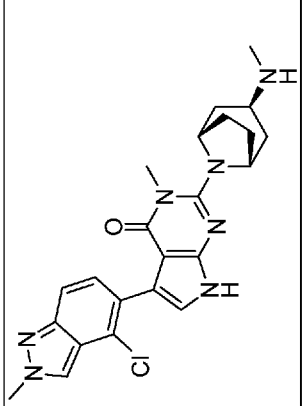
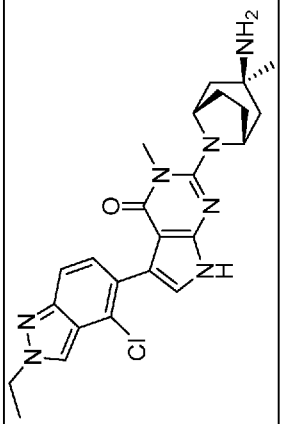
[0788]

[Table 10-4]

10		2-(*exo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74-11.56 (1H, m), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 6.95 (1H, s), 4.23-4.15 (6H, m), 3.42 (3H, s), 2.09-1.64 (8H, m).	438, 440	1
11		(*R*)-2-(1-amino-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.45 (1H, s), 7.50 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 4.48 (2H, q, *J* = 7.2 Hz), 3.39 (3H, s), 3.35-3.27 (1H, m), 2.88-2.83 (2H, m), 2.73-2.71 (1H, m), 1.88-1.50 (10H, m), 1.39-1.15 (5H, m).	480, 482	1
12		(*S*)-2-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.45 (1H, s), 7.50 (1H, d, *J* = 9.0 Hz), 7.31 (1H, d, *J* = 9.0 Hz), 7.01 (1H, s), 4.48 (2H, q, *J* = 7.2 Hz), 3.97-3.93 (1H, m), 3.70-3.68 (1H, m), 3.60-3.58 (1H, m), 3.40 (3H, s), 3.32-3.24 (1H, m), 3.18-3.13 (1H, m), 3.09-3.06 (1H, m), 2.90-2.83 (2H, m), 1.84-1.69 (4H, m), 1.60-1.45 (5H, m).	482, 484	1

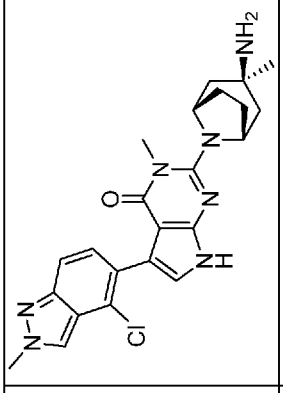
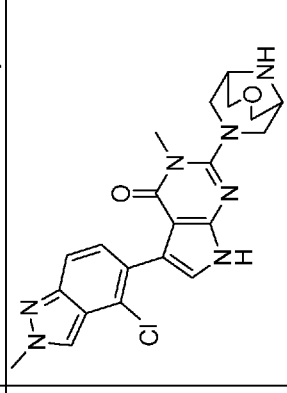
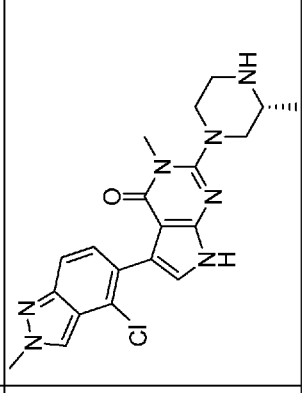
[0789]

[Table 10-5]

13		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-2-(*endo*-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.94 (1H, s), 4.48 (2H, q, *J* = 7.3 Hz), 4.07 (2H, br s), 3.42 (3H, s), 2.78-2.74 (1H, m), 2.29 (3H, s), 2.11-2.03 (4H, m), 1.93-1.92 (2H, m), 1.75-1.71 (2H, m), 1.52 (3H, t, *J* = 7.3 Hz).	466, 468	1
14		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(*endo*-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, *J* = 4.9 Hz), 7.32 (1H, d, *J* = 9.2 Hz), 6.95 (1H, s), 4.19 (3H, s), 4.08 (2H, br s), 3.42 (3H, s), 2.82-2.80 (1H, m), 2.31 (3H, s), 2.14-2.03 (4H, m), 1.97-1.89 (2H, m), 1.77-1.70 (2H, m).	452, 454	1
15		2-(*endo*-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, s), 8.42 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.92 (1H, s), 4.47 (2H, q, *J* = 7.2 Hz), 4.08 (2H, br s), 3.40 (3H, s), 2.29-2.23 (2H, m), 1.94-1.85 (4H, m), 1.64-1.58 (2H, m), 1.51 (3H, t, *J* = 7.2 Hz), 1.09 (3H, s).	466, 468	1

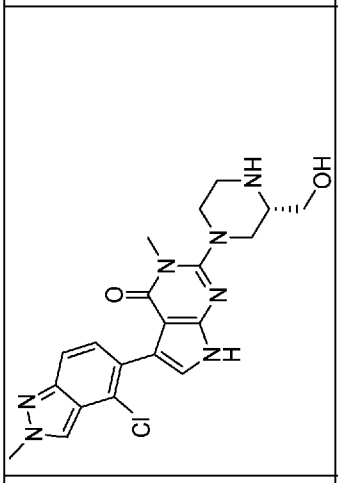
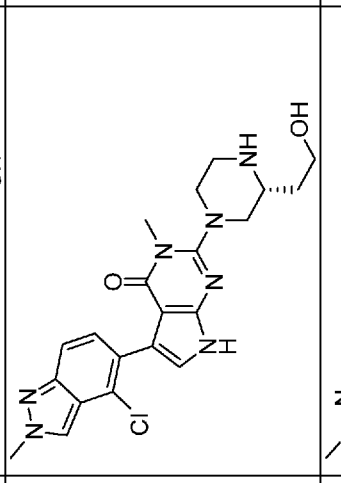
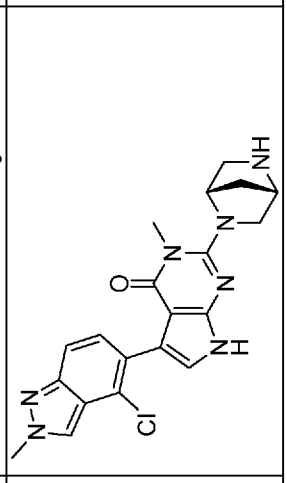
[0790]

[Table 10-6]

16		2-(*endo*-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.94 (1H, s), 4.19 (3H, s), 4.09 (2H, br s), 3.41 (3H, s), 2.34-2.27 (2H, m), 1.93-1.86 (4H, m), 1.67-1.59 (2H, m), 1.47-1.35 (1H, m), 1.09 (3H, s).	452, 454	1
17		2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.41 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.96-3.79 (4H, m), 3.54-3.43 (5H, m), 3.23-3.14 (2H, m), 2.87-2.80 (2H, m).	440, 442	1
18		(*R*)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.80 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.41-3.22 (5H, m), 2.97-2.65 (4H, m), 2.46-2.36 (1H, m), 1.01 (3H, d, *J* = 6.0 Hz).	412, 414	1

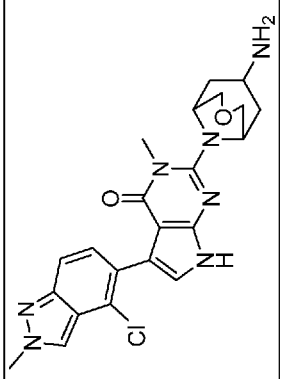
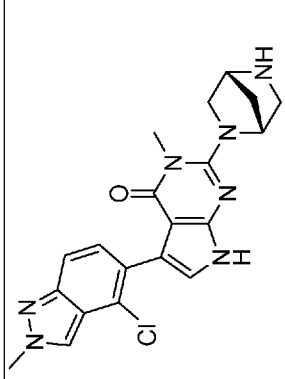
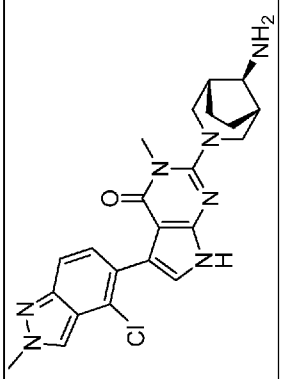
[0791]

[Table 10-7]

19		(*S*)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-(3-(hydroxymethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J*= 8.8 Hz), 7.31 (1H, d, *J*= 8.8 Hz), 7.01 (1H, s), 4.18 (3H, s), 3.39 (3H, s), 3.39-3.21 (4H, m), 3.06-2.72 (4H, m), 2.65-2.52 (1H, m).	428, 430	2
20		(*R*)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-(3-(2-hydroxyethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.79 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 4.18 (3H, s), 3.39 (3H, s), 3.39-3.21 (4H, m), 3.07-2.98 (2H, m), 2.94 (1H, t, *J* = 10.8 Hz), 2.81 (1H, t, *J* = 10.4 Hz), 2.58 (1H, t, *J* = 11.5 Hz), 1.63-1.51 (2H, m).	442, 444	2
21		2-((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.54 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.91 (1H, s), 4.43 (1H, br s), 4.20 (3H, s), 3.67-3.61 (2H, m), 3.33-3.30 (4H, m), 3.19-3.14 (1H, m), 2.91-2.85 (1H, m), 1.77-1.73 (1H, m), 1.65-1.62 (1H, m).	410, 412	1

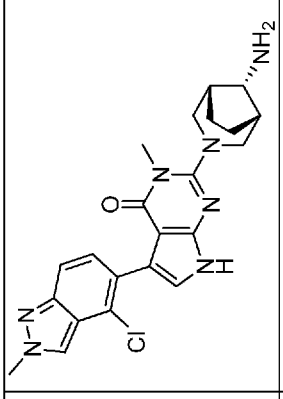
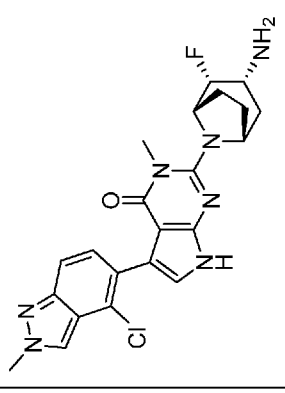
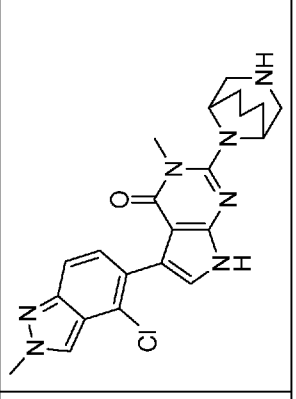
[0792]

[Table 10-8]

22		2-(7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.38 (1H, s), 7.52-7.26 (2H, m), 6.97 (1H, s), 4.18 (3H, s), 4.01-3.08 (9H, m), 2.18-2.01 (4H, m).	454, 456	2
23		2-((1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.54 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.91 (1H, s), 4.43 (1H, br s), 4.20 (3H, s), 3.67-3.61 (2H, m), 3.33-3.30 (4H, m), 3.19-3.14 (1H, m), 2.91-2.85 (1H, m), 1.77-1.73 (1H, m), 1.65-1.62 (1H, m).	410, 412	1
24		2-(*exo*-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.38 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.30 (1H, d, J = 8.8 Hz), 7.01 (1H, s), 4.18 (3H, s), 3.43 (3H, s), 3.43-3.39 (1H, m), 3.31-3.17 (4H, m), 2.95 (2H, d, J = 11.6 Hz), 2.29-2.23 (2H, m), 1.94-1.74 (4H, m).	438, 440	2

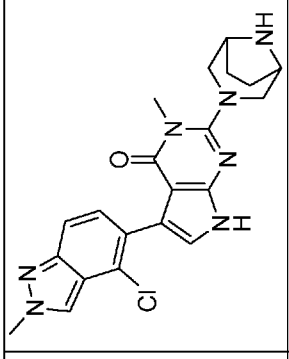
[0793]

[Table 10-9]

25		2-(*endo*-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.69 (1H, br s), 8.38 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.00 (1H, s), 4.18 (3H, s), 3.42 (3H, s), 3.42-3.36 (1H, m), 3.15-3.00 (4H, m), 2.13-2.06 (2H, br s), 1.85-1.70 (4H, m).	438, 440	1
26		*rac*-2-((1*S*,2*R*,3*R*,5*R*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, s), 8.38 (1H, s), 7.47 (1H, dd, *J* = 8.8, 0.9 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.96-6.94 (1H, m), 4.56-4.38 (2H, m), 4.18 (3H, s), 4.14-4.09 (1H, m), 3.44 (3H, s), 3.06-2.89 (1H, m), 2.07-1.92 (2H, m), 1.89-1.79 (1H, m), 1.77-1.57 (5H, m).	456, 458	4
27		2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.94 (1H, s), 4.19 (3H, s), 3.65 (2H, br s), 3.34-3.32 (4H, m), 3.27-3.25 (1H, m), 2.92-2.88 (2H, m), 2.80-2.70 (1H, m), 2.16-2.10 (2H, m), 1.76-1.71 (2H, m), 1.62-1.55 (1H, m).	438, 440	1

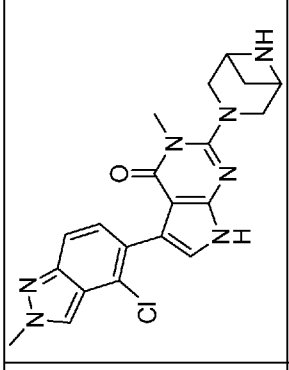
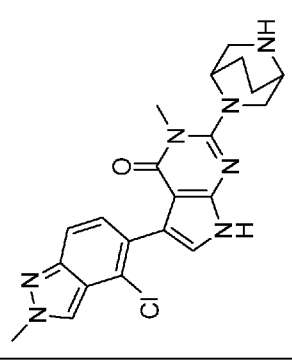
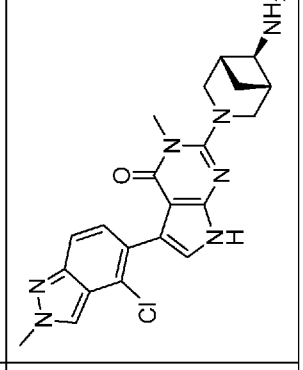
[0794]

[Table 10-10]

28		2-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.81 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.7 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 4.18 (3H, s), 3.72 (2H, br s), 3.42 (3H, s), 3.21 (2H, d, *J* = 12.3 Hz), 3.09 (2H, d, *J* = 12.1 Hz), 2.02-1.95 (2H, m), 1.86-1.78 (2H, m).	424, 426	1
29		2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.55 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.93 (1H, s), 4.48 (2H, d, *J* = 6.2 Hz), 4.19 (3H, s), 3.68-3.41 (2H, m), 3.28 (3H, s), 3.08 (2H, d, *J* = 12.1 Hz), 2.79-2.72 (1H, m), 1.84 (1H, d, *J* = 8.8 Hz).	410, 412	1
30		2-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.46 (3H, s), 3.39-3.36 (2H, m), 3.14-3.11 (2H, m), 3.05-3.03 (2H, m), 2.51-2.49 (1H, m), 1.89-1.76 (4H, m), 1.65-1.58 (1H, m).	438, 440	1

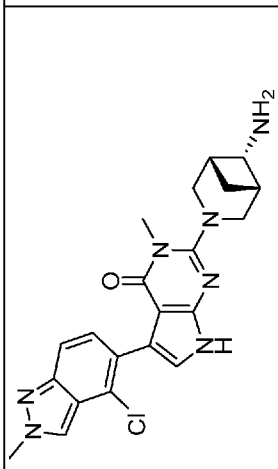
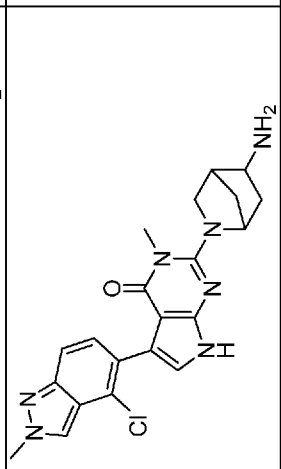
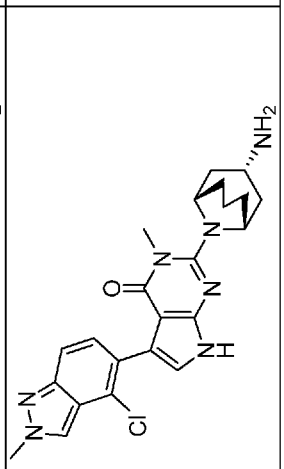
[0795]

[Table 10-11]

31		2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.69 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.00 (1H, s), 4.19 (3H, s), 3.90 (2H, d, *J* = 5.6 Hz), 3.83-3.73 (4H, m), 3.39 (3H, s), 2.63-2.56 (1H, m), 1.84 (1H, d, *J* = 8.7 Hz).	410, 412	1
32		2-(2,5-diazabicyclo[2.2.2]octan-2-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2.3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.3 Hz), 6.93 (1H, s), 4.18 (3H, s), 3.78-3.74 (1H, m), 3.65 (1H, d, *J* = 10.1 Hz), 3.53-3.45 (3H, m), 3.32 (1H, s), 3.30-3.27 (1H, m), 3.08 (1H, br s), 2.98 (1H, d, *J* = 10.9 Hz), 2.28-2.13 (1H, m), 1.94-1.67 (3H, m).	424, 426	1
33		2-(*exo*-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2.3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.97 (1H, s), 4.18 (3H, s), 3.84 (2H, d, *J* = 11.3 Hz), 3.62-3.59 (2H, m), 3.37 (3H, s), 3.18-3.15 (1H, m), 2.67-2.59 (1H, m), 2.34-2.29 (2H, m), 1.66-1.60 (1H, m).	424, 426	1

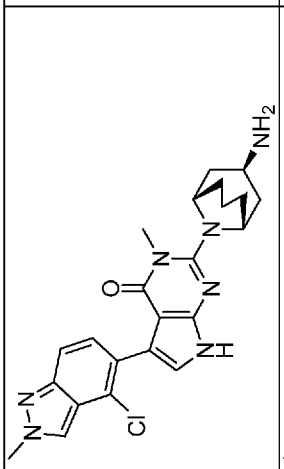
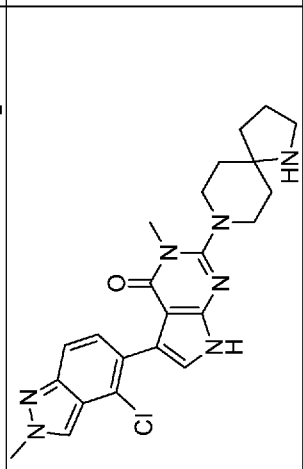
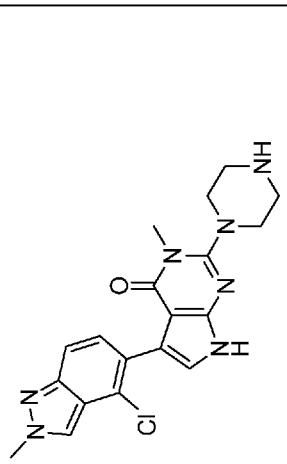
[0796]

[Table 10-12]

34		2-(*endo*-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2.3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.96 (1H, s), 4.18 (3H, s), 3.80-3.27 (7H, m), 2.44-2.39 (2H, m), 1.75-1.61 (1H, m), 1.46 (1H, d, *J* = 9.0 Hz).	424, 426	1
35		2-(5-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2.3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.53 (1H, br s), 8.37 (1H, s), 7.48-7.45 (1H, m), 7.32 (1H, d, *J* = 8.7 Hz), 6.88 (1H, s), 4.23-4.14 (5H, m), 3.39-3.21 (5H, m), 2.65-2.60 (1H, m), 2.09-2.00 (1H, m), 1.82-1.59 (2H, m).	424, 426	1
36		2-(*exo*-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2.3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.38 (1H, s), 7.52-7.28 (2H, m), 6.94 (1H, s), 4.18 (3H, s), 4.00-3.87 (3H, m), 3.33 (3H, s), 2.17-1.59 (10H, m).	452, 454	2

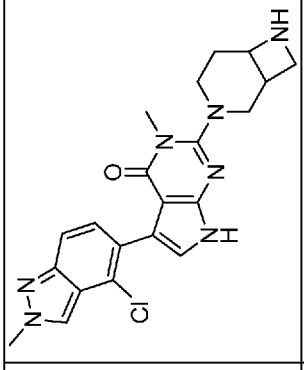
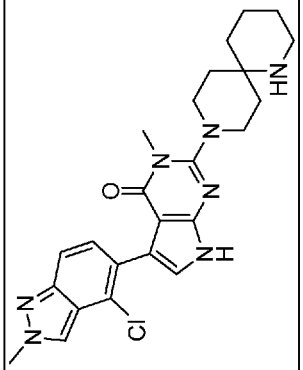
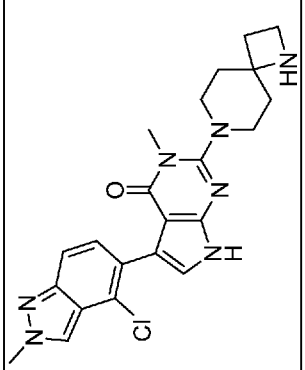
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[Table 10-13]

37		2-(*endo*-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.94 (1H, s), 4.18 (3H, s), 4.11-4.04 (2H, m), 3.31 (3H, s), 2.55-2.36 (1H, m), 2.12-1.76 (2H, m), 1.61-1.37 (6H, m).	452, 454	1
38		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(1,8-diazaspiro[4.5]decan-8-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.71 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.99 (1H, s), 4.18 (3H, s), 3.37 (3H, s), 3.21-3.14 (2H, m), 3.08-3.00 (2H, m), 2.85-2.81 (2H, m), 1.80-1.49 (8H, m).	452, 454	1
39		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(piperazin-1-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.78 (1H, s), 8.38 (1H, s), 7.46 (1H, d, *J* = 8.8 Hz), 7.29 (1H, d, J = 8.8 Hz), 6.99 (1H, s), 4.17 (3H, s), 3.36 (3H, s), 3.02-2.96 (4H, m), 2.86-2.78 (4H, m).	398, 400	2, After purifying by r-HPLC, obtained fractions were basified with sat. $NaHCO_3$ and extracted with $CHCl_3$ - MeOH. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was suspended in EtOAc - hexane.

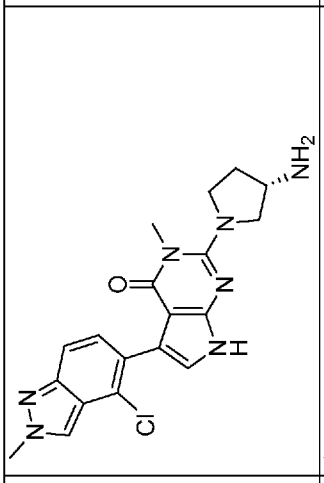
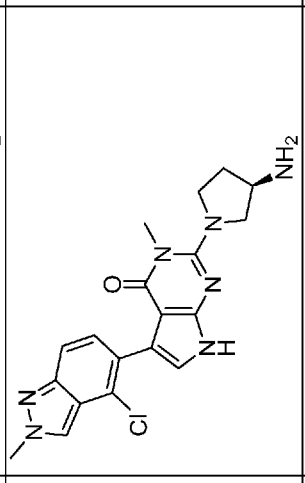
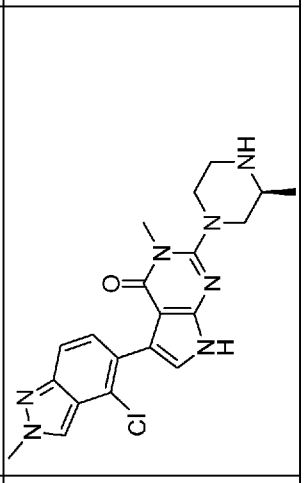
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[Table 10-14]

40		2-(3,7-diazabicyclo[4.2.0]octan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 7.01 (1H, d, *J* = 2.7 Hz), 4.23-4.14 (4H, m), 3.75-3.66 (2H, m), 3.36 (3H, s), 3.21-3.01 (2H, m), 2.94-2.87 (2H, m), 2.53-2.50 (1H, m), 1.81-1.73 (2H, m).	424, 426	1
41		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(1,9-diazaspiro[5.5]undecan-9-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.40 (1H, s), 7.55-7.30 (2H, m), 7.03-7.01 (1H, m), 4.19 (3H, s), 3.37 (3H, s), 3.09-2.86 (4H, m), 1.95-1.76 (4H, m), 1.68-1.48 (6H, m).	466, 468	1
42		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(1,7-diazaspiro[3.5]nonan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.82 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 9.2 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.78-3.14 (9H, m), 2.95-2.89 (2H, m), 2.35-2.20 (4H, m).	438, 440	1,using 4 M HCl in dioxane instead of TFA and $CHCl_3$

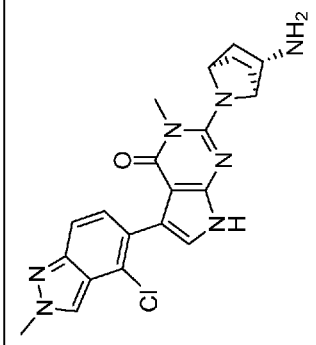
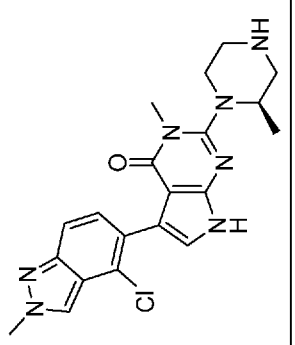
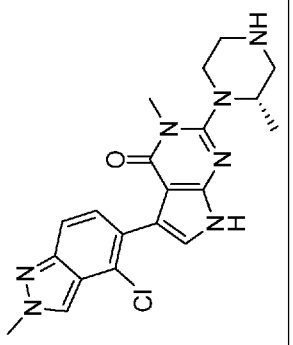
[0799]

[Table 10-15]

43		(S)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.90 (1H, s), 4.19 (3H, s), 3.66-3.41 (4H, m), 3.33 (3H, s), 3.13-3.06 (1H, m), 2.04-1.58 (4H, m).	398, 400	1
44		(*R*)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.90 (1H, s), 4.19 (3H, s), 3.66-3.39 (4H, m), 3.33 (3H, s), 3.13-3.07 (1H, m), 2.05-1.59 (4H, m).	398, 400	1
45		(S)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.00 (1H, s), 4.19 (3H, s), 3.51-3.45 (1H, m), 3.38 (3H, s), 2.96-2.79 (3H, m), 2.74-2.65 (1H, m), 2.42-2.35 (2H, m), 1.00 (3H, d, *J* = 6.6 Hz).	412, 414	1

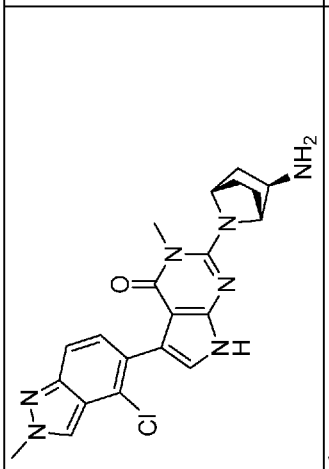
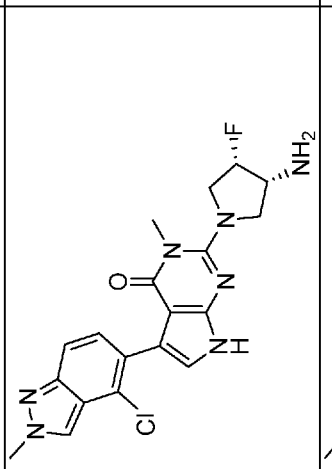
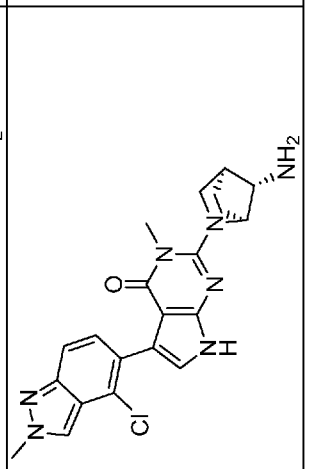
[0800]

[Table 10-16]

46		2-((1*S*,2*S*,4*R*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 9.0 Hz), 7.32 (1H, d, *J* = 9.0 Hz), 6.94 (1H, s), 4.19 (3H, s), 4.15-4.12 (1H, m), 4.01-3.98 (1H, m), 3.49-3.42 (1H, m), 3.39 (3H, s), 2.30-2.24 (1H, m), 2.19-2.14 (1H, m), 2.00-1.79 (2H, m), 1.72-1.64 (1H, m), 1.54-1.45 (1H, m), 0.90-0.85 (1H, m).	424, 426	1
47		(*R*)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.88 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 9.0 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.06 (1H, s), 4.19 (3H, s), 3.48-3.43 (1H, m), 3.42 (3H, s), 3.23-3.15 (1H, m), 3.10-3.02 (1H, m), 3.00-2.87 (2H, m), 2.85-2.77 (1H, m), 2.70-2.61 (1H, m), 1.04 (3H, d, *J* = 6.2 Hz).	412, 414	1
48		(*S*)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.84 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 7.05 (1H, s), 4.18 (3H, s), 3.42 (3H, s), 3.42-3.35 (1H, m), 3.17-3.09 (1H, m), 2.99-2.93 (1H, m), 2.86-2.80 (1H, m), 2.77-2.69 (2H, m), 2.58-2.51 (1H, m), 1.02 (3H, d, *J* = 6.1 Hz).	412, 414	1

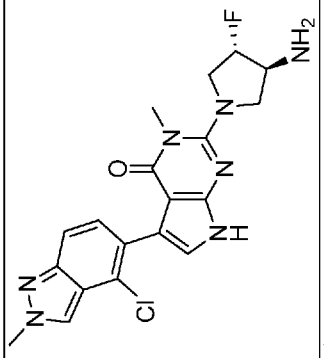
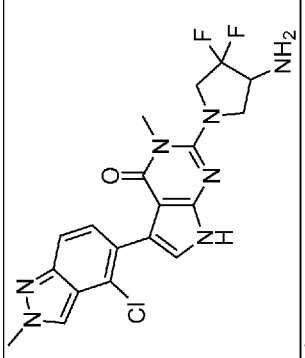
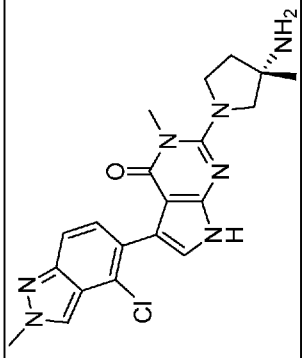
[0801]

[Table 10-17]

49		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 6.93 (1H, s), 4.18 (3H, s), 4.15-4.10 (1H, m), 4.02-3.97 (1H, m), 3.50-3.42 (1H, m), 3.38 (3H, s), 2.34-2.07 (2H, m), 1.97-1.79 (1H, m), 1.78-1.60 (1H, m), 1.57-1.40 (1H, m), 0.91-0.83 (1H, m).	424, 426	1
50		2-((3*R*,4*S*)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.52 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.91 (1H, d, *J* = 2.3 Hz), 5.05-4.88 (1H, m), 4.18 (3H, s), 4.07-3.90 (1H, m), 3.56-3.35 (4H, m), 3.32 (3H, s), 1.77 (2H, br s).	416, 418	1
51		*rac*-2-((1*S*,4*S*,7*S*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.37 (1H, s), 7.46 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.88 (1H, s), 4.18 (3H, s), 3.84 (1H, s), 3.73-3.65 (1H, m), 3.28-3.23 (4H, m), 3.02 (1H, d, *J* = 8.8 Hz), 2.15 (1H, s), 2.01-1.83 (3H, m), 1.74-1.49 (2H, m), 1.42-1.31 (1H, m).	424, 426	1

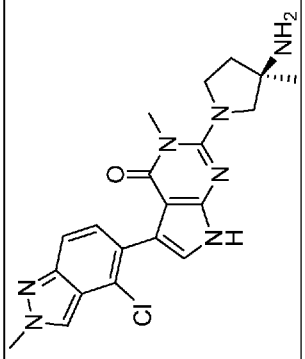
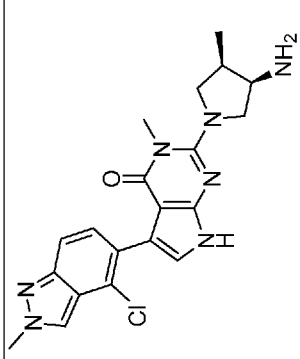
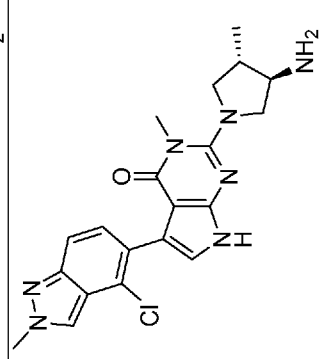
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[Table 10-18]

52		2-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.52 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.92 (1H, d, *J* = 2.2 Hz), 5.07-4.87 (1H, m), 4.22-3.99 (4H, m), 3.90-3.84 (1H, m), 3.62-3.40 (2H, m), 3.36 (3H, s), 3.16 (1H, d, *J* = 10.7 Hz).	416, 418	1
53		2-(4-amino-3,3-difluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, br s), 8.41 (1H, s), 7.50 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 6.98 (1H, d, *J* = 2.4 Hz), 4.21 (3H, s), 3.98-3.88 (2H, m), 3.82-3.76 (1H, m), 3.69-3.59 (1H, m), 3.36 (3H, s), 3.33-3.27 (1H, m), 2.09-1.93 (2H, br s).	434, 436	1
54		(S)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.47 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.32 (1H, d, *J* = 8.7 Hz), 6.89 (1H, s), 4.20-4.16 (3H, m), 3.75-3.65 (2H, m), 3.53-3.43 (2H, m), 3.33 (3H, s), 3.30-3.13 (2H, m), 2.02-1.76 (4H, m), 1.22 (3H, s).	412, 414	1

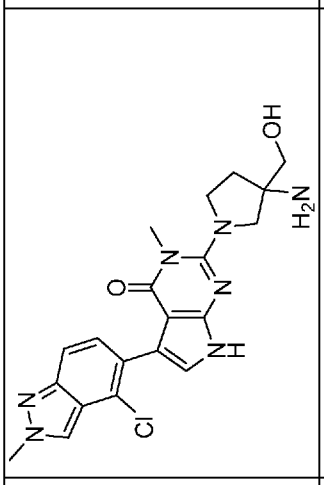
[0803]

[Table 10-19]

55		(*R*)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, br s), 8.40 (1H, s), 7.50 (1H, d, *J* = 8.7 Hz), 7.35 (1H, d, *J* = 8.8 Hz), 6.92 (1H, s), 4.21 (3H, s), 3.78-3.67 (1H, m), 3.56-3.45 (1H, m), 3.39-3.29 (4H, m), 3.20 (1H, d, *J* = 10.1 Hz), 1.83-1.75 (4H, m), 1.25 (3H, s).	412, 414	1
56		2-((3*R*,4*R*)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.48 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.35 (1H, d, *J* = 8.8 Hz), 6.91 (1H, s), 4.21 (3H, s), 3.69 (1H, q, *J* = 5.2 Hz), 3.47-3.28 (5H, m), 3.20-3.12 (2H, m), 2.26-2.13 (1H, m), 1.01 (1H, d, *J* = 7.0 Hz).	412, 414	1
57		2-((3*R*,4*S*)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.55 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 8.8 Hz), 6.92 (1H, s), 4.21 (3H, s), 3.61-3.51 (2H, m), 3.34 (3H, s), 3.28-3.17 (2H, m), 2.95-2.87 (1H, m), 1.92-1.76 (1H, m), 1.05 (3H, d, *J* = 6.6 Hz).	412, 414	1

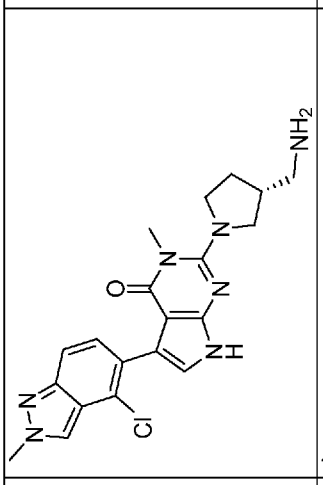
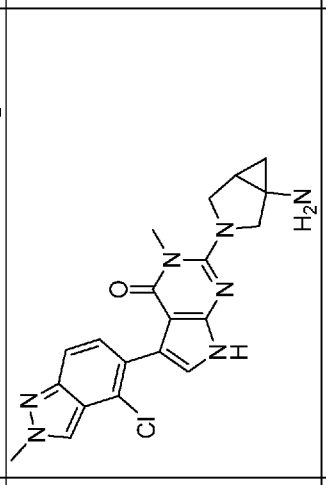
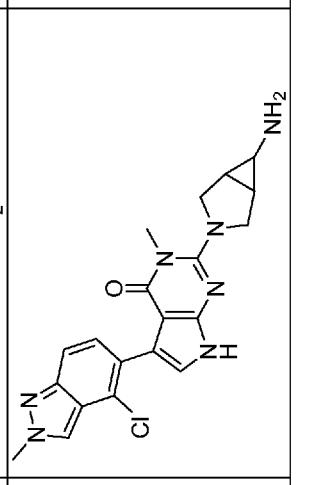
[0804]

[Table 10-20]

58		2-(3-amino-3-(hydroxymethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.47 (1H, br s), 8.37 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.32 (1H, d, *J* = 8.7 Hz), 6.89 (1H, s), 4.86 (1H, br s), 4.18 (3H, s), 3.76-3.67 (1H, m), 3.51-3.01 (8H, m), 1.93-1.83 (1H, m), 1.67-1.54 (1H, m).	428, 430	1
59		2-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.01 (1H, d, *J* = 2.0 Hz), 4.19 (3H, s), 4.09-4.02 (1H, m), 3.66 (1H, d, *J* = 8.3 Hz), 3.49 (1H, d, *J* = 8.5 Hz), 3.40 (3H, s), 3.27-3.19 (1H, m), 3.00-2.85 (3H, m), 1.90-1.84 (1H, m), 1.80-1.73 (1H, m), 1.66-1.55 (2H, m), 1.36-1.24 (2H, m), 1.09 (3H, d, *J* = 6.3 Hz).	482, 484	1

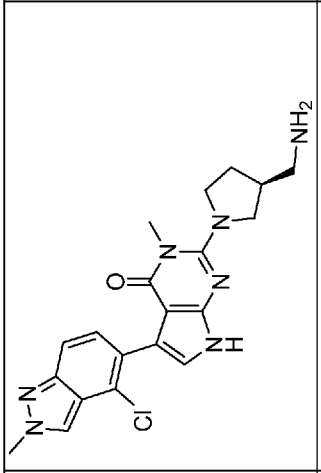
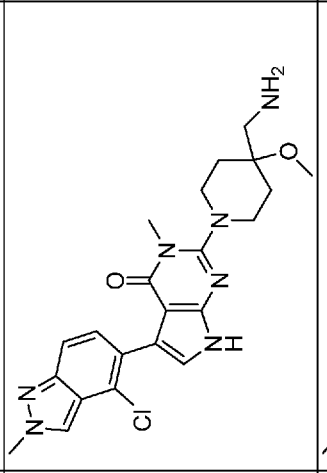
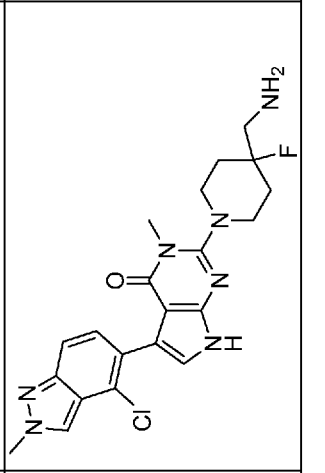
[0805]

[Table 10-21]

60		(*R*)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.7 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.91 (1H, s), 4.18 (3H, s), 3.55-3.26 (7H, m), 2.87-2.76 (2H, m), 2.45-2.36 (1H, m), 2.13-2.00 (1H, m), 1.76-1.61 (1H, m).	412, 414	1
61		2-(1-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.94 (1H, d, *J* = 2.3 Hz), 4.18 (3H, s), 3.73 (1H, d, *J* = 9.9 Hz), 3.58-3.46 (2H, m), 3.36-3.25 (4H, m), 1.39-1.31 (1H, m), 0.81-0.74 (1H, m), 0.69-0.62 (1H, m).	410, 412	1
62		2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.59 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.94 (1H, d, *J* = 2.3 Hz), 4.18 (3H, s), 3.73 (1H, d, *J* = 9.9 Hz), 3.58-3.46 (2H, m), 3.36-3.25 (4H, m), 1.39-1.31 (1H, m), 0.81-0.74 (1H, m), 0.69-0.62 (1H, m).	410, 412	1

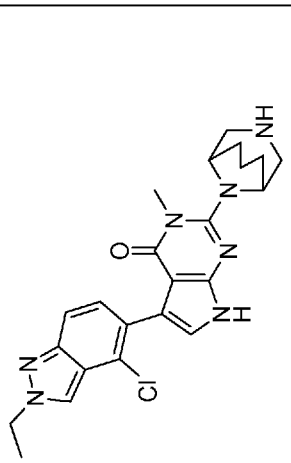
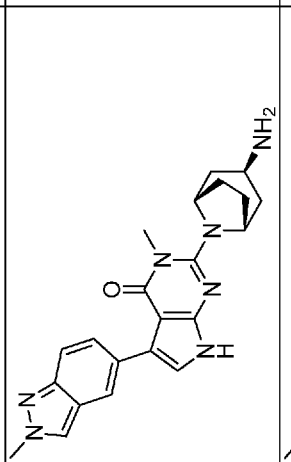
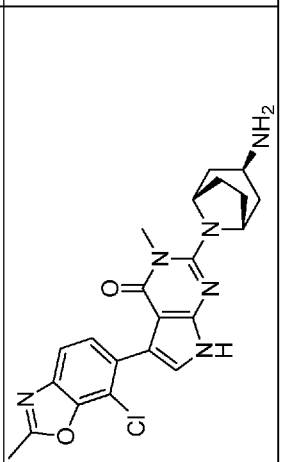
[0806]

[Table 10-22]

63		(S)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.38 (1H, s), 7.47 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.90 (1H, s), 4.18 (3H, s), 3.51-3.22 (7H, m), 2.64-2.53 (2H, m), 2.26-2.12 (1H, m), 2.03-1.92 (1H, m), 1.68-1.54 (1H, m).	412, 414	1
64		2-(4-(aminomethyl)-4-methoxypiperidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.39 (3H, s), 3.17-3.14 (5H, m), 3.01-2.98 (2H, m), 2.60 (2H, s), 1.83-1.80 (2H, m), 1.65-1.59 (2H, m).	456, 458	2
65		2-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, s), 7.48 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.40 (3H, s), 3.01-2.99 (2H, m), 2.72 (2H, d, *J* = 19.8 Hz), 2.54 (2H, s), 1.90-1.80 (4H, m).	444, 446	2

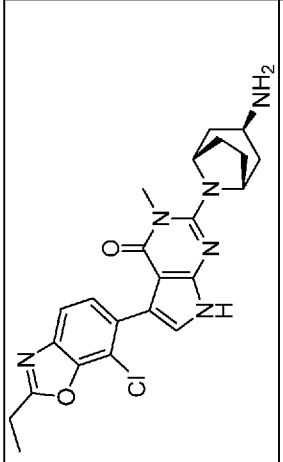
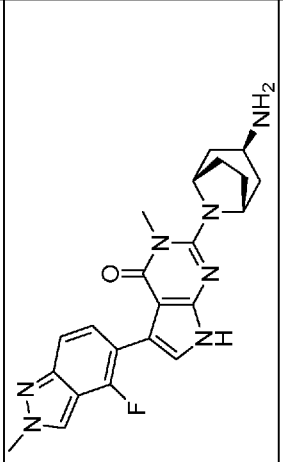
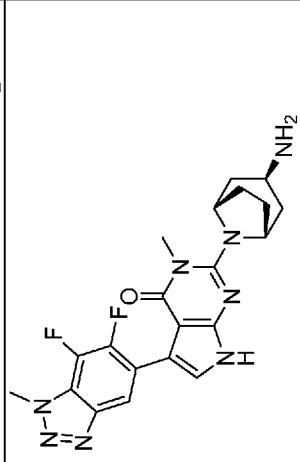
[0807]

[Table 10-23]

66		2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.43 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.93 (1H, d, *J* = 2.4 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 3.65 (2H, br s), 3.37-3.33 (4H, m), 3.28-3.25 (1H, m), 2.92-2.89 (2H, m), 2.79-2.67 (1H, m), 2.20-2.07 (2H, m), 1.76-1.70 (2H, m), 1.63-1.56 (1H, m), 1.52 (3H, t, *J* = 7.2 Hz).	452, 454	1
67		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-methyl-5-(2-methyl-2H-indazol-5-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, br s), 8.26 (1H, s), 7.75-7.46 (2H, m), 7.14 (1H, s), 4.16-4.06 (5H, m), 3.51-3.40 (4H, m), 2.27-2.10 (4H, m), 2.00-1.90 (2H, m), 1.58 (2H, d, *J* = 13.6 Hz).	404	1
68		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[*d*]oxazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.65 (1H, br s), 7.55 (1H, d, *J* = 8.3 Hz), 7.40 (1H, d, *J* = 8.3 Hz), 6.96 (1H, s), 4.08 (2H, br s), 3.40 (3H, s), 3.35-3.31 (1H, m), 2.65 (3H, s), 2.26-2.20 (2H, m), 2.17-2.09 (2H, m), 1.98-1.90 (2H, m), 1.60-1.53 (2H, m).	439, 441	2

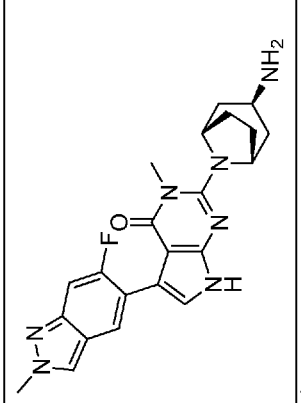
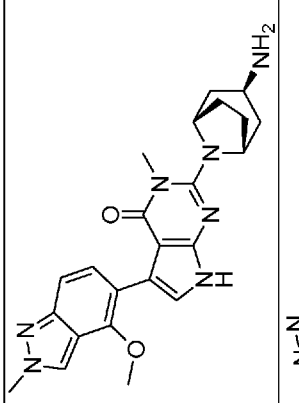
[0808]

[Table 10-24]

69		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[*d*]oxazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (CD_3OD) δ: 7.52 (1H, d, *J* = 8.4 Hz), 7.46 (1H, d, *J* = 8.4 Hz), 6.96 (1H, s), 4.22 (2H, br s), 3.55 (3H, s), 3.37-3.33 (1H, m), 3.03 (2H, q, *J* = 7.7 Hz), 2.56-2.44 (2H, m), 2.27-2.17 (2H, m), 2.06-1.98 (2H, m), 1.68 (2H, br d, *J* = 13.6 Hz), 1.46 (3H, t, *J* = 7.7 Hz).	453, 455	1
70		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.60-7.31 (2H, m), 6.99 (1H, s), 4.19-4.09 (5H, m), 3.55-3.32 (4H, m), 2.33-2.19 (2H, m), 2.13-1.95 (4H, m), 1.67-1.55 (2H, m).	422	2
71		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6,7-difluoro-1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.78 (1H, s), 8.29 (1H, d, *J* = 4.6 Hz), 7.16 (1H, d, *J* = 1.8 Hz), 4.42 (3H, s), 4.17-4.03 (2H, m), 3.45 (3H, s), 2.63-2.61 (1H, m), 2.27-2.21 (2H, m), 2.18-2.12 (2H, m), 1.98-1.92 (2H, m), 1.61-1.56 (2H, m).	441	2

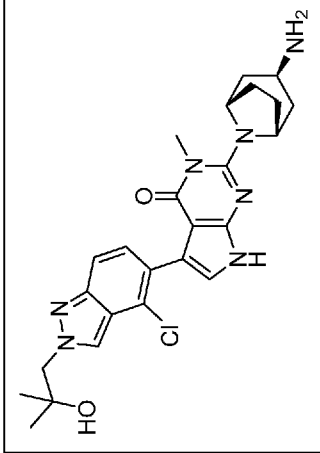
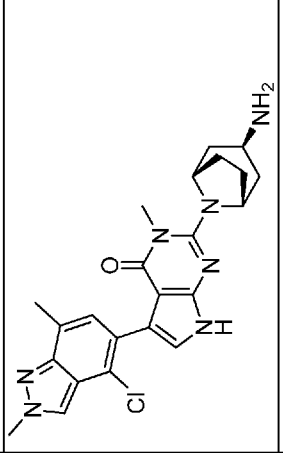
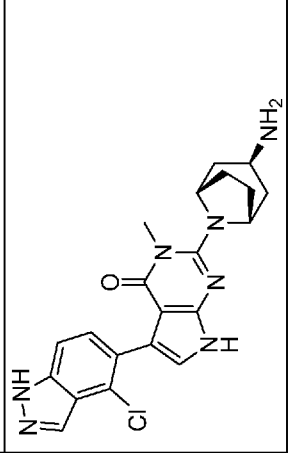
[0809]

[Table 10-25]

72		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, s), 8.34 (1H, s), 8.06 (1H, d, *J* = 7.9 Hz), 7.28 (1H, d, *J* = 11.9 Hz), 6.97 (1H, d, *J* = 2.4 Hz), 4.14 (3H, s), 4.11-4.06 (2H, m), 3.44 (3H, s), 2.63-2.59 (1H, m), 2.25-2.21 (2H, m), 2.17-2.11 (2H, m), 1.98-1.92 (2H, m), 1.61-1.54 (2H, m).	422	2
73		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-methoxy-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.43 (1H, s), 8.51 (1H, s), 7.42 (1H, d, *J* = 8.9 Hz), 7.17 (1H, dd, *J* = 8.7, 1.1 Hz), 6.90 (1H, d, *J* = 2.4 Hz), 4.15 (3H, s), 4.11-4.07 (2H, m), 3.89 (3H, s), 3.43 (3H, s), 2.55-2.53 (1H, m), 2.23-2.12 (4H, m), 2.00-1.93 (2H, m), 1.61-1.55 (2H, m).	434	2
74		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, s), 7.92 (1H, d, *J* = 8.5 Hz), 7.44 (1H, d, *J* = 8.5 Hz), 7.02 (1H, d, *J* = 1.5 Hz), 4.53 (3H, s), 4.11-4.08 (2H, m), 3.41 (3H, s), 2.53-2.51 (1H, m), 2.27-2.22 (2H, m), 2.16-2.10 (2H, m), 1.99-1.92 (2H, m), 1.60-1.55 (2H, m).	439, 441	2

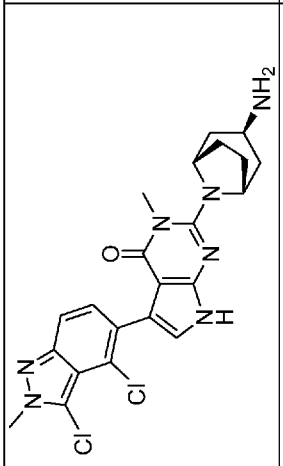
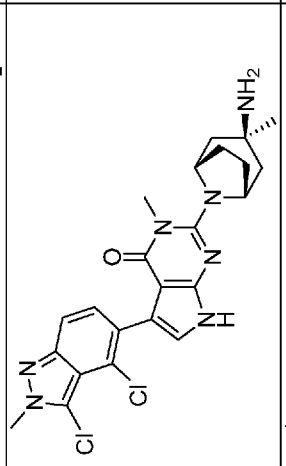
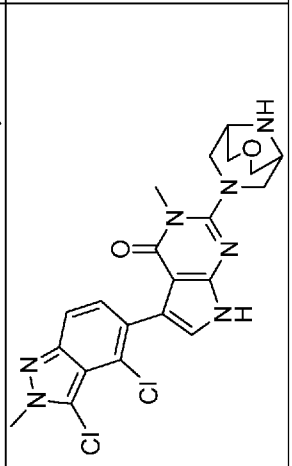
[0810]

[Table 10-26]

75		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-(2-hydroxy-2-methylpropyl)-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, s), 8.30 (1H, d, *J* = 0.9 Hz), 7.51 (1H, dd, *J* = 8.9, 0.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.94 (1H, s), 4.88 (1H, s), 4.36 (2H, s), 4.11-4.07 (2H, m), 3.41 (3H, s), 2.69-2.65 (1H, m), 2.25-2.20 (2H, m), 2.18-2.11 (2H, m), 1.99-1.92 (2H, m), 1.60-1.55 (2H, m), 1.13 (6H, s).	496, 498	2
76		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2,7-dimethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($CDCl_3$) δ: 8.46 (1H, br s), 7.93 (1H, s), 7.25 (1H, s), 6.90 (1H, d, *J* = 2.2 Hz), 4.23 (3H, s), 4.10 (2H, br s), 3.55 (3H, s), 3.43 (1H, br t, *J* = 6.1 Hz), 2.60 (3H, s), 2.38-2.26 (2H, m), 2.23-2.13 (2H, m), 2.13-2.04 (2H, m), 1.60 (2H, br d, *J* = 13.9 Hz).	452, 454	1
77		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(1*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.32 (1H, s), 11.58 (1H, s), 8.07 (1H, s), 7.45-7.42 (2H, m), 6.93 (1H, d, *J* = 1.5 Hz), 4.11-4.05 (2H, m), 3.28 (3H, s), 2.47-2.43 (1H, m), 2.25-2.20 (2H, m), 2.16-2.09 (2H, m), 1.98-1.91 (2H, m), 1.59-1.54 (2H, m).	424, 426	2

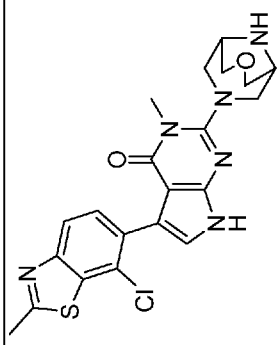
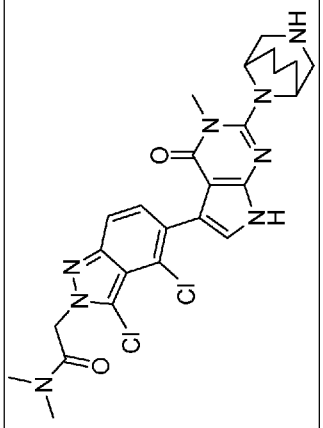
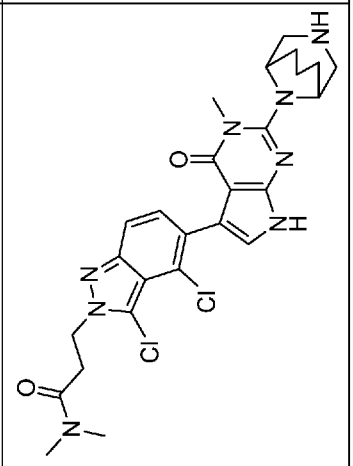
[0811]

[Table 10-27]

78		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($CDCl_3$) δ: 8.37 (1H, br s), 7.53 (1H, d, *J* = 8.8 Hz), 7.46 (1H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 2.2 Hz), 4.14 (3H, s), 4.13 - 4.07 (2H, m), 3.55 (3H, s), 3.48-3.38 (1H, m), 2.39-2.25 (2H, m), 2.25-2.07 (4H, m), 1.61 (2H, br d, *J* = 13.9 Hz).	472, 474	1
79		2-(*endo*-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($DMSO$-d_6) δ: 11.63 (1H, br s), 7.50 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.97 (1H, s), 4.14 (3H, s), 4.09 (2H, br s), 3.41 (3H, s), 2.35-2.23 (2H, m), 1.96-1.81 (4H, m), 1.61 (2H, br d, *J* = 13.6 Hz), 1.09 (3H, s).	486, 488	1
80		2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($CDCl_3$) δ: 8.45 (1H, br s), 7.54 (1H, d, *J* = 8.8 Hz), 7.46 (1H, d, *J* = 8.8 Hz), 7.00 (1H, d, *J* = 1.8 Hz), 4.15 (3H, s), 4.03 (4H, s), 3.67 (3H, s), 3.57 (2H, br d, *J* = 12.1 Hz), 3.37 (2H, br d, *J* = 12.1 Hz), 3.01 (2H, br s).	474, 476	1

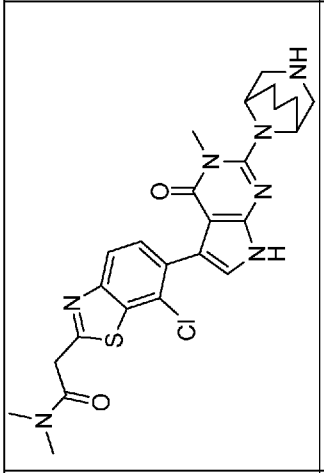
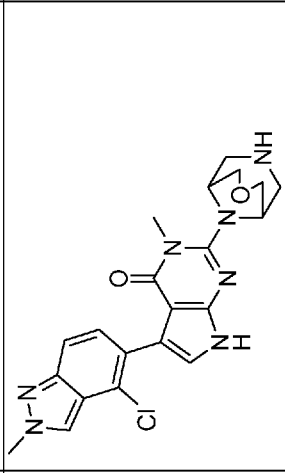
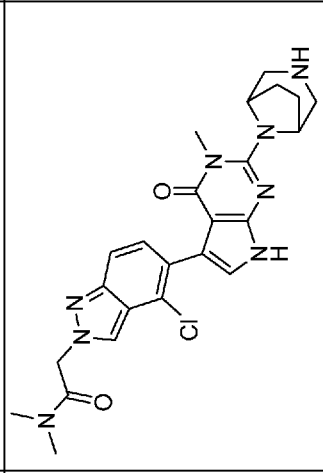
[0812]

[Table 10-28]

81		2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.86 (1H, br s), 7.84 (1H, d, *J* = 8.4 Hz), 7.57 (1H, d, *J* = 8.4 Hz), 7.07 (1H, d, *J* = 2.6 Hz), 3.91 (2H, d, *J* = 11.0 Hz), 3.83 (2H, br d, *J* = 11.0 Hz), 3.51 (3H, s), 3.48 (2H, br d, *J* = 11.7 Hz), 3.20 (2H, br d, *J* = 11.7 Hz), 2.88-2.81 (5H, m).	457, 459	1
82		2-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-3,4-dichloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, s), 7.51-7.48 (1H, m), 7.36-7.33 (1H, m), 6.97 (1H, d, *J* = 2.4 Hz), 5.52 (2H, s), 3.67-3.65 (2H, m), 3.28-3.24 (5H, m), 3.12 (3H, s), 2.93-2.88 (5H, m), 2.78-2.71 (1H, m), 2.17-2.06 (2H, m), 1.75-1.70 (2H, m), 1.61-1.54 (1H, m).	543, 545	2
83		3-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-3,4-dichloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, s), 7.50 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 6.96 (1H, d, *J* = 2.4 Hz), 4.63 (2H, t, *J* = 7.0 Hz), 3.68-3.63 (2H, m), 3.30-3.26 (5H, m), 3.07 (2H, t, *J* = 7.0 Hz), 2.96 (3H, s), 2.91 (2H, d, *J* = 11.3 Hz), 2.81 (3H, s), 2.76-2.70 (1H, m), 2.15-2.10 (2H, m), 1.75-1.71 (2H, m), 1.62-1.56 (1H, m).	557, 559	2

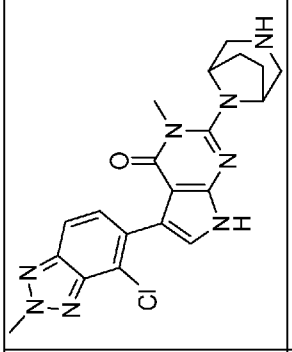
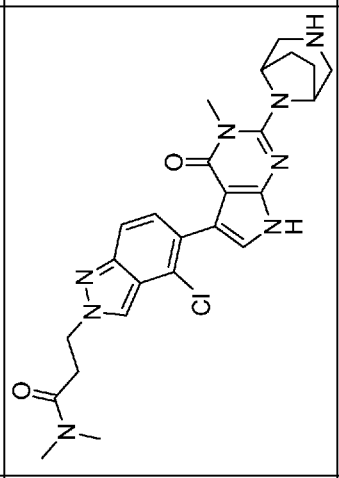
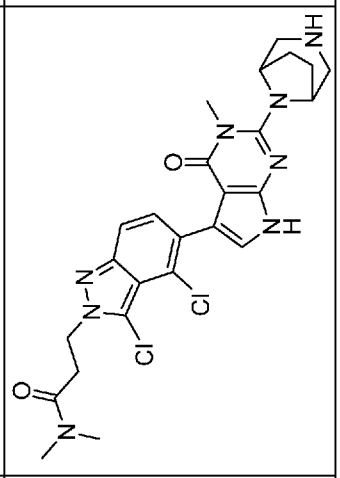
[0813]

[Table 10-29]

84		2-(6-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-7-chlorobenzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylacetamide	526, 528	2
85		2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 9.6 Hz), 6.97 (1H, s), 4.18 (3H, s), 4.12 (2H, d, *J* = 11.3 Hz), 3.96 (2H, d, *J* = 10.9 Hz), 3.51-3.43 (2H, m), 3.33-3.24 (2H, m), 3.33 (3H, s), 3.09 (2H, d, *J* = 13.9 Hz).	440, 442	1
86		2-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-chloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylacetamide	^{1}H-NMR (DMSO-d6) δ: 11.64 (1H, s), 8.32 (1H, d, *J* = 0.9 Hz), 7.47 (1H, dd, *J* = 8.9, 0.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 6.96 (1H, d, *J* = 2.4 Hz), 5.47 (2H, s), 3.99-3.96 (2H, m), 3.45 (3H, s), 3.10 (3H, s), 3.01-2.96 (2H, m), 2.88 (3H, s), 2.66-2.63 (2H, m), 1.97-1.90 (2H, m), 1.86-1.82 (2H, m).	495, 497	2

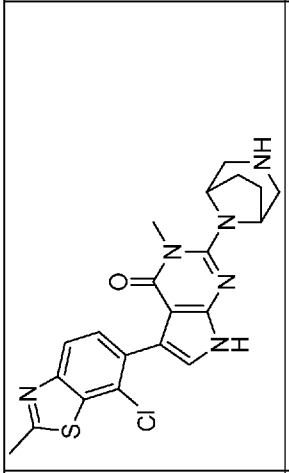
[0814]

[Table 10-30]

87		2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.76 (1H, s), 7.79 (1H, d, *J* = 8.9 Hz), 7.53 (1H, d, *J* = 8.9 Hz), 7.07 (1H, d, *J* = 2.1 Hz), 4.53 (3H, s), 4.00-3.97 (2H, m), 3.46 (3H, s), 3.00-2.95 (2H, m), 2.67-2.63 (2H, m), 1.96-1.91 (2H, m), 1.86-1.82 (2H, m).	425, 427	2
88		3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-chloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, s), 8.42 (1H, d, *J* = 0.9 Hz), 7.48 (1H, dd, *J* = 8.5, 0.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.94 (1H, d, *J* = 2.1 Hz), 4.66 (2H, t, *J* = 6.9 Hz), 3.99-3.95 (2H, m), 3.45 (3H, s), 3.05 (2H, t, *J* = 6.9 Hz), 2.99-2.95 (2H, m), 2.94 (3H, s), 2.82 (3H, s), 2.66-2.63 (2H, m), 1.96-1.90 (2H, m), 1.86-1.82 (2H, m).	509, 511	2
89		3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-3,4-dichloro-2*H*-indazol-2-yl)-*N*,*N*-dimethylpropanamide	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, s), 7.50 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.96 (1H, d, *J* = 2.4 Hz), 4.63 (2H, t, *J* = 7.0 Hz), 3.99-3.95 (2H, m), 3.45 (3H, s), 3.07 (2H, t, *J* = 7.0 Hz), 2.99-2.96 (5H, m), 2.81 (3H, s), 2.67-2.63 (2H, m), 1.96-1.90 (2H, m), 1.86-1.80 (2H, m).	543, 545	2

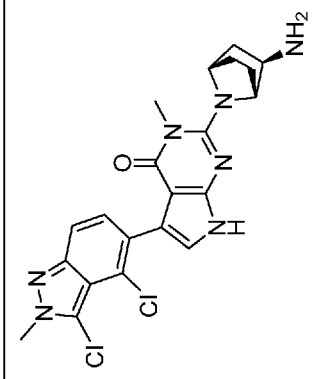
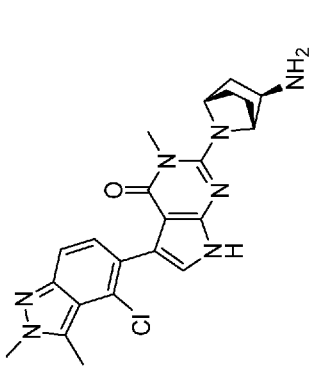
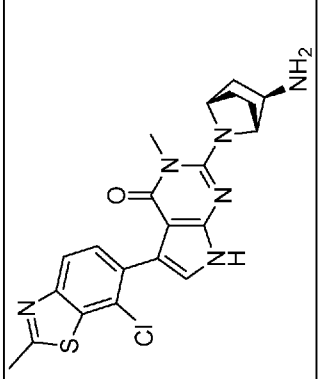
[0815]

[Table 10-31]

90		2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 7.83 (1H, d, *J* = 8.5 Hz), 7.57 (1H, d, *J* = 8.5 Hz), 7.02 (1H, s), 3.98 (2H, br s), 3.45 (3H, s), 2.99-2.96 (2H, m), 2.83 (3H, s), 2.65-2.62 (2H, m), 1.94-1.82 (4H, m).	441, 443	1
91		2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.43 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 2.4 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 3.98 (2H, br s), 3.45 (3H, s), 3.00-2.96 (2H, m), 2.68-2.64 (2H, m), 1.97-1.81 (4H, m), 1.52 (3H, t, *J* = 7.2 Hz).	438, 440	1
92		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.93 (1H, s), 4.48 (2H, q, *J* = 7.2 Hz), 4.14-4.12 (1H, m), 4.00-3.98 (1H, m), 3.48-3.43 (1H, m), 3.39 (3H, s), 2.30-2.22 (1H, m), 2.21-2.14 (1H, m), 1.96-1.88 (1H, m), 1.71-1.63 (2H, m), 1.54-1.46 (5H, m), 0.89-0.84 (1H, m).	438, 440	1

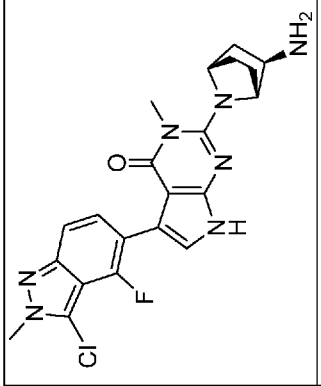
[0816]

[Table 10-32]

93		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, br s), 7.50 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.97 (1H, s), 4.20-4.09 (4H, m), 4.01 (1H, br t, *J* = 4.0 Hz), 3.54-3.44 (1H, m), 3.39 (3H, s), 2.33-2.21 (1H, m), 2.20-2.07 (1H, m), 1.98-1.84 (1H, m), 1.80-1.61 (1H, m), 1.56-1.41 (1H, m), 0.90 (1H, br dd, *J* = 12.1, 4.0 Hz).	458, 460	1
94		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2,3-dimethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.58 (1H, s), 7.38 (1H, d, *J* = 8.9 Hz), 7.20 (1H, d, *J* = 8.9 Hz), 6.88 (1H, d, *J* = 2.4 Hz), 4.15-4.12 (1H, m), 4.06 (3H, s), 4.02-3.98 (1H, m), 3.49-3.44 (1H, m), 3.38 (3H, s), 2.82 (3H, s), 2.29-2.23 (1H, m), 2.19-2.13 (1H, m), 1.94-1.86 (1H, m), 1.72-1.63 (1H, m), 1.52-1.46 (1H, m), 0.91-0.85 (1H, m).	438, 440	2
95		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.83 (1H, d, *J* = 8.3 Hz), 7.57 (1H, d, *J* = 8.3 Hz), 7.01 (1H, s), 4.16-4.14 (1H, m), 4.05-4.02 (1H, m), 3.52-3.48 (2H, m), 3.39 (3H, s), 2.83 (3H, s), 2.32-2.21 (1H, m), 2.17-2.10 (1H, m), 1.94-1.85 (1H, m), 1.74-1.65 (1H, m), 1.54-1.47 (1H, m), 0.94-0.90 (1H, m).	441, 443	2

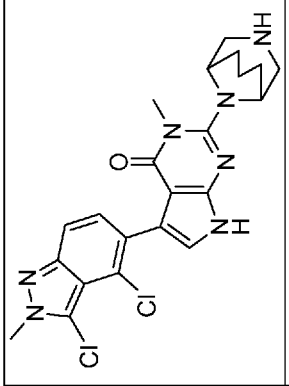
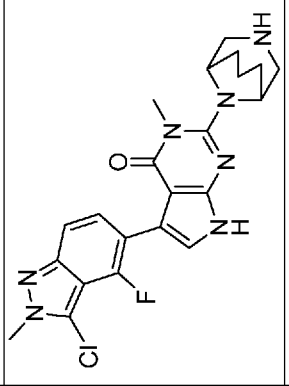
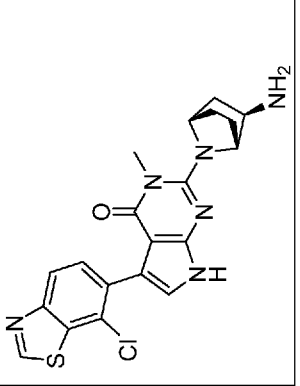
[0817]

[Table 10-33]

96		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, br s), 7.66-7.60 (1H, m), 7.35 (1H, d, *J* = 8.9 Hz), 7.02 (1H, s), 4.14-4.09 (4H, m), 4.01-3.97 (1H, m), 3.48-3.39 (4H, m), 2.33-2.10 (2H, m), 1.95-1.83 (2H, m), 1.74-1.60 (1H, m), 1.53-1.43 (1H, m), 0.91-0.80 (1H, m).	442, 444	2
97		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 8.40 (1H, s), 7.48 (1H, d, *J* = 8.7 Hz), 7.32 (1H, d, *J* = 8.7 Hz), 6.95 (1H, s), 4.23-4.15 (5H, m), 3.40 (3H, s), 3.15-3.11 (1H, m), 2.26-2.19 (4H, m), 2.09-2.03 (1H, m), 1.92-1.86 (1H, m), 1.71-1.65 (1H, m), 1.47-1.42 (1H, m), 0.95-0.90 (1H, m).	438, 440	2
98		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 8.44 (1H, s), 7.49 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 2.4 Hz), 6.94 (1H, d, *J* = 7.3 Hz), 4.48 (2H, q, *J* = 7.3 Hz), 4.24-4.20 (1H, m), 4.18-4.14 (1H, m), 3.40 (3H, s), 3.16-3.12 (1H, m), 2.27-2.19 (4H, m), 2.08-2.03 (1H, m), 1.91-1.85 (1H, m), 1.72-1.65 (1H, m), 1.52 (3H, t, *J* = 7.3 Hz), 1.48-1.42 (1H, m), 0.95-0.90 (1H, m).	452, 454	2

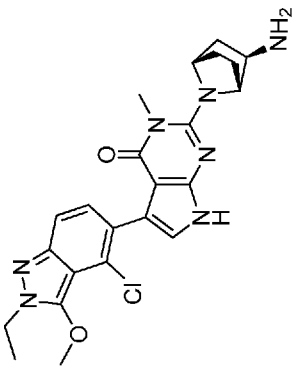
[0818]

[Table 10-34]

99		2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.65-11.59 (1H, m), 7.50 (1H, br d, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 8.8 Hz), 7.01-6.95 (1H, m), 4.14 (3H, s), 3.65 (2H, br s), 2.90 (2H, d, *J* = 12.1 Hz), 2.84-2.70 (1H, m), 2.21-2.05 (2H, m), 1.80-1.68 (2H, m), 1.65-1.51 (1H, m).	472, 474	1
100		2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 7.68-7.62 (1H, m), 7.37 (1H, d, *J* = 8.8 Hz), 7.05 (1H, s), 4.12 (3H, s),3.66 (2H, br s), 3.52-3.14 (4H, m), 2.97-2.88 (2H, m), 2.18-2.06 (2H, m), 1.78-1.69 (2H, m), 1.64-1.54 (1H, m).	456, 458	1
101		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 9.42 (1H, s), 8.00 (1H, d, *J* = 8.3 Hz), 7.64 (1H, d, *J* = 8.4 Hz), 7.03 (1H, s), 4.17-3.95 (2H, m), 3.48-3.41 (1H, m), 3.39 (3H, s), 2.34-2.09 (2H, m), 1.97-1.43 (5H, m), 0.91-0.80 (1H, m).	428, 430	2

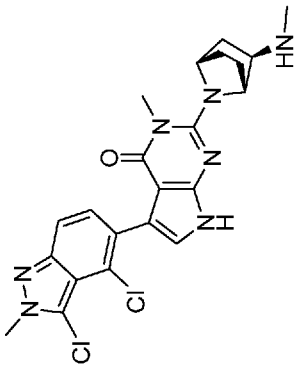
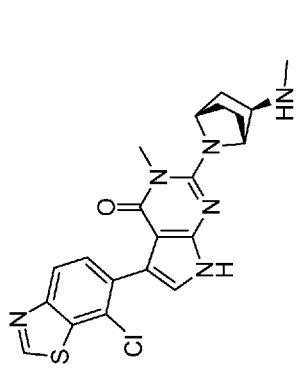
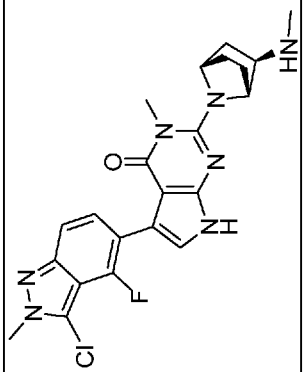
[0819]

[Table 10-35]

102		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-methoxy-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 7.34 (1H, d, *J* = 8.8 Hz), 7.22 (1H, d, *J* = 8.8 Hz), 6.91 (1H, s), 4.30 (2H, q, *J* = 7.2 Hz), 4.14-4.09 (1H, m), 4.06 (3H, s), 4.01-3.96 (1H, m), 3.48-3.42 (1H, m), 3.37 (3H, s), 2.29-2.11 (2H,m), 1.94-1.85 (1H, m), 1.71-1.60 (1H, m), 1.52-1.41 (1H, m), 1.44 (3H, t, *J* = 7.2 Hz), 0.90-0.81 (1H,m).	468, 470	1
103		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-(fluoromethyl)-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, br s), 7.57 (1H, d, *J* = 8.8 Hz), 7.42 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 6.51 (2H, d, *J* = 51.2 Hz), 4.15-4.10 (1H, m), 4.01-3.96 (1H, m), 3.48-3.42 (1H, m), 3.38 (3H, s), 2.28-2.13 (2H, m), 1.92-1.86 (1H, m), 1.75-1.65 (1H, m), 1.52-1.45 (1H, m), 0.89-0.82 (1H, m).	476, 478	1

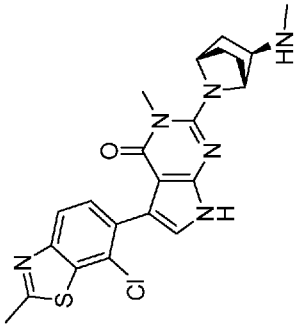
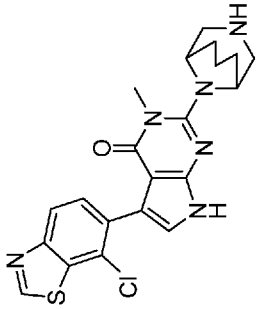
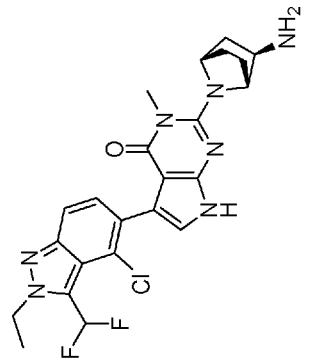
[0820]

[Table 10-36]

104		5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br d, *J* = 2.2 Hz), 7.50 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.97 (1H, d, *J* = 2.2 Hz), 4.22 (1H, t, *J* = 4.4 Hz), 4.18-4.11 (4H, m), 3.40 (3H, s), 3.19-3.07 (1H, m), 2.28-2.17 (4H, m), 2.11-1.98 (1H, m), 1.95-1.79 (1H, m), 1.75-1.61 (1H, m), 1.51-1.38 (1H, m), 0.92 (1H, dd, *J* = 11.7, 4.4 Hz).	472, 474	1
105		5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.75 (1H, br s), 9.44 (1H, s), 8.01 (1H, d, *J* = 8.5 Hz), 7.65 (1H, d, *J* = 8.5 Hz), 7.04 (1H, d, *J* = 2.0 Hz), 4.24-4.22 (1H, m), 4.19-4.15 (1H, m), 3.41 (3H, s), 3.16-3.10 (1H, m), 2.24 (4H, br s), 2.10-2.03 (1H, m), 1.92-1.85 (1H, m), 1.72-1.65 (1H, m), 1.48-1.42 (1H, m), 0.95-0.90 (1H, m).	441, 443	2
106		5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br s), 7.67-7.58 (1H, m), 7.36 (1H, d, *J* = 9.1 Hz), 7.06-7.00 (1H, m), 4.23-4.19 (1H, m), 4.17-4.13 (1H, m), 4.11 (3H, s), 3.43-3.42 (1H, m), 3.17-3.07 (1H, m), 2.23 (3H, s), 2.11-1.80 (3H, m), 1.73-1.60 (1H, m), 1.51-1.38 (1H, m), 0.99-0.86 (1H, m).	456, 458	2

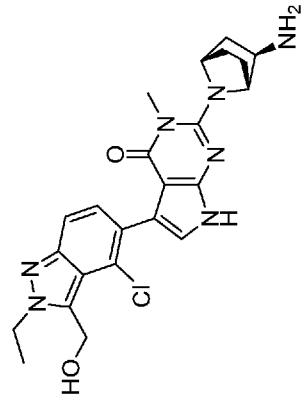
[0821]

[Table 10-37]

107		5-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-3-methyl-2-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, br s), 7.82 (1H, d, *J* = 8.4 Hz), 7.56 (1H, d, *J* = 8.4 Hz), 7.01 (1H, s), 4.25-4.14 (2H, m), 3.40 (3H, s), 3.17-3.10 (1H, m), 2.82 (3H, s), 2.26-2.16 (1H, m), 2.24 (3H, s), 2.08-1.99 (1H, m), 1.93-1.81 (1H, m), 1.73-1.62 (1H, m), 1.49-1.40 (1H, m), 0.98-0.90 (1H, m).	455, 457	1
108		2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.70 (1H, s), 9.44 (1H, s), 8.01 (1H, d, *J* = 8.4 Hz), 7.66 (1H, d, *J* = 8.4 Hz), 7.04 (1H, d, *J* = 2.2 Hz), 3.66 (2H, br s), 3.27 (2H, br d, *J* = 11.7 Hz), 2.91 (2H, d, *J* = 11.7 Hz), 2.81-2.63 (1H, m), 2.22-2.04 (2H, m), 1.81-1.66 (2H, m), 1.64-1.49 (1H, m).	441, 443	1
109		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-3-(difluoromethyl)-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR ($CDCl_3$) δ: 8.43 (1H, br s), 7.90 (1H, t, *J* = 52.8 Hz), 7.67 (1H, d, *J* = 8.8 Hz), 7.47 (1H, d, *J* = 8.8 Hz), 6.90 (1H, d, *J* = 2.2 Hz), 4.70 (2H, q, *J* = 7.3 Hz), 4.21-4.14 (1H, m), 4.06 (1H, br t, *J* = 4.4 Hz), 3.73-3.61 (1H, m), 3.53 (3H, s), 2.53-2.39 (1H, m), 2.19-2.09 (1H, m), 2.08-1.97 (1H, m), 1.91-1.81 (1H, m), 1.63 (3H, t, *J* = 7.3 Hz), 0.96 (1H, dd, *J* = 12.5, 4.4 Hz).	488, 490	1

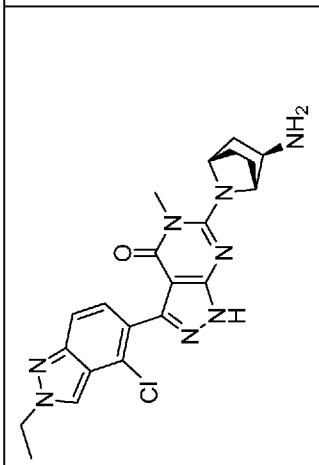
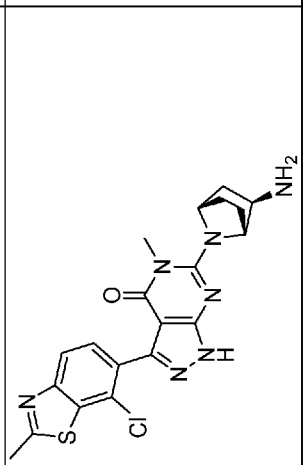
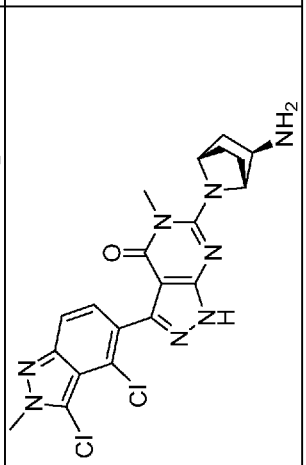
[0822]

[Table 10-38]

110		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-(hydroxymethyl)-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 7.47 (1H, d, *J* = 8.8 Hz), 7.25 (1H, d, *J* = 8.8 Hz), 6.89 (1H, br s), 5.42 (1H, br s), 5.12 (2H, s), 4.51 (2H, q, *J* = 7.2 Hz), 4.14 (1H, br t, *J* = 4.8 Hz), 4.01 (1H, br t, *J* = 4.2 Hz), 3.53-3.44 (1H, m), 3.38 (3H, s), 2.33-2.21 (1H, m), 2.20-2.08 (1H, m), 1.98-1.84 (1H, m), 1.79-1.61 (1H, m), 1.57-1.44 (4H, m), 0.90 (1H, dd, *J* = 11.7, 4.0 Hz).	468, 470	1
111		6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.27 (1H, s), 8.54 (1H, s), 7.57 (1H, d, *J* = 8.8 Hz), 7.29 (1H, d, *J* = 8.8 Hz), 4.48 (2H, q, *J* = 7.3 Hz), 3.74-3.71 (2H, m), 3.28 (3H, s), 3.23-3.17 (2H, m), 2.89 (2H, d, *J* = 12.1 Hz), 2.76-2.65 (1H, m), 2.13-2.01 (2H, m), 1.76-1.69 (2H, m), 1.58-1.52 (1H, m), 1.52 (3H, t, *J* = 7.3 Hz).	453, 455	2

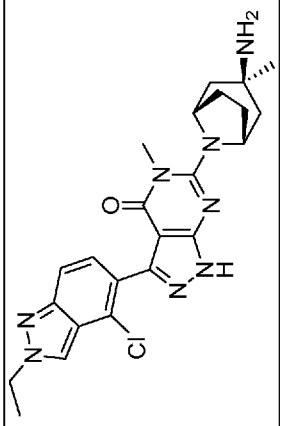
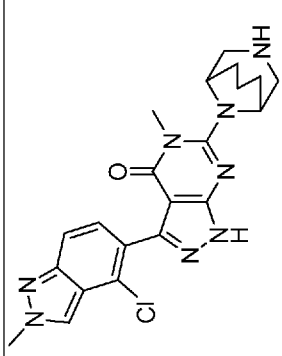
[0823]

[Table 10-39]

112		6-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.36 (1H, s), 8.57 (1H, s), 7.60 (1H, d, *J* = 8.7 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 4.51 (2H, q, *J* = 7.2 Hz), 4.24-4.19 (1H, m), 4.10-4.05 (1H, m), 3.49-3.43 (1H, m), 3.37 (3H, s), 2.30-2.23 (1H, m), 2.22-2.16 (1H, m), 1.92-1.85 (1H, m), 1.71-1.63 (1H, m), 1.57-1.49 (4H, m), 0.92-0.87 (1H, m).	439, 441	3
113		6-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, d, *J* = 8.3 Hz), 7.63 (1H, d, *J* = 8.5 Hz), 4.25-4.22 (1H, m), 4.12-4.10 (1H, m), 3.49-3.48 (2H, m), 3.38 (3H, s), 2.87 (3H, s), 2.29-2.26 (1H, m), 2.19-2.16 (1H, m), 1.90-1.88 (1H, m), 1.71-1.69 (1H, m), 1.55-1.52 (1H, m), 0.95-0.92 (1H, m).	442, 444	3
114		6-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.39 (1H, s), 7.61 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 4.24-4.20 (1H, m), 4.17 (3H, s), 4.11-4.06 (1H, m), 3.50-3.44 (1H, m), 3.38 (3H, s), 2.31-2.23 (1H, m), 2.21-2.16 (1H, m), 1.93-1.85 (1H, m), 1.73-1.65 (1H, m), 1.55-1.48 (1H, m), 0.93-0.88 (1H, m).	459, 461	3

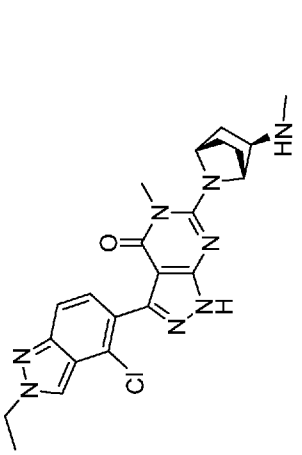
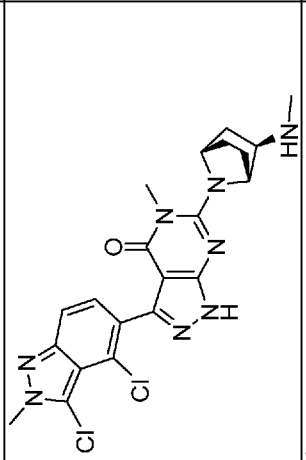
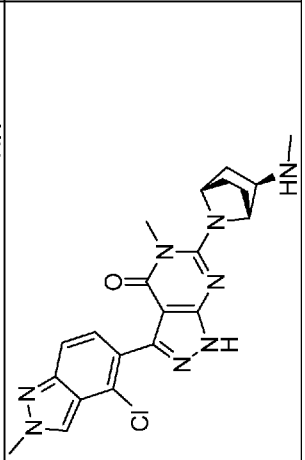
[0824]

[Table 10-40]

115		6-(*endo*-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.55 (1H, s), 7.59 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 4.54-4.46 (2H, m), 4.18 (2H, br s), 3.38 (3H, s), 2.34-2.26 (2H, m), 1.92-1.83 (4H, m), 1.64-1.50 (5H, m), 1.08 (3H, s).	467, 469	3
116		6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.31 (1H, s), 7.58 (1H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 8.5 Hz), 4.14 (3H, s), 3.75-3.72 (2H, m), 3.29 (3H, s), 3.24-3.17 (2H, m), 2.90 (2H, d, *J* = 11.7 Hz), 2.78-2.64 (1H, m), 2.10-2.04 (2H, m), 1.76-1.69 (2H, m), 1.60-1.51 (1H, m).	473, 475	3
117		6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.27 (1H, s), 8.50 (1H, s), 7.56 (1H, d, *J* = 9.5 Hz), 7.29 (1H, d, *J* = 8.8 Hz), 4.19 (3H, s), 3.74-3.72 (2H, m), 3.29 (3H, s), 3.25-3.18 (2H, m), 2.93-2.87 (2H, br m), 2.77-2.68 (1H, m), 2.13-2.01 (2H, m), 1.78-1.69 (2H, m), 1.58-1.53 (1H, m).	439, 441	3

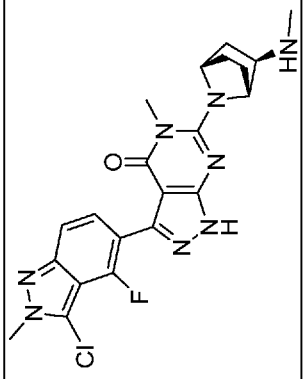
[0825]

[Table 10-41]

118		3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.37 (1H, s), 8.58 (1H, s), 7.60 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 4.51 (2H, q, *J* = 7.2 Hz), 4.33-4.29 (1H, m), 4.27-4.23 (1H, m), 3.39 (3H, s), 3.18-3.13 (1H, m), 2.27-2.19 (4H, m), 2.10-2.04 (1H, m), 1.91-1.84 (1H, m), 1.73-1.65 (1H, m), 1.54 (3H, t, *J* = 7.2 Hz), 1.51-1.44 (1H, m), 0.98-0.93 (1H, m).	453, 455	3
119		3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.61 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 4.33-4.29 (1H, m), 4.28-4.23 (1H, m), 4.17 (3H, s), 3.39 (3H, s), 3.18-3.12 (1H, m), 2.28-2.19 (4H, m), 2.10-2.05 (1H, m), 1.91-1.84 (1H, m), 1.72-1.65 (1H, m), 1.51-1.43 (1H, m), 0.98-0.93 (1H, m).	473, 475	3
120		3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.37 (1H, br s), 8.52 (1H, s), 7.58 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 4.32-4.29 (1H, m), 4.26-4.22 (4H, m), 3.39 (3H, s), 3.17-3.12 (1H, m), 2.25 (4H, br s), 2.11-2.05 (1H, m), 1.91-1.84 (1H, m), 1.72-1.64 (1H, m), 1.51-1.44 (1H, m), 0.97-0.93 (1H, m).	439, 441	3

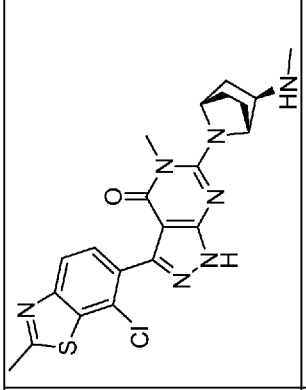
[0826]

[Table 10-42]

121		3-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.55-7.43 (2H, m), 4.32-4.21 (2H, m), 4.14 (3H, s), 3.41 (3H, s), 3.17-3.09 (1H, m), 2.27-2.15 (4H, m), 2.11-2.03 (1H, m), 1.92-1.81 (1H, m), 1.73-1.61 (1H, m), 1.51-1.40 (1H, m), 0.98-0.90 (1H, m).	457, 459	3
122		6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, br s), 9.53 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 7.70 (1H, d, *J* = 8.5 Hz), 3.78 (2H, br s), 3.41-3.23 (5H, m), 2.94 (2H, d, *J* = 11.7 Hz), 2.77-2.63 (1H, m), 2.15-2.03 (2H, m), 1.81-1.71 (2H, m), 1.62-1.53 (1H, m).	442, 444	3
123		3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.51 (1H, s), 9.54 (1H, s), 8.12 (1H, d, *J* = 8.2 Hz), 7.70 (1H, d, *J* = 8.2 Hz), 4.34-4.29 (1H, m), 4.28-4.24 (1H, m), 3.40 (3H, s), 3.18-3.11 (1H, m), 2.26-2.18 (4H, m), 2.11-2.05 (1H, m), 1.92-1.84 (1H, m), 1.73-1.65 (1H, m), 1.52-1.44 (1H, m), 0.98-0.93 (1H, m).	442, 444	3

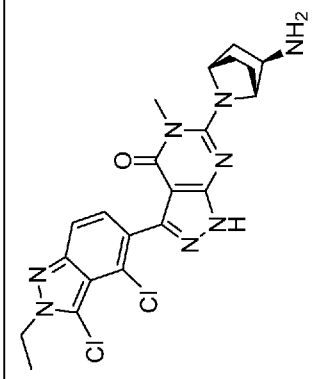
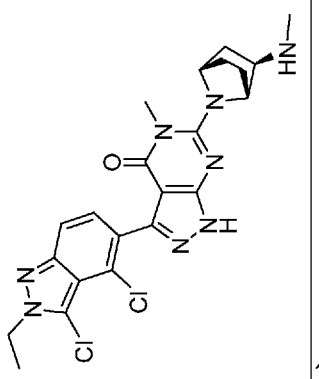
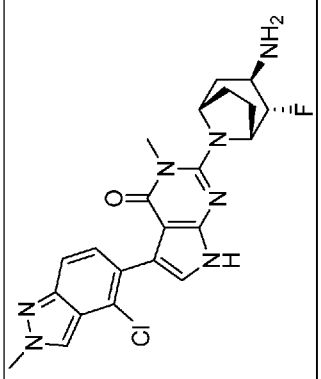
[0827]

[Table 10-43]

124		3-(7-chloro-2-methylbenzo[*d*]thiazol-6-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.48 (1H, s), 7.94 (1H, d, *J* = 8.2 Hz), 7.63 (1H, d, *J* = 8.2 Hz), 4.33-4.29 (1H, m), 4.28-4.23 (1H, m), 3.40 (3H, s), 3.17-3.11 (1H, m), 2.87 (3H, s), 2.24-2.18 (4H, m), 2.11-2.05 (1H, m), 1.91-1.83 (1H, m), 1.72-1.64 (1H, m), 1.51-1.44 (1H, m), 0.97-0.92 (1H, m).	456, 458	3
125		*rac*-6-((1*S*,4*S*,7*S*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.55-8.53 (1H, m), 7.58 (2H, d, *J* = 8.7 Hz), 7.29 (1H, d, *J* = 8.7 Hz), 4.54-4.45 (2H, m), 3.96-3.91 (1H, m), 3.79-3.72 (1H, m), 3.27 (3H, s), 3.07 (1H, d, *J* = 9.0 Hz), 2.20-2.12 (1H, m), 2.02-1.81 (4H, m), 1.53 (3H, t, *J* = 7.4 Hz), 1.40-1.32 (1H, m).	439, 441	3
126		*rac*-6-((1*S*,4*S*,7*S*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.59 (1H, d, *J* = 9.1 Hz), 7.31 (1H, d, *J* = 9.0 Hz), 4.15 (3H, s), 3.96-3.93 (1H, m), 3.79-3.73 (1H, m), 3.27 (3H, s), 3.09-3.05 (1H, m), 2.21-2.11 (1H, br m), 2.03-1.82 (4H, m), 1.45-1.30 (1H, m).	459, 461	3

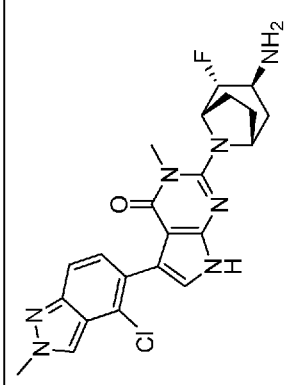
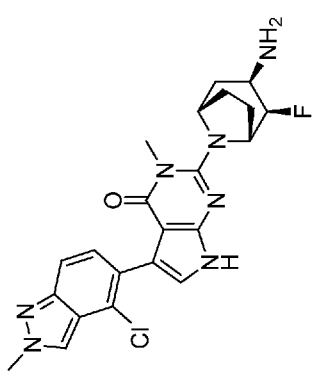
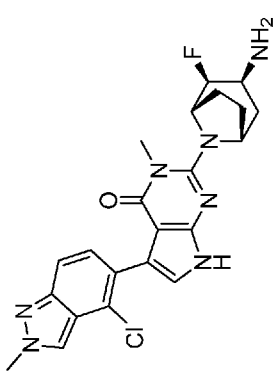
[0828]

[Table 10-44]

127		6-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.40 (1H, s), 7.63 (1H, d, *J* = 8.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 4.52 (2H, q, *J* = 7.3 Hz), 4.24-4.20 (1H, m), 4.10-4.06 (1H, m), 3.49-3.44 (1H, m), 3.38 (3H, s), 2.30-2.24 (1H, m), 2.22-2.16 (1H, m), 1.93-1.86 (1H, m), 1.72-1.64 (1H, m), 1.54-1.47 (4H, m), 0.93-0.87 (1H, m).	473, 475	3
128		3-(3,4-dichloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-6-((1*R*,2*R*,4*S*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.63 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 4.52 (2H, q, *J* = 7.2 Hz), 4.33-4.29 (1H, m), 4.27-4.23 (1H, m), 3.39 (3H, s), 3.16-3.12 (1H, m), 2.25-2.19 (4H, m), 2.10-2.05 (1H, m), 1.90-1.84 (1H, m), 1.72-1.65 (1H, m), 1.51-1.45 (4H, m), 0.98-0.93 (1H, m).	487, 489	3
129		2-((1*R*,2*S*,3*R*,5*S*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.65 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 6.97 (1H, s), 4.50-4.31 (2H, m), 4.19 (3H, s), 4.15-4.07 (1H, m), 3.45 (3H, s), 3.28-3.17 (1H, m), 2.45-2.28 (1H, m), 2.23-1.69 (4H, m), 1.49-1.37 (1 H, m).	456, 458	5

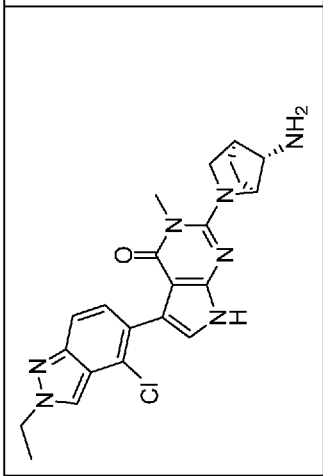
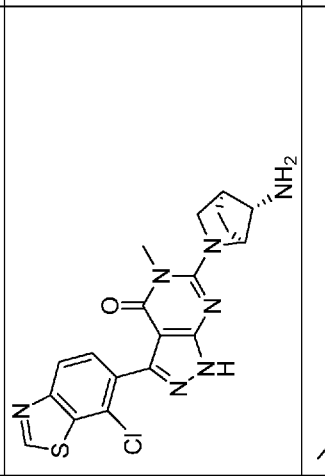
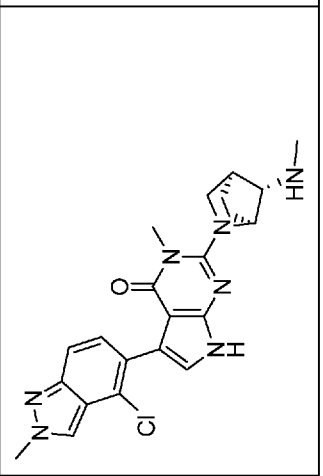
[0829]

[Table 10-45]

130		2-((1*S*,2*R*,3*S*,5*R*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.39 (1H, s), 7.47 (1H, dd, *J* = 8.8, 0.8 Hz), 7.31 (1H d, *J* = 8.8 Hz), 6.96 (1H, s), 4.48-4.45 (1H, m), 4.39-4.32 (2H, m), 4.18 (3H, s), 4.13-4.07 (1H, m), 3.44 (3H, s), 3.28-3.19 (1H, m), 2.18-1.75 (4H, m), 1.48-1.41 (1H, m).	456, 458	5
131		2-((1*R*,2*R*,3*R*,5*S*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, br s), 8.39 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 8.9 Hz), 6.97 (1H, s), 4.85 (1H, dt, *J* = 46.5, 5.2 Hz), 4.26-4.19 (1H, m), 4.18 (3H, s), 4.03 (1H, br s), 3.68-3.60 (1H, m), 3.40 (3H, s), 2.55-2.47 (1H, m), 2.21-2.07 (2H, m), 2.00-1.84 (2H, m), 1.75-1.66 (1H, m), 1.62-1.46 (1H, m).	456, 458	5
132		2-((1*S*,2*S*,3*S*,5*R*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, s), 8.39 (1H, s), 7.47 (1H, dd, *J* = 8.8, 0.9 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 6.98-6.96 (1H, m), 4.85 (1H, ddd, *J* = 46.4, 5.0, 5.0 Hz), 4.25-4.20 (1H, m), 4.18 (3H, s), 4.06-4.01 (1H, m), 3.66-3.62 (1H, m), 3.40 (3H, s), 2.55-2.44 (1H, m), 2.19-2.09 (2H, m), 1.98-1.86 (2H, m), 1.74-1.67 (1H, m).	456, 458	5

[0830]

[Table 10-46]

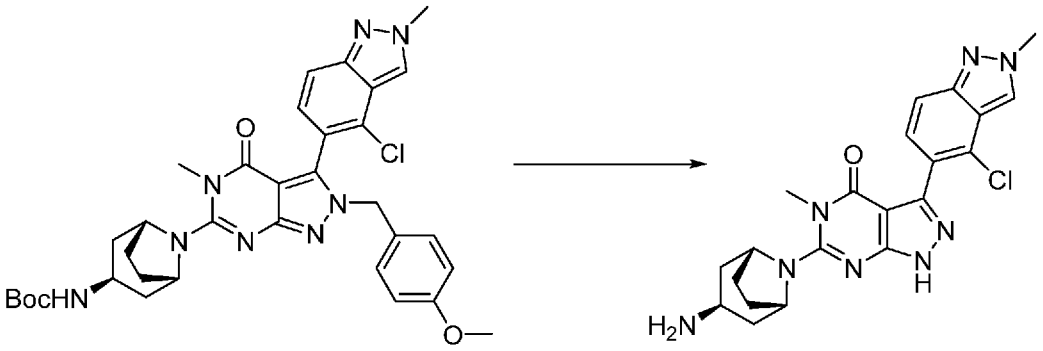
133		*rac*-2-((1*S*,4*S*,7*S*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.42 (1H, s), 7.47 (1H, dd, *J* = 9.0, 0.7 Hz), 7.30 (1H, d, *J* = 9.0 Hz), 6.87 (1H, s), 4.46 (2H, q, *J* = 7.3 Hz), 3.86-3.66 (2H, m), 3.30-3.26 (3H, m), 3.17-3.14 (1H, m), 3.04-2.98 (1H, m), 2.18-2.11 (1H, m), 2.01-1.82 (3H, m), 1.51 (3H, t, *J* = 7.1 Hz), 1.40-1.31 (1H, m).	438, 440	2
134		*rac*-((1*S*,4*S*,7*S*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(7-chlorobenzo[*d*]thiazol-6-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 9.52 (1H, s), 8.10 (1H, d, *J* = 8.4 Hz), 7.68 (1H, d, *J* = 8.4 Hz), 3.97-3.92 (1H, br), 3.81-3.72 (1H, m), 3.28 (3H, s), 3.16 (1H, d, *J* = 5.2 Hz), 3.08 (1H, d, *J* = 9.0 Hz), 2.21-2.11 (1H, m), 2.04-1.29 (5H, m).	428, 430	3
135		*rac*-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-((1*S*,4*S*,7*S*)-7-(methylamino)-2-azabicyclo[2.2.1]heptan-2-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, s), 8.39 (1H, s), 7.47 (1H, dd, *J* = 8.9, 0.8 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.89 (1H, d, *J* = 2.4 Hz), 4.19 (3H, s), 4.07-4.03 (1H, m), 3.77-3.72 (1H, m), 3.30 (3H, s), 3.05 (1H, d, *J* = 9.2 Hz), 2.94 (1H, s), 2.36-2.32 (1H, m), 2.30 (3H, s), 1.96-1.78 (3H, m), 1.38-1.33 (1H, m).	438, 440	2

[0831] The following procedures are illustrative for general methods used in the preparation

of Examples listed in Table 11 below.

[0832] Method 6: endo-6-[3-Amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0833] [Chem.161]

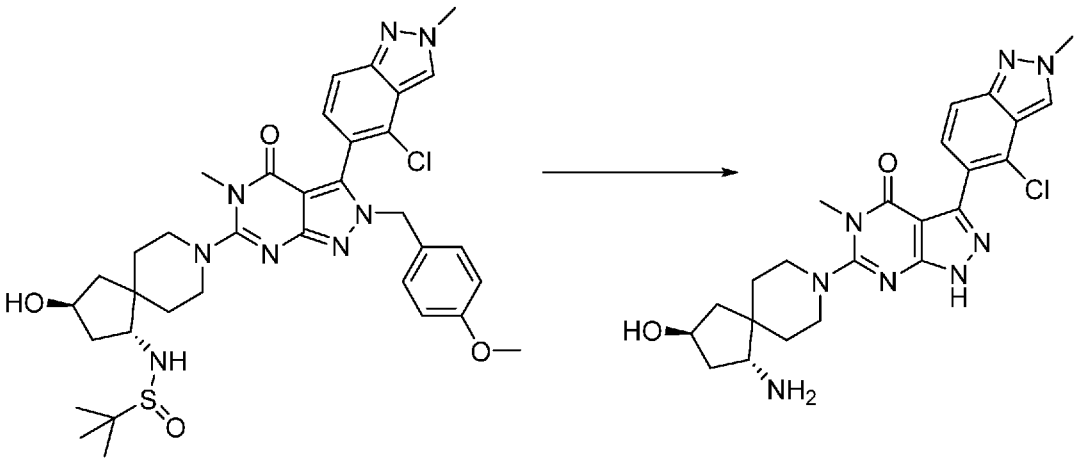


[0834] Trifluoromethanesulfonic acid (2 mL, 22.5 mmol) was added dropwise to tert-butyl N-[endo-8-[3-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate (100 mg, 0.15 mmol) in TFA (0.935 mL, 12.14 mmol) and DCM (10 mL). The resulting purple mixture was stirred at RT for 1 hour and 30 minutes and then evaporated in vacuo to a red liquid, which was added dropwise to saturated sodium carbonate (50 mL). The aqueous layer was extracted with DCM (2 x 50 mL), and the organic layer recovered through a Phase Separator and evaporated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-10% MeOH/DCM) to afford a first crop of crude product (38 mg). The crude product was purified by preparative HPLC to afford the title compound (15 mg, 0.03 mmol, 22% yield) as a clear colourless solid.

[0835] Method 7: 6-[(1R,3S)-1-Amino-3-hydroxy-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0836]

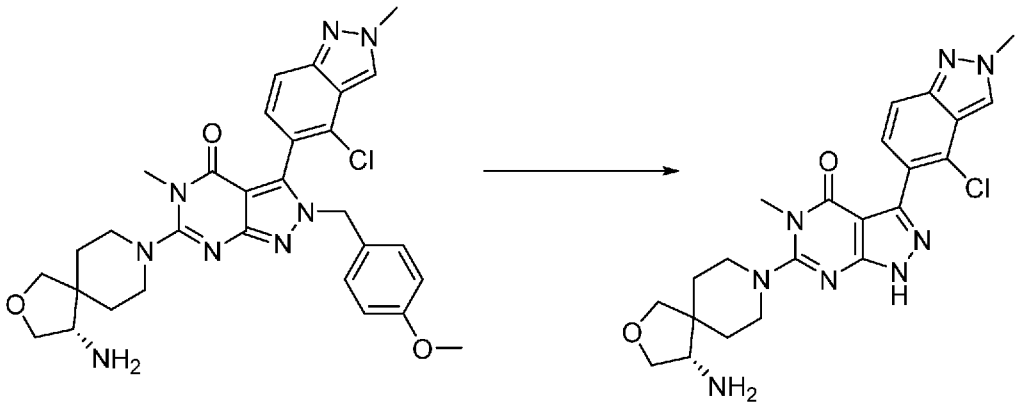
[Chem.162]



[0837] N-[(1R,3S)-8-[3-(4-Chloro-2-methyl-2H-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-4-oxo-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-3-hydroxy-8-azaspiro[4.5]decan-1-yl]-2-methylpropane-2-sulfinamide (123 mg, 0.17 mmol) was dissolved in methanol (0.2 mL, 4.94 mmol) and then HCl (4M in 1,4-dioxane) (0.435 mL, 1.74 mmol) was added and the reaction was stirred at 50 °C for 1 hour. The reaction mixture was concentrated to give very pale brown solid. DCM (2 mL) and trifluoromethanesulfonic acid (0.154 mL, 1.739 mmol) were added to the solid and the resultant purple solution was stirred at room temperature for 2 hours. The mixture was loaded onto SCX (~5 g) and eluted with DCM, MeOH, and then 0.7M NH_3 in MeOH. The NH_3 in MeOH fractions were concentrated to give the title compound (70 mg, 0.14 mmol, 81 % yield).

[0838] Method 8:
6-[(4S)-4-Amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0839] [Chem.163]



[0840] 6-[(4S)-4-Amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(4-methoxyphenyl)methyl]-5-methyl-2H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-

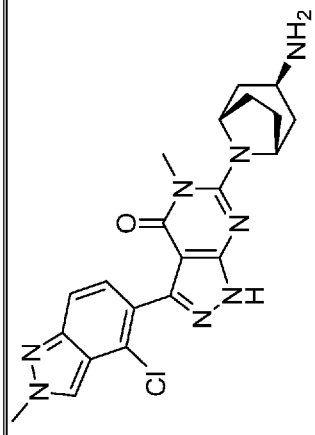
one (145 mg, 0.25 mmol) was dissolved in DCM (2 mL) and trifluoromethanesulfonic acid (0.22 mL, 2.46 mmol) was added. The mixture was stirred at room temperature for 2 hours. The mixture was then loaded on SCX (~5 g) and eluted with DCM, MeOH, and then 0.7 M NH_3 in MeOH. The NH_3 in MeOH fractions were concentrated to give the title compound (83 mg, 0.18 mmol, 72% yield).

[0841] By following methods similar and/or analogous to those described for method 6 - 8 the title compounds in Table 11 were either isolated directly as the free base or as the appropriate salt without further purification. Alternatively, compounds were purified (e.g. using mass-directed preparative HPLC, chromatography, crystallization or trituration). In some cases, the coompound was isolated as the hydrochloride salt; by treating a solution of the final compound (e.g. in MeOH) with excess HCl (2N HCl in Et_2O) and then evaporating to dryness.

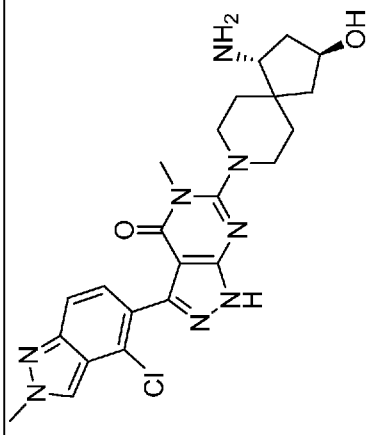
[0842]

[Table 11-1]

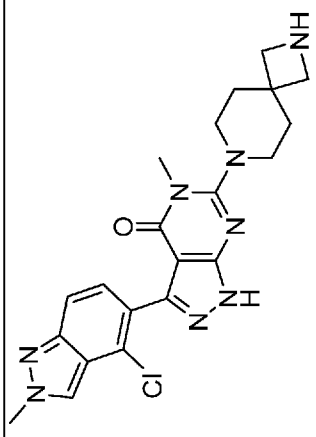
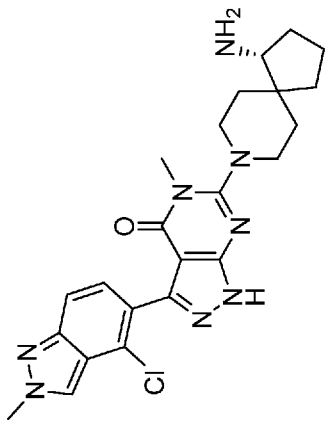
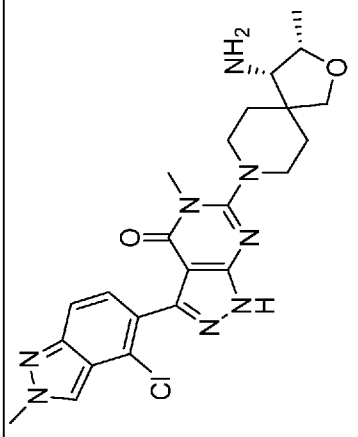
TABLE 11

Example	Structure	Name	NMR Data	[M+H]+ m/z	Method
136		*endo*-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.37 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 4.34-4.28 (m, 2H), 4.26 (s, 3H), 3.53 (s, 3H), 3.31-3.25 (m, 1H), 2.47 (app. dt, *J* = 12.7, 6.1 Hz, 2H), 2.23-2.16 (m, 2H), 2.11-2.03 (m, 2H), 1.67 (app. d, *J* = 14.4 Hz, 2H).	439	6
137		3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.39 (s, 1H), 8.53 (s, 1H), 7.60 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 4.23 (s, 3H), 4.12 (br s, 2H), 3.44 (s, 3H), 3.04 (d, *J* = 11.9 Hz, 2H), 2.73 (d, *J* = 10.8 Hz, 2H), 2.02-1.83 (m, 4H).	425	6, isolated by SCX chromatography

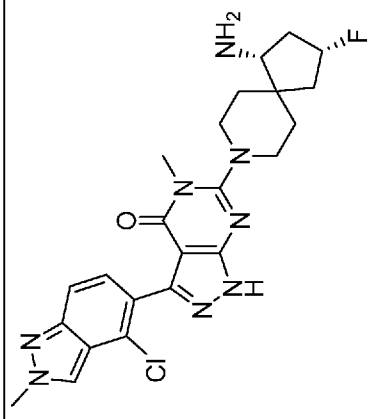
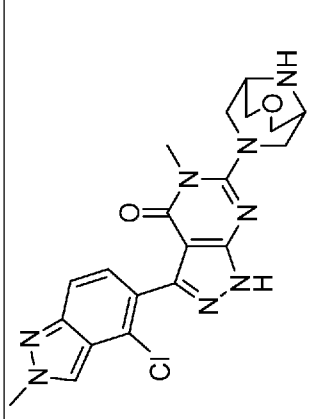
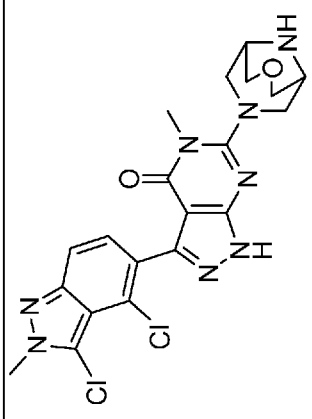
[0843] [Table 11-2]

138		6-[(1*R*,3*S*)-1-amino-3-hydroxy-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.54 (s, 1H), 7.60 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 4.50 (br s, 1H), 4.23 (s, 3H), 4.20-4.13 (m, 1H), 3.48-3.39 (m, 2H), 3.38 (s, 3H), 3.06-2.99 (m, 1H), 2.95-2.84 (m, 2H), 2.09 (dd, *J* = 13.6, 7.1 Hz, 1H), 1.88-1.74 (m, 2H), 1.74-1.60 (m, 2H), 1.43-1.32 (m, 2H), 1.23 (app. d, *J* = 12.5 Hz, 1H).	483	7
139		6-[(4*S*)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.48 (br s, 1H), 8.53 (s, 1H), 7.59 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 3H), 3.96 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.69 (d, *J* = 8.4 Hz, 1H), 3.60 (d, *J* = 8.4 Hz, 1H), 3.38 (s, 3H), 3.09 (t, *J* = 6.0 Hz, 1H), 3.00-2.90 (m, 2H), 1.81 (ddd, *J* = 13.5, 10.9, 3.5 Hz, 1H), 1.72 (ddd, *J* = 13.8, 10.8, 3.8 Hz, 1H), 1.55-1.44 (m, 2H).	469	8
140		*exo*-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.52 (s, 1H), 7.58 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 4.24-4.18 (m, 2H), 4.22 (s, 3H), 3.41 (s, 3H), 3.07-2.98 (m, 1H), 2.02-1.92 (m, 2H), 1.84-1.76 (m, 2H), 1.73-1.67 (m, 2H), 1.53 (app. t, *J* = 11.0 Hz, 2H).	439	8

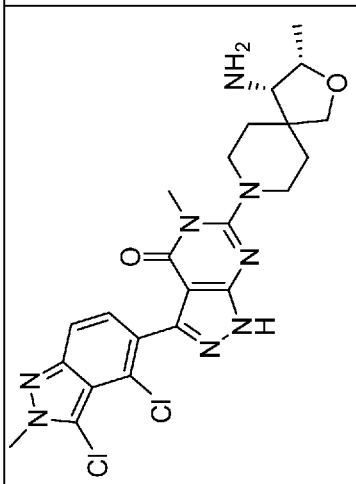
[0844] [Table 11-3]

141		3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-6-[2,7-diazaspiro[3.5]nonan-7-yl]-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 7.59 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 3H), 3.36 (s, 3H), 3.13-3.04 (m, 4H), 1.90-1.78 (m, 4H).	439	8
142		6-[(1*R*)-1-amino-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, Methanol-d_4) δ: 8.38 (s, 1H), 7.59 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 4.26 (s, 3H), 3.56-3.46 (m, 2H), 3.50 (s, 3H), 3.06 (dq, *J* = 12.6, 2.5 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 1H), 2.04 (dddd, *J* = 13.2, 9.1, 7.1, 4.5 Hz, 1H), 1.92-1.81 (m, 2H), 1.84-1.71 (m, 2H), 1.72-1.61 (m, 1 H), 1.61-1.52 (m, 1 H), 1.52-1.42 (m, 2H), 1.41-1.35 (m, 1 H).	467	8
143		6-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.47 (br s, 1H), 8.53 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 3H), 4.12-4.03 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.51 (d, *J* = 8.5 Hz, 1H), 3.37 (s, 3H), 3.09-3.01 (m, 1H), 3.01-2.91 (m, 2H), 1.92-1.83 (m, 1H), 1.82-1.73 (m, 1H), 1.67-1.60 (m, 1H), 1.60-1.53 (m, 1 H), 1.10 (d, *J* = 6.3 Hz, 3H).	483	8

[0845] [Table 11-4]

144		6-[(1*R*,3*R*)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one hydrochloride salt	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 8.20 (br s, 3H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 5.32-5.12 (m, 1H), 4.23 (s, 3H), 3.55 (app. d, *J* = 12.4 Hz, 1H), 3.45 (app. d, *J* = 12.4 Hz, 1H), 3.39 (s, 3H), 3.31-3.24 (m, 1H), 3.04-2.89 (m, 2H), 2.27 (d, *J* = 14.8 Hz, 1H), 2.22 (d, *J* = 14.8 Hz, 1H), 2.10-1.90 (m, 3H), 1.81-1.68 (m, 2H), 1.41 (app. d, *J* = 12.9 Hz, 1H).	485	8
145		3-(4-chloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.44 (br s, 1H), 8.53 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 4.23 (s, 3H), 3.93 (app. d, *J* = 11.0 Hz, 2H), 3.83 (app. d, *J* = 11.0 Hz, 2H), 3.62 (app. d, *J* = 12.0 Hz, 2H), 3.48 (s, 3H), 3.26 (app. d, *J* = 12.0 Hz, 2H), 2.90 (br. s, 2H).	441	8
146		3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one hydrochloride salt	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.59 (br s, 1H), 9.93 (br s, 1H), 9.81 (br s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 4.17 (s, 3H), 4.15 (app. d, *J* = 12.8 Hz, 2H), 4.08 (app. d, *J* = 12.8 Hz, 2H), 3.85 (app. d, *J* = 13.3 Hz, 2H), 3.67 (app. br s, 2H), 3.56 (app. d, *J* = 13.3 Hz, 2H), 3.48 (s, 3H).	475	8

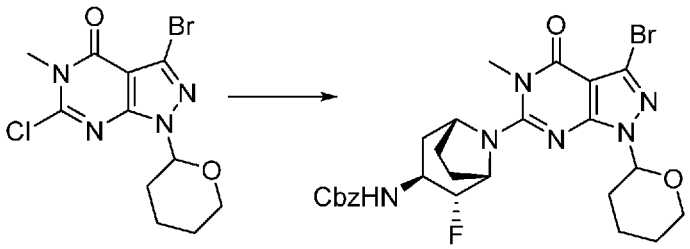
[0846] [Table 11-5]

147		6-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one hydrochloride salt	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.21 (br s, 3H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 4.25-4.18 (m, 1H), 4.17 (s, 3H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.65 (d, *J* = 9.0 Hz, 1H), 3.54-3.46 (m, 1H), 3.46-3.40 (m, 2H), 3.39 (s, 3H), 2.97-2.85 (m, 2H), 2.00-1.89 (m, 2H), 1.79-1.70 (m, 1H), 1.69-1.60 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H).	517	8
148		6-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-5-methyl-1*H*,4*H*,5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one hydrochloride salt	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.48 (s, 1H), 8.58 (s, 1H), 8.18 (br s, 3H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 4.52 (q, *J* = 7.3 Hz, 2H), 4.25-4.18 (m, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.66 (d, *J* = 9.0 Hz, 1H), 3.54-3.46 (m, 1H), 3.46-3.40 (m, 2H), 3.39 (s, 3H), 2.91 (app. q, *J* = 11.6 Hz, 2H), 2.00-1.89 (m, 2H), 1.75 (app. d, *J* = 13.6 Hz, 1H), 1.65 (app. d, *J* = 12.8 Hz, 1H), 1.54 (t, *J* = 7.3 Hz, 3H), 1.24 (d, *J* = 6.5 Hz, 3H).	497	8

[0847] Example 149:
6-[(1S,2R,3S,5R)-3-Amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0848] Step 1: Benzyl N-[(1S,2R,3S,5R)-8-[3-bromo-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

[0849] [Chem.164]

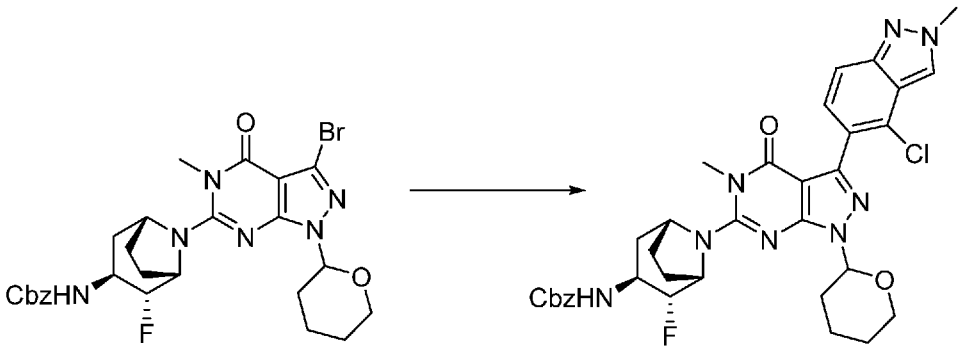


[0850] A mixture of 3-bromo-6-chloro-5-methyl-1-(oxan-2-yl)-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one (0.15 g, 0.43 mmol), benzyl N-[(1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (0.144 g, 0.52 mmol) and diisopropylethylamine (0.38 mL, 2.16 mmol) in NMP (10 mL) was heated to 130 °C for 30 min. The reaction was cooled to ambient temperature, diluted in TBME/DCM 1:1 (20 mL) and washed with aqueous 1M LiCl (2 x 10 mL). Aqueous layers were combined and extracted with 10 mL DCM. The combined organic extracts were washed with HCl (1 M, 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford benzyl N-[(1S,2R,3S,5R)-8-[3-bromo-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (310 mg, 0.40 mmol, 94 % yield) as an off white solid. MS: $[M+H]^+ = 591$.

[0851] Step 2: Benzyl N-[(1S,2R,3S,5R)-8-[3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

[0852]

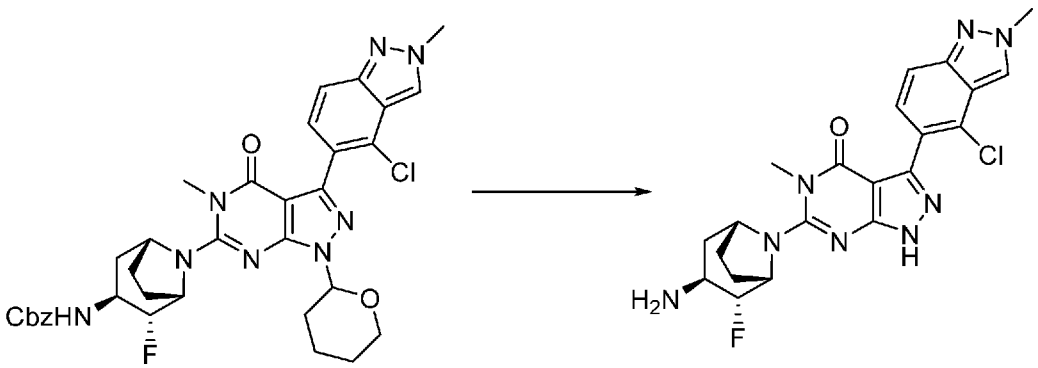
[Chem.165]



[0853] A mixture of benzyl N-[(1S,2R,3S,5R)-8-[3-bromo-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (0.3 g, 0.51 mmol), 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (0.18 g, 0.61 mmol), Na_2CO_3 (0.16 g, 1.53 mmol) and $PdCl_2$(dppf).DCM (0.042 g, 0.05 mmol) in1,4-dioxane (5 mL) and water (0.6 mL) was degassed under a flow of N_2. The reaction was heated to 100 °C for 2 h. Once cooled to ambient temperature, the reaction mixture was partitioned with 2 mL water and 10 mL DCM, the organic layer separated, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% MeOH/DCM) to afford product as a brown solid. The crude product was purified by chromatography on silica gel (12 g gold cartridge, 2-4% (0.7 M Ammonia/MeOH)/DCM) to afford benzyl N-[(1S,2R,3S,5R)-8-[3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (0.07 g, 0.10 mmol, 20 % yield) as a white powder. MS: $[M+H]^+$ = 675.

[0854] Step 3: 6-[(1S,2R,3S,5R)-3-Amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one

[0855] [Chem.166]

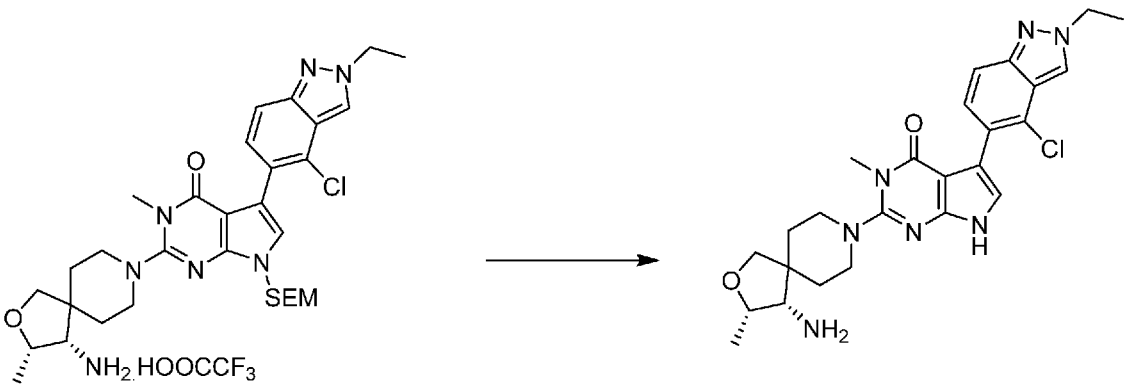


[0856] A solution of benzyl N-[(1S,2R,3S,5R)-8-[3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1-(oxan-2-yl)-4-oxo-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-6-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (0.07 g, 0.10 mmol) in TFA (1.04 mL, 13.5 mmol) was treated with trifluoromethanesulfonic acid (0.11 mL, 1.24 mmol) and stirred at RT for 5 minutes. The reaction mixture was quenched by adding it dropwise to saturated aqueous sodium carbonate (10 mL), then it was diluted with LiCl 0.1 M (50 mL), and extracted with DCM (3x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude material. The crude product was purified by chromatography on silica gel (4 g gold cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM) to afford 6-[(1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one as a colourless glass. Product was treated with 5 mL 2M HCl in ether, sonicated for 10 min and filtered to afford 6-[(1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one hydrochloride (10 mg, 0.02 mmol, 19 % yield) as a white powder. MS: $[M+H]^+ = 457$.

^{1}H NMR (500 MHz, Methanol-d_4) δ: 8.48 (s, 1H), 7.64 (dd, J = 8.8, 0.9 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 4.75-4.68 (m, 1H), 4.64 (dd, J = 16.7, 7.7 Hz, 1H), 4.49 (t, J = 7.8 Hz, 1H), 4.30 (s, 3H), 3.75-3.65 (m, 1H), 3.60 (s, 3H), 2.91 (q, J = 11.5, 11.1 Hz, 1H), 2.48 (d, J = 11.8 Hz, 1H), 2.12 (dq, J = 12.5, 6.4 Hz, 1H), 1.91 (dt, J = 14.4, 8.0 Hz, 1H), 1.68 (t, J = 10.0 Hz, 1H), 1.44-1.35 (m, 1H).

[0857] Method 9:
2-[(3S,4S)-4-Amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

[0858] [Chem.167]



[0859] TFA (1 mL) was added to a solution of 2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2

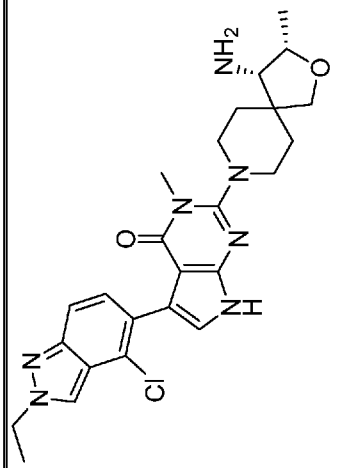
H-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one (256 mg, 1.82 mmol) in DCM (1 mL) and the mixture was stirred at RT for 18 h. The mixture was concentrated and azeotroped with toluene twice, MeOH (2 mL) and ethylenediamine (0.23 mL, 3.46 mmol) were added to the residue and it was stirred at RT for 5 h. The reaction mixture was concentrated, suspended in MeOH and the solid collected by filtration to afford the title compound (24 mg, 0.048 mmol, 14%).

[0860] The compounds shown in Table 12 were prepared using methods similar to those described in method 9. The compounds could be isolated directly, by trituration/precipitation from solution, or were purified (e.g. using mass-directed preparative HPLC, chromatography, crystallization). In some cases, the compound was isolated as the hydrochloride salt; by treating a solution of the final compound (e.g. in MeOH) with excess HCl (2N HCl in Et_2O) and then evaporating to dryness.

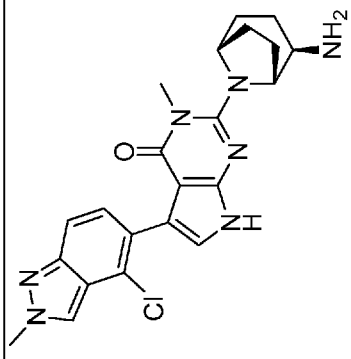
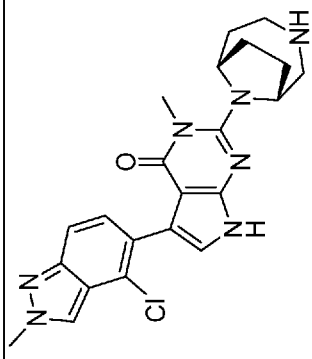
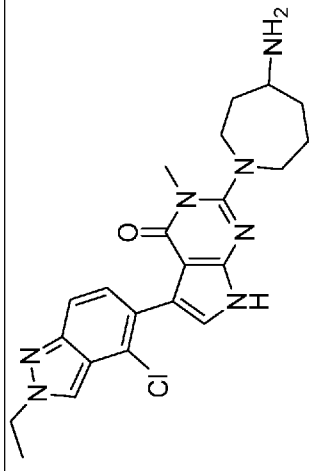
[0861]

[Table 12-1]

TABLE 12:

Example	Structure	Name	NMR Data	$[M+H]^+$ m/z	Method
150		2-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.74 (1H, s), 8.45 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.01 (1H, s), 4.49 (2H, q), 4.12-4.03 (1H, m), 3.67 (1H, d), 3.50 (1H, d), 3.40 (3H, s), 3.29-3.16 (2H, m), 3.02-2.84 (3H, m), 1.94-1.82 (1H, m), 1.82-1.71 (1H, m), 1.71-1.57 (2H, m), 1.53 (3H, t), 1.33 (2H, br s), 1.10 (3H, d).	496	9
151		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-(1,4-diazepan-1-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (1H, s), 7.54 (1H, dd), 7.48 (1H, d), 7.06 (1H, s), 4.55 (2H, q), 3.80 (2H, t), 3.65-3.52 (7H, m), 3.46 (2H, t), 2.26-2.17 (2H, m), 1.65 (3H, t).	426	9

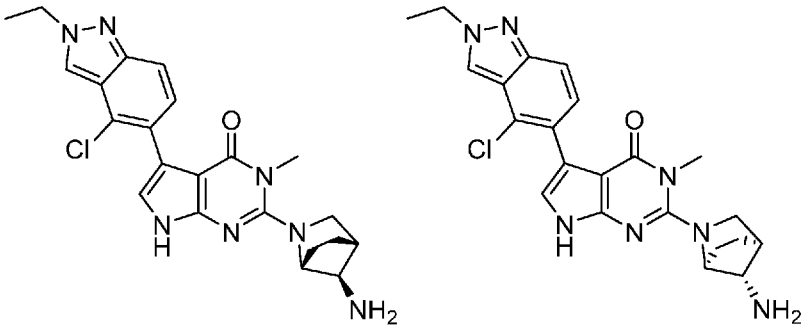
[0862] [Table 12-2]

152		*rac*-2-[(1*R*,2*R*,5*R*)-2-amino-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.26-10.98 (1H, m), 8.40 (1H, s), 7.49 (1H, dd), 7.34 (1H, d), 6.96 (1H, s), 4.20 (3H, s), 4.11-4.04 (1H, m), 3.87-3.80 (1H, m), 3.44 (3H, s), 3.05-2.98 (1H, m), 2.04-1.92 (2H, m), 1.89-1.74 (2H, m), 1.71-1.64 (1H, m), 1.57-1.47 (2H, m), 1.28-1.14 (1H, m).	438	9
153		*rac*-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(1*R*,6*S*)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.25-10.77 (1H, m), 8.40 (1H, s), 7.49 (1H, dd), 7.33 (1H, d), 6.96 (1H, s), 4.46-4.40 (1H, m), 4.28 (1H, t), 4.20 (3H, s), 3.44 (3H, s), 3.02-2.94 (1H, m), 2.87-2.69 (3H, m), 2.18-1.97 (3H, m), 1.84-1.74 (2H, m), 1.53-1.43 (1H, m).	438	9
154		*rac*-2-(4-aminoazepan-1-yl)-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (1H, d), 8.45 (1H, d), 8.02 (3H, br s), 7.51 (1H, dd), 7.32 (1H, d), 6.99 (1H, d), 4.49 (2H, q), 3.56-3.45 (1H, m), 3.45-3.24 (7H, m), 2.22-2.11 (1H, m), 2.10-2.00 (1H, m), 2.00-1.84 (2H, m), 1.84-1.67 (2H, m), 1.53 (3H, t).	440	9

[0863] Example 155 and 156

rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (Example 155) and rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (Example 156)

[0864] [Chem.168]



[0865] rac-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one was dissolved as a 2.0 mg/mL ethanol/DMSO/$CHCl_3$ = 1/1/3 solution, and separation was performed under the following conditions.

Column: Daicel CHIRALPAK IG 2 x 25 cm

Mobile phase: hexane/2-propanol = 40/60

Flow rate: 25 mL/min

[0866] Retention time of each isomer:

rel-2-((1R,4R,7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one: 8.15 minutes

rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one: 13.5 minutes.

[0867] Chiral analysis conditions:

Column: CHIRALPAK IG 4.6 x 150 mm

Mobile phase: hexane/2-propanol = 40/60

Flow rate: 1.0 mL/min

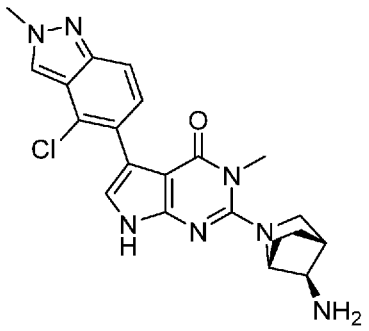
[0868] Retention time of each isomer:

rel-2-((1R,4R,7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one: 7.406 minutes. MS: $[M+H]^+$ = 438, 440. ^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.42 (1H, s), 7.47 (1H, dd, J = 9.0, 0.7 Hz), 7.30 (1H, d, J = 9.0 Hz), 6.87 (1H, s), 4.46 (2H, q, J = 7.3 Hz), 3.86-3.66 (2H, m), 3.30-3.26 (3H, m), 3.17-3.14 (1H, m), 3.04-2.98 (1H, m), 2.18-2.11 (1H, m), 2.01-1.82 (3H, m), 1.51 (3H, t, J = 7.1 Hz), 1.40-1.31 (1H, m).

rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one: 11.246 minutes. MS: $[M+H]^+$ = 438, 440. ^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.42 (1H, s), 7.47 (1H, dd, J = 9.0, 0.7 Hz), 7.30 (1H, d, J = 9.0 Hz), 6.87 (1H, s), 4.46 (2H, q, J = 7.3 Hz), 3.86-3.66 (2H, m), 3.30-3.26 (3H, m), 3.17-3.14 (1H, m), 3.04-2.98 (1H, m), 2.18-2.11 (1H, m), 2.01-1.82 (3H, m), 1.51 (3H, t, J = 7.1 Hz), 1.40-1.31 (1H, m).

[0869] Example 157: rel-2-((1R,4R,7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0870] [Chem.169]



[0871] Step 1

rac-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (200 mg, 0.472 mmol) was dissolved in $CHCl_3$/MeOH = 4/1 (5.0 mL). Di-tert-butyl dicarbonate (206 mg, 0.944 mmol) dissolved in $CHCl_3$ (1.0 mL) was added thereto at 0 °C, followed by stirring at RT for 3 h. The solvent was distilled off, and the residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/EtOAc) to give rac-tert-butyl ((1S,4S,7S)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate. rac-tert-Butyl ((1S,4S,7S) -2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate was dissolvedas a 25 mg/mL ethanol/$CHCl_3$ = 1/1 solution, and separation was performed under the following conditions.

[0872] Column: Daicel CHIRALPAK IG 2 x 25 cm
Mobile phase: hexane/2-propanol = 45/55
Flow rate: 25 mL/min

[0873] Retention time of each isomer:

rel-tert-Butyl ((1R,4R,7R)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 7.5 minutes

rel-tert-Butyl ((1S,4S,7S)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 12.5 minutes.

[0874] Chiral analysis conditions:

Column: CHIRALPAK IG 4.6 x 150 mm

Mobile phase: hexane/2-propanol = 40/60

Flow rate: 1.0 mL/min

[0875] Retention time of each isomer:

rel-tert-Butyl ((1R,4R,7R)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 5.668 minutes

rel-tert-Butyl ((1S,4S,7S)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 9.407 minutes.

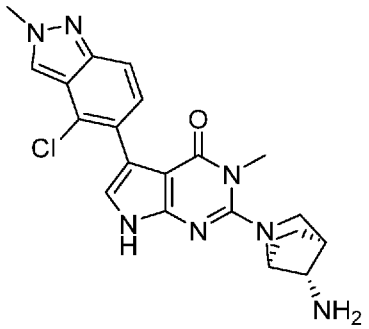
[0876] Step 2

rel-tert-Butyl ((1R,4R,7R)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (81.5 mg, 0.155 mmol) and TFA (1.0 mL) were dissolved in methanol (1.0 mL). The mixture was stirred at RT for 30 minutes. The solvent was distilled off, and the residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/EtOAc) to give the title compound. MS: $[M+H]^+$ = 424, 426. ^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.37 (1H, s), 7.46 (1H, d, J = 8.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.88 (1H, s), 4.18 (3H, s), 3.84 (1H, s), 3.73-3.65 (1H, m), 3.28-3.23 (4H, m), 3.02 (1H, d, J = 8.8 Hz), 2.15 (1H, s), 2.01-1.83 (3H, m), 1.74-1.49 (2H, m), 1.42-1.31 (1H, m).

[0877] Example 158: rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0878]

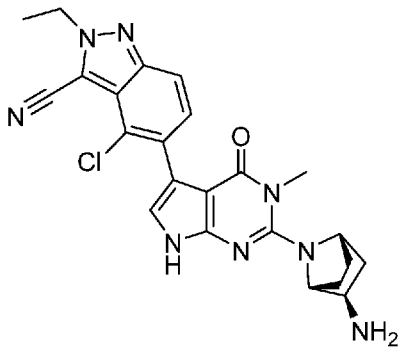
[Chem.170]



[0879] In accordance with Step 2 of Example 157, except that rel-tert-butyl ((1S,4S,7S)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate obtained in Step 1 of Example 157 was used in place of rel-tert-butyl ((1R,4R,7R)-2-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate, the title compound was obtained. MS: $[M+H]^+$ = 424, 426. ^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.37 (1H, s), 7.46 (1H, d, J = 8.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.88 (1H, s), 4.18 (3H, s), 3.84 (1H, s), 3.73-3.65 (1H, m), 3.28-3.23 (4H, m), 3.02 (1H, d, J = 8.8 Hz), 2.15 (1H, s), 2.01-1.83 (3H, m), 1.74-1.49 (2H, m), 1.42-1.31 (1H, m).

[0880] Example 159:
5-(2-((1R,2R,4S)-2-Amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2-ethyl-2H-indazole-3-carbonitrile

[0881] [Chem.171]

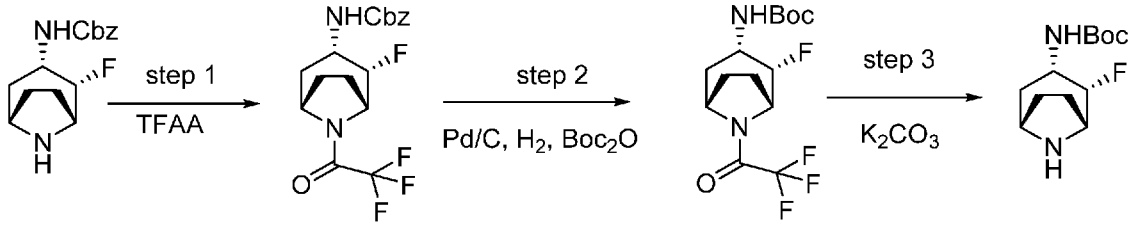


[0882] tert-Butyl ((1R,2R,4S)-7-(5-(4-chloro-3-cyano-2-ethyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (50 mg, 0.072 mmol) was dissolved in N,N-dimethylformamide (0.5 mL). To the solution was added tetrabutylammonium fluoride (1 M in THF, 0.22 mL, 0.22 mmol) and stirred at 80 °C for 1 d. To the

mixture was added 5 M NaOH aq. (0.072 mL, 0.36 mmol, 5 mol/L), and stirred at RT for 1 h. The mixture was concentrated in vacuo and the residue was purified by r-HPLC. The obtained fractions were concentrated in vacuo, and the residue was dissolved in acetonitrile (1.0 mL). To the solution was added sodium iodide (5.8 mg, 0.039 mmol) and chlorotrimethylsilane (0.0031 mL, 0.024 mmol), and the mixture was stirred at RT for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on NH silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (4.9 mg). MS: $[M+H]^+$ = 463, 465. ^{1}H-NMR (DMSO-d_6) δ: 11.78 (1H, br s), 7.79 (1H, d, J = 8.8 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.07 (1H, s), 4.68 (2H, q, J = 7.2 Hz), 4.15 (1H, br t, J = 4.8 Hz), 4.02 (1H, br t, J = 4.4 Hz), 3.53-3.45 (1H, m), 3.40 (3H, s), 2.36-2.21 (1H, m), 2.20-2.09 (1H, m), 1.96-1.84 (1H, m), 1.75-1.64 (1H, m), 1.58 (3H, t, J = 7.2 Hz), 1.54-1.44 (1H, m), 0.97-0.87 (1H, m).

[0883] Preparation 117: tert-Butyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

[0884] [Chem.172]



[0885] Step 1: Benzyl N-[(1R,2S,3S,5S)-2-fluoro-8-(2,2,2-trifluoroacetyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate

To a solution of benzyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate (1.0 g, 3.6 mmol) and Et_3N (1.0 mL, 7.2 mmol) in DCM (15 mL) was added trifluoroacetic anhydride (0.53 mL, 3.78 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction was diluted with DCM and sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with DCM, the organic phase was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography on silica gel (gradient elution, 0-60%, EtOAc/petrol), to give the title compound (1.32 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.47 (1H, d), 7.42-7.25 (5H, m), 5.05 (2H, s), 4.88-4.60 (2H, m), 4.59-4.33 (1H, m), 4.01-3.85 (1H, m), 3.35 (1H, s), 2.13-2.01 (1H, m), 1.99-1.68 (5H, m).

[0886] Step 2: tert-Butyl N-[(1R,2S,3S,5S)-2-fluoro-8-(2,2,2-trifluoroacetyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate

To a solution of benzyl N-

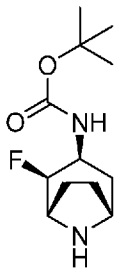
[(1R,2S,3S,5S)-2-fluoro-8-(2,2,2-trifluoroacetyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (1.32 g, 3.53 mmol) in ethanol (15 mL) were added di-tert-butyl dicarbonate (1.0 g, 4.58 mmol) and Pd/C (10%, 0.13 g) and the mixture was hydrogenated for 6 h. The reaction was filtered and the filtrate evaporated. The residue was purified by column chromatography on silica gel (gradient elution, 0-40%, EtOAc/petrol), to give the title compound (1.04 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.98 (1H, d), 4.89-4.21 (3H, m), 3.86 (1H, d), 2.19-1.53 (6H, m), 1.39 (9H, s).

[0887] Step 3: tert-Butyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

To a solution of tert-butyl N-[(1R,2S,3S,5S)-2-fluoro-8-(2,2,2-trifluoroacetyl)-8-azabicyclo[3.2.1]octan-3-yl]carbamate (1.04 g, 3.07 mmol) in MeOH (15 mL) and H_2O (3 mL) was added K_2CO_3 (2.11 g, 15.35 mmol) and the mixture was stirred overnight. The MeOH was evaporated, H_2O was added and the product was extracted with DCM. The organic phase was dried ($MgSO_4$), filtered and evaporated, to give the title compound (0.733 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.75 (1H, d), 4.34 (1H, d), 3.72-3.52 (1H, m), 3.46 (1H, s), 3.35 (1H, s), 2.14 (1H, s), 1.69 (2H, d), 1.60-1.25 (13H, m).

[0888] Preparation 118: tert-Butyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate

[0889] [Chem.173]

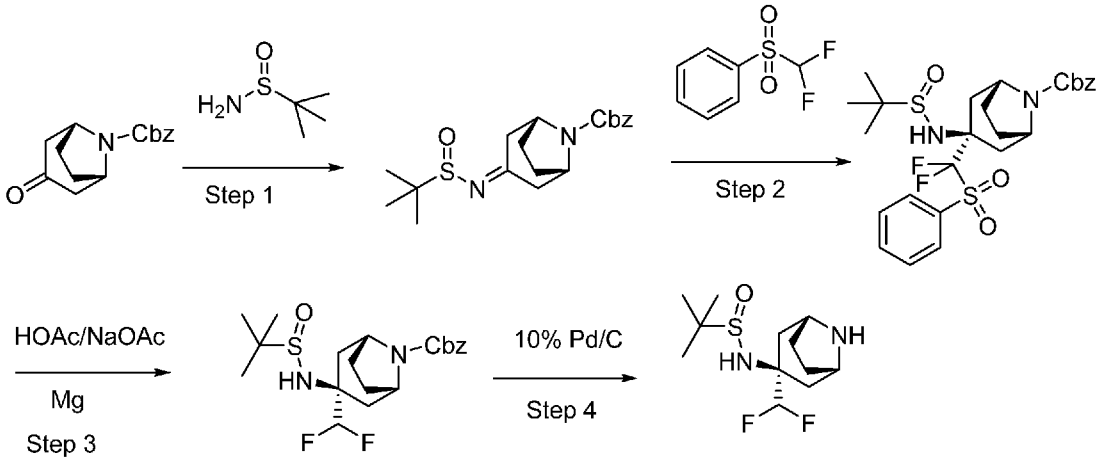


[0890] The title compound was prepared using similar method as in preparation 117 using benzyl N-[(1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate instead of benzyl N-[(1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate, to give the title compound, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.02 (1H, s), 4.96-4.44 (1H, m), 4.11-3.85 (1H, m), 3.40 (1H, q), 3.27 (1H, d), 2.35 (1H, s), 2.18-1.97 (1H, m), 1.97-1.83 (1H, m), 1.83-1.68 (1H, m), 1.68-1.48 (3H, m), 1.39 (9H, s).

[0891] Preparation 119: N-[(endo)-3-(Difluoromethyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-methylpropane-2-sulfinamide

[0892]

[Chem.174]



[0893] Step 1. Benzyl-3-[(2-methylpropane-2-sulfinyl)imino]-8-azabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of benzyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (75.0 g, 289.2 mmol, 1.0 eq) in THF (1.5 L) was added 2-methyl-2-propanesulfinamide (43.0 g, 354.8 mmol, 1.2 eq) and $Ti(OEt)_4$ (200.0 g, 876.8 mmol,3.0 eq). The reaction was heated to reflux for 3 hours and cooled to rt. The mixture was quenched by adding H_2O (550 mL) slowly and stirred for 1h. The solid was removed by filtration and the filtrate was diluted with EtOAc and washed with saturated brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product (103 g) as a yellow powder. It was recrystallized from pet.ether/EtOAc=4:1 to afford the pure product (36 g, 34%) as a white solid. LC-MS: $[M+H]^+ = 363$.

[0894] Step 2. Benzyl (endo)-3-[(benzenesulfonyl)difluoromethyl]-3-[(2-methylpropane-2-sulfinyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate

To the mixture of benzyl-3-[(2-methylpropane-2-sulfinyl)imino]-8-azabicyclo[3.2.1]octane-8-carboxylate (75.1 g, 207.0 mmol, 1.0 eq) and difluoromethanesulfonylbenzene (47.8 g, 248.0 mmol, 1.2 eq) in toluene (750 mL) was added KHMDS (269 ml, 269.0 mmol, 1.3 eq) at -78 °C drop wise under N_2. After the addition was complete, the reaction was stirred for another 2 hours at the same temperature and then quenched by adding H_2O (280 mL). The organic layer separated and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column (EtOAc in pet.ether 0-30%, v/v) to afford the product (30.0 g, yield 26%) as yellow solid. LC-MS: $[M+H]^+ = 555$.

[0895] Step 3. Benzyl (endo)-3-(difluoromethyl)-3-[(2-methylpropane-2-sulfinyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate

To the solution of benzyl

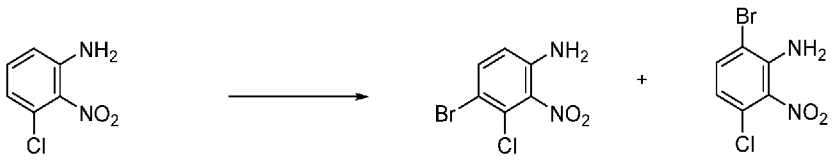
(endo)-3-[(benzenesulfonyl)difluoromethyl]-3-[(2-methylpropane-2-sulfinyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (56.6 g, 102 mmol, 1.0 eq) in DMF (1050 mL) and HOAc/NaOAc(8 mol/L) (1:1,1050 mL), Mg (50.9 g, 2.09 mol, 20.5 eq) was added portionwise at r.t. After the addition complete, the reaction was stirred for another 4 hours at r.t. LC-MS showed the reaction completed. The reaction mixture was diluted with water and extracted with EtOAc (1000 mL×2). The combined extracts were washed with water, dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was purified using reverse phase column (Eluant: MeOH in H_2O/TFA) to give the pure product (24.5 g, 58% yield) as a white solid. LC-MS: $[M+H]^+ = 415$.

[0896] Step 4. N-[(endo)-3-(Difluoromethyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-methylpropane-2-sulfinamide

The mixture of benzyl (endo)-3-(difluoromethyl)-3-[(2-methylpropane-2-sulfinyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (24.5 g, 59.0 mmol, 1.0 eq) and Pd/C (10%, 3.0 g) in MeOH (100 mL) was stirred at 50°C for about 20 h under H_2. The Pd/C was removed by filtration and the filtrate was concentrated in vacuo to give the crude product, which was purified by silica gel column (MeOH in DCM 0-10% NH_4OH) to afford the title compound (10.8 g, 65% yield) as a colorless oil. LC-MS: $[M+H]^+ = 281$. ^1H NMR ($CDCl_3$) δ: 5.79 (1H, t), 3.65 (3H, br s), 2.22 (2H, m), 1.94 (2H, m), 1.83 (3H, m), 1.54 (1H, d), 1.28 (9H, s).

[0897] Preparation 120: 4-Bromo-3-chloro-2-nitroaniline and 6-bromo-3-chloro-2-nitroaniline

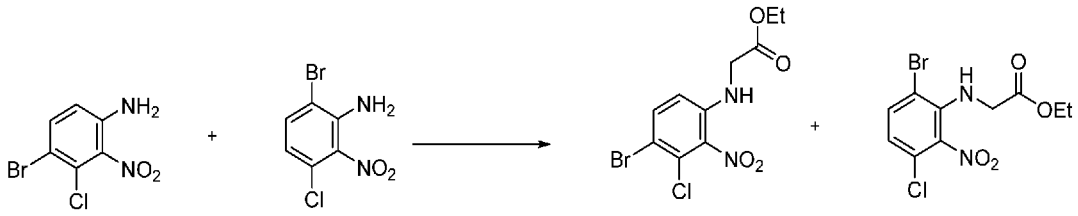
[0898] [Chem.175]



[0899] A solution of 3-chloro-2-nitroaniline (25 g, 145 mmol) and N-bromosuccinimide (25.5 g, 143 mmol) in AcOH (600 mL) was refluxed for 45 min. After cooling to RT, the reaction mixture was poured into ice-cold water (2 L). The precipitate was collected by filtration, washed with ice-cold water (2 x 200 mL) and dried in a vacuum oven overnight, to give the title compounds (36 g) as a mixture of isomers (4-bromo/6-bromo in 9:1 ratio). ^1H NMR (500 MHz, DMSO-d_6) δ: 7.56 (1H, d), 6.84 (1H, d), 6.40 (2H, s).

[0900] Preparation 121: Ethyl 2-[(4-bromo-3-chloro-2-nitrophenyl)amino]acetate and ethyl 2-[(6-bromo-3-chloro-2-nitrophenyl)amino]acetate

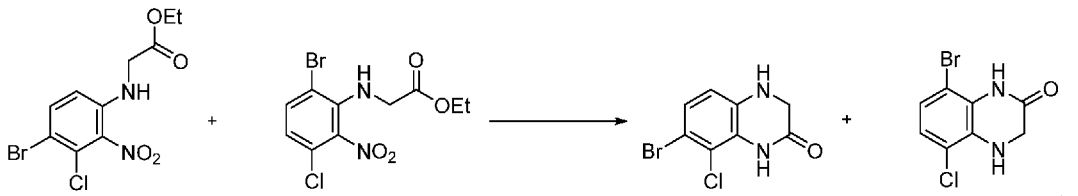
[0901] [Chem.176]



[0902] A mixture of 4-bromo-3-chloro-2-nitroaniline and 6-bromo-3-chloro-2-nitroaniline in a 9:1 ratio (30 g, 119 mmol), ethyl bromoacetate (133 mL, 119 mmol) and K_2CO_3 (26.4 g, 191 mmol) was heated at 140 °C under nitrogen for 30 h. The mixture was cooled to RT, then 1M aq. NaOH solution (250 mL) was added over 10 min. The mixture was stirred for a further 10 min, then extracted with DCM (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (gradient elution, 5-30%, EtOAc/isohexane). The purified mixture was recrystallised from boiling IPA (70 mL). The solid was filtered, washed with cyclohexane (2 x 50 mL), and dried in a vacuum oven overnight, to give the title compounds (4 g) as a mixture of isomers (4-bromo/6-bromo in 9:1 ratio). MS: $[M+H]^+ = 337$.

[0903] Preparation 122: 7-Bromo-8-chloro-1,2,3,4-tetrahydroquinoxalin-2-one and 8-bromo-5-chloro-1,2,3,4-tetrahydroquinoxalin-2-one

[0904] [Chem.177]

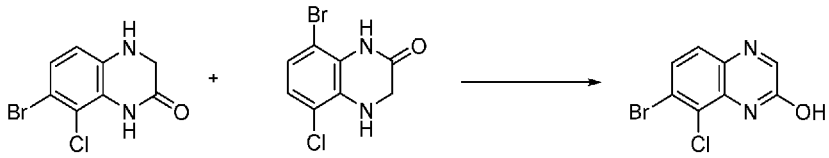


[0905] A mixture of ethyl 2-[(4-bromo-3-chloro-2-nitrophenyl)amino]acetate and ethyl 2-[(6-bromo-3-chloro-2-nitrophenyl)amino]acetate in a 9:1 ratio (3.5 g, 10.4 mmol), iron (3.5 g, 62.7 mmol) and NH_4Cl (0.555 g, 10.4 mmol) in EtOH (75 mL) was refluxed for 30 min. AcOH (30 mL) was added and heating was continued for 30 min. The reaction mixture was diluted with water (300 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum, to give the title compounds (2.8 g) as a mixture of isomers (7-bromo/8-bromo in 9:1 ratio). MS: $[M+H]^+ = 261$.

[0906] Preparation 123: 7-Bromo-8-chloroquinoxalin-2-ol

[0907]

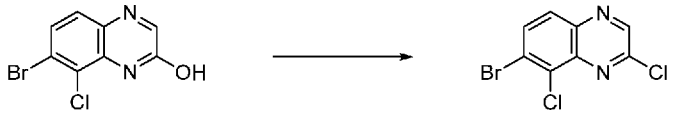
[Chem.178]



[0908] 7-Bromo-8-chloro-1,2,3,4-tetrahydroquinoxalin-2-one and 8-bromo-5-chloro-1,2,3,4-tetrahydroquinoxalin-2-one in a 9:1 ratio (3.2 g, 12.2 mmol) were suspended in 50 wt% aq. NaOH (1.5 mL, 29.3 mmol) and 3 wt% aq. H_2O_2 (32 mL, 28.1 mmol). The reaction mixture was refluxed for 3 h. The mixture was cooled to RT, causing product to precipitate. AcOH (1.6 mL) was added. The precipitate was collected by filtration, washing with water (2 x 5 mL). The solid was azeotroped with acetonitrile (2 x 20 mL), to give the title compound (2.8 g). MS: $[M+H]^+ = 259$.

[0909] Preparation 124: 7-Bromo-2,8-dichloroquinoxaline

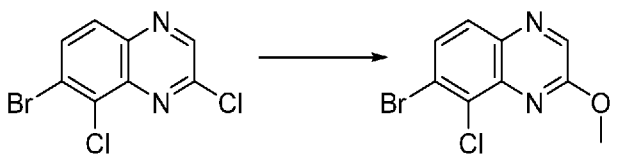
[0910] [Chem.179]



To a solution of 7-bromo-8-chloroquinoxalin-2-ol (3 g, 11.6 mmol) in toluene (23 mL) was added phosphorus(V) oxychloride (4.85 mL, 52.0 mmol) and the reaction mixture was stirred overnight at 70 °C. The reaction mixture was quenched by dropwise addition into ice-cold sat. aq. $NaHCO_3$ (200 mL) and stirred for 2 h at RT. The mixture was then extracted with DCM (3 x 80 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give the title compound (2.5 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ: 9.13 (1H, s), 8.22 (1H, d), 8.07 (1H, d).

[0911] Preparation 125: 7-Bromo-8-chloro-2-methoxyquinoxaline

[0912] [Chem.180]

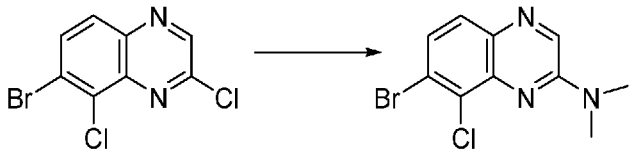


[0913] 7-Bromo-2,8-dichloroquinoxaline (2 g, 7.12 mmol) and potassium carbonate (3.94 g, 28.5 mmol) were combined in a 100 mL three necked flask in MeOH (40 mL). The resultant colourless suspension was heated at 65 °C (internal temperature) for 18 h. The reaction mixture was cooled to RT. Water (150 mL) was added and the precipitate was filtered to give 7-bromo-8-chloro-2-methoxyquinoxaline (1.79 g, 6.48 mmol, 91 %

yield) as a light colourless solid. MS: $[M+H]^+ = 275$. ^1H NMR (DMSO-d_6) δ: 8.69 (1H, s), 8.00 - 7.89 (2H, m), 4.10 (3H, s).

[0914] Preparation 126: 7-Bromo-8-chloro-N,N-dimethylquinoxalin-2-amine

[0915] [Chem.181]

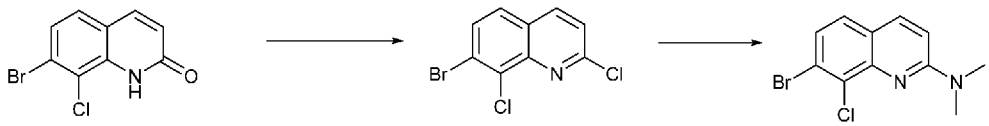


[0916] In a 100 mL three necked flask, dimethylamine, 2M in THF solution (22 mL, 44.0 mmol) was treated with 7-bromo-2,8-dichloroquinoxaline (2.01 g, 7.16 mmol) at 0 °C (internal temperature, ice bath). The resultant yellow solution was warmed to RT and stirred for 3 h. The reaction mixture was concentrated in vacuo and was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO3 (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The organic extracts were combined and washed with saturated brine (1 x 50 mL) and then dried over MgSO4, filtered and concentrated in vacuo to afford 7-bromo-8-chloro-N,N-dimethylquinoxalin-2-amine (1.98 g, 6.77 mmol, 95 % yield) as a light yellow solid. MS: $[M+H]^+ = 288$.

^1H NMR (500 MHz, DMSO-d_6) δ: 8.76 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 3.29 (s, 6H).

[0917] Preparation 127: 7-Bromo-8-chloro-N,N-dimethylquinolin-2-amine

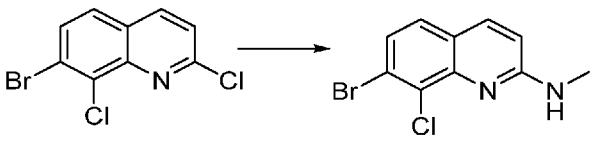
[0918] [Chem.182]



[0919] A solution of 7-bromo-8-chloro-1,2-dihydroquinolin-2-one (1.0 g, 3.87 mmol) in $POCl_3$ was heated at reflux for 1 h. After cooling, most of the $POCl_3$ was evaporated, ice and NH_4OH were added and the product extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and evaporated to afford 7-bromo-2,8-dichloroquinoline (0.79 g), MS: $[M+H]^+ = 278$. 7-Bromo-2,8-dichloroquinoline (250 mg, 0.9 mmol) was dissolved in pyridine (1.5 mL), dimethylamine (40% solution in water, 1.5 mL) was added and the reaction mixture was heated in a sealed tube for 3 h. After cooling, water (10 ml) was added and the product extracted with EtOAc (2 x 15 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (gradient elution, 0-50%, EtOAc/petrol), to give the title compound (220 mg), MS: $[M+H]^+ = 287$.

[0920] Preparation 128: 7-Bromo-8-chloro-N-methylquinolin-2-amine

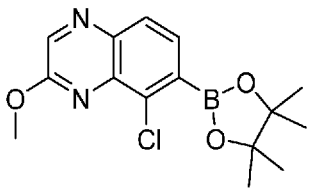
[0921] [Chem.183]



[0922] 7-Bromo-2,8-dichloroquinoline (500 mg, 1.8 mmol) was dissolved in pyridine (3.0 mL), methylamine (40% solution in water, 3.0 mL) was added and the reaction mixture was heated in a sealed tube for 3 h. After cooling, water (20 ml) was added and the product extracted with EtOAc (2 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (gradient elution, 0-50%, EtOAc/petrol), to give the title compound (360 mg), MS: $[M+H]^+ = 271$.

[0923] Preparation 129:
8-Chloro-2-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline

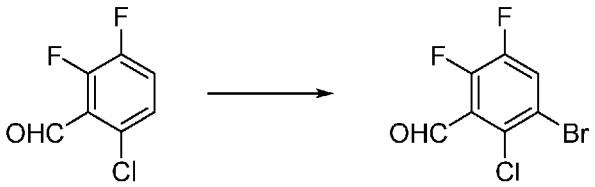
[0924] [Chem.184]



[0925] 8-Chloro-2-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline was prepared as preparation 82 above using 7-bromo-8-chloro-2-methoxyquinoxaline. MS: $[M+H]^+ = 321, 323$.

[0926] Preparation 130: 3-Bromo-2-chloro-5,6-difluorobenzaldehyde

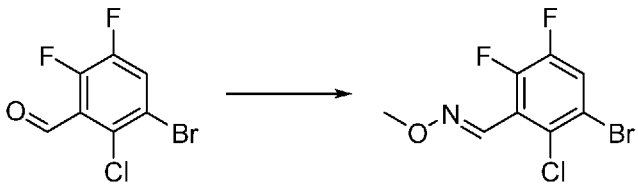
[0927] [Chem.185]



[0928] To a mixture of 2-chloro-5,6-difluorobenzaldehyde (5.3 g, 30 mmol) and sulfuric acid (15 mL) was added N-bromosuccinimide (6.6 g, 37 mmol) at 60 °C. The resulting mixture was stirred at the same temperature for 5 h. The mixture was poured onto crushed ice, and then extracted with EtOAc. The organic phase was washed with brine and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0-20%, EtOAc/hexane), to give the title compound (6.5 g), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.37 (1H, s), 7.72 (1H, dd).

[0929] Preparation 131: 3-Bromo-2-chloro-5,6-difluorobenzaldehyde O-methyl oxime

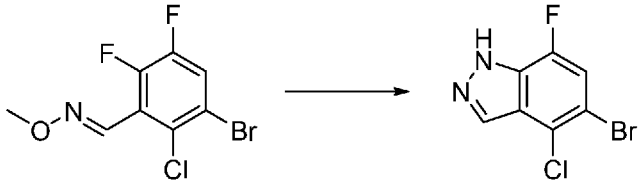
[0930] [Chem.186]



[0931] A mixture of 3-bromo-2-chloro-5,6-difluorobenzaldehyde (6.5 g, 26 mmol), O-methylhydroxylamine hydrochloride (2.4 g, 29 mmol), potassium carbonate (4.6 g, 33 mmol) and 1,2-dimethoxyethane (26 mL) was stirred at 60 °C overnight. The mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0-20%, EtOAc/hexane), to give the title compound (7.2 g), MS: $[M+H]^+$ = 284.

[0932] Preparation 132: 5-Bromo-4-chloro-7-fluoro-1H-indazole

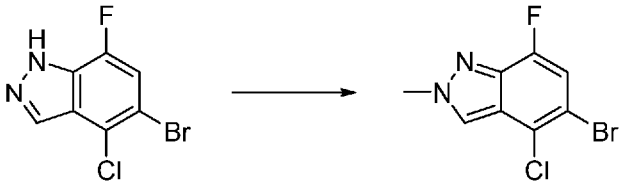
[0933] [Chem.187]



[0934] A mixture of 3-bromo-2-chloro-5,6-difluorobenzaldehyde O-methyl oxime (7.1 g, 25 mmol), tetrahydrofuran (25 mL) and hydrazine monohydrate (25 mL) was stirred under reflux for 30 h. To the cooled mixture was added EtOAc (120 mL) and water (50 mL). The separated organic layer was concentrated in vacuo. The residue was suspended in EtOAc and hexane. The precipitate was collected and dried at 50 °C under reduced pressure, to give the title compound (4.4 g), MS: $[M+H]^+$ = 249.

[0935] Preparation 133: 5-Bromo-4-chloro-7-fluoro-2-methyl-2H-indazole

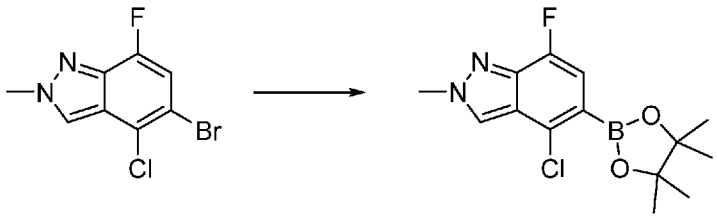
[0936] [Chem.188]



[0937] To a solution of 5-bromo-4-chloro-7-fluoro-1H-indazole (1.8 g, 7.4 mmol) in EtOAc (40 mL) was added trimethyloxonium tetrafluoroborate (1.7 g, 12 mmol) and the resulting mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc, quenched with sat. aq. $NaHCO_3$ and the phases were separated. The organic phase was washed with brine and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0-60%, EtOAc/hexane), to give the title compound (0.76 g), MS: $[M+H]^+$ = 263.

[0938] Preparation 134: 4-Chloro-7-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

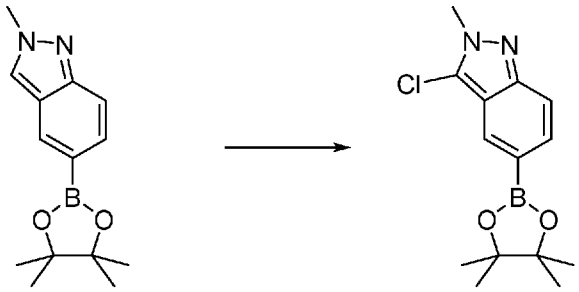
[0939] [Chem.189]



[0940] Prepared as preparation 82, except using 5-bromo-4-chloro-7-fluoro-2-methyl-2H-indazole, to give the title compound. MS: $[M+H]^+ = 311$.

[0941] Preparation 135: 3-Chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

[0942] [Chem.190]

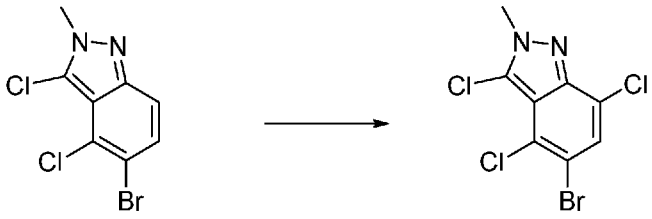


[0943] 2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (190.8 mg, 0.7392 mmol) was dissolved into THF (10 mL). To the solution was added N-chlorosuccinimide (109.2 mg, 0.8178 mmol) at RT under stirring. After stirring at RT for 2 hours, DMF (5 mL) was added. And the mixture was heated to 60 °C under stirring. After further stirring for 1 hour, the mixture was cooled to RT. The mixture was poured into 5% aq. of $NaHCO_3$ and extracted with EtOAc. The extract was washed by water, dried over Na_2SO_4 and concentrated. The residue was purified with silica gel column chromatography (Biotage SNAP Ultra HP-Sphere, 25 g), eluting with hexane / EtOAc to give the titled compound (142.9 mg) as a off-white wax. MS: $[M+H]^+ = 292$.

[0944] Preparation 136: 5-Bromo-3,4,7-trichloro-2-methyl-2H-indazole

[0945]

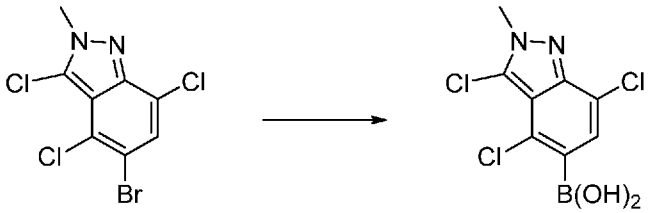
[Chem.191]



[0946] 5-Bromo-3,4-dichloro-2-methyl-2H-indazole (5.001 g, 17.863 mmol) was suspended into DMF (50 mL). The suspension was heated to 65 °C under stirring to give a solution. To the hot solution was added N-chlorosuccinimide (3.578 g, 26.80 mmol) in some portions. After stirring at 65 °C for 1.5 hours, the mixture was cooled to RT. The mixture was pourd into 9% aq. of $NaHCO_3$ and extracted with EtOAc. The extract was washed by water, dried over Na_2SO_4 and concentrated. The residue was purified with silica gel column chromatography (Biotage SNAP Ultra HP-Sphere, 100 g), eluting with hexane / EtOAc to give the titled compound (2.037 g) as a colourless solid. MS: $[M+H]^+ = 313$.

[0947] Preparation 137: (3,4,7-Trichloro-2-methyl-2H-indazol-5-yl)boronic acid

[0948] [Chem.192]

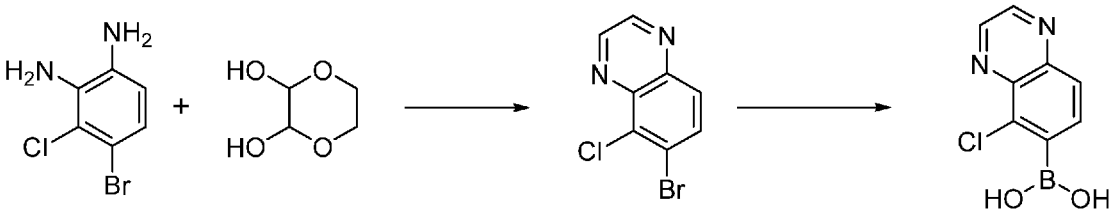


[0949] 5-Bromo-3,4,7-trichloro-2-methyl-2H-indazole (2.037 g, 6.479 mmol) was dissolved into THF (40 mL). The solution was degassed under reduced pressure, purged with N_2 gas, and cooled to 0 °C under stirring. To the cooled solution was added dropwise THF solution of i-PrMgCl · LiCl complex (2.0 M, 7.75 mL, 15.5 mmol) at 0 °C under stirring. After 1 hour stirring, triisopropyl borate (7.50 ml, 32.7 mmol) was added at 0°C. And the mixture was allowed to be RT under stirring. After 1.5 hours stirring, acetic acid (5.60 mL, 97.80 mmol) was added for quenching the reaction. The resulting mixture was diluted with 2-methyltetrahydrofuran. And then, the titled compound was extracted to 3 M aq. of NaOH (300 mL). The pH value of aqueous layer was adjusted to around 2 to 3. The precipitate was collected by filtration, washed by H_2O, and dried in vacuo at 70 °C to give the titled compound (1.340 g, 74%) as a colourless solid. MS: $[M+H]^+ = 279$.

[0950] Preparation 138: (5-Chloroquinoxalin-6-yl)boronic acid

[0951]

[Chem.193]

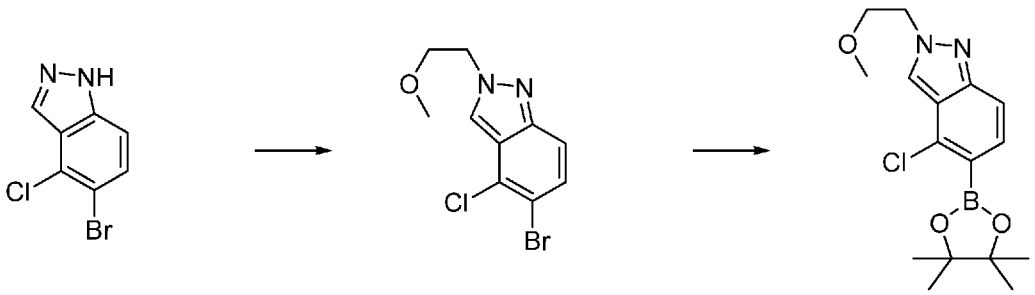


[0952] To a solution of 4-bromo-3-chloro-benzene-1,2-diamine (500 mg, 2.26 mmol) in EtOH (20.0 mL), 1,4- dioxane-2,3-diol (380 mg, 3.16 mmol) was added at r.t.. The mixture was stirred at r.t. for 18 h. The reaction mixture was then vacuum-concentrated, and the residue was purified by column chromatography on silica gel (gradient elution, 20 - 40% EtOAc/hexane) to give 6-bromo-5-chloroquinoxaline (269 mg). MS: $[M+H]^+$ = 243, 245.

To a solution of 6-bromo-5-chloroquinoxaline (200 mg, 0.823 mmol) in 1,4-dioxane (2.00 mL), bis(pinacolato)diboron (313 mg, 1.23 mmol), KOAc (161 mg, 1.64 mmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (53.7 mg, 0.0657 mmol) were added at r.t.. The mixture was stirred at 100 °C for 18h, diluted with MTBE and added 2M NaOH. The aqueous layer was added 6M HCl and extracted with $CHCl_3$ three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (108 mg). MS: $[M+H]^+$ = 209.

[0953] Preparation 139:
4-Chloro-2-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

[0954] [Chem.194]



[0955] Step 1. 5-Bromo-4-chloro-2-(2-methoxyethyl)-2H-indazole

To a suspension of 5-bromo-4-chloro-1H-indazole (1.0 g, 4.7 mmol) and potassium carbonate (1.79 g, 13 mmol) in DMSO (5 ml) was added 1-bromo-2-methoxy-ethane (0.83 ml, 8.6401 mmol) at room temperature. After stirring at the same temperature over weekend, the mixture was diluted with EtOAc and washed with water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (SNAP Ultra 50 g, gradient elution, 0-100% EtOAc in

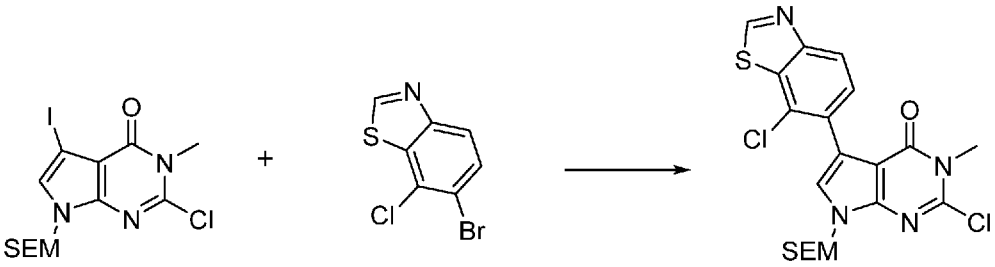
hexane) gave the title compound (0.45 g, 1.5 mmol, 36%) as a brown solid. MS: $[M+H]^+$ = 289, 291, 293.

[0956] Step 2. 4-Chloro-2-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole

To a suspension of 5-bromo-4-chloro-2-(2-methoxyethyl)-2H-indazole (0.45 g, 1.5 mmol) in 1,4-dioxane (10 mL) was added potassium acetate (0.30 g, 3.13 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'- bi(1,3,2-dioxaborolane) (0.59 g, 2.3 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.12 g, 0.15 mmol) at room temperature. After stirring at 120 °C for 4 h, the mixture was diluted with EtOAc and filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated in vacuo. Column chromatography (SNAP Ultra 25 g, gradient elution, 0-100% EtOAc in hexane) gave the title compound (0.68 g) as a pale brown oil. The material was not pure but was used without further purification. MS: $[M+H]^+$ =337, 339.

[0957] Preparation 140:
2-chloro-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

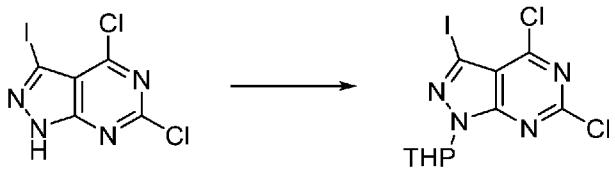
[0958] [Chem.195]



[0959] A mixture of 6-bromo-7-chloro-1,3-benzothiazole (300 mg, 1.21 mmol), bis(pinacolato)diboron (460 mg, 1.81 mmol), $Pd(dppf)Cl_2$ (177 mg, 0.24 mmol) and potassium acetate (592 mg, 6.04 mmol) in 1,4-dioxane (6 mL) was heated at 100 °C for 2 h and then allowed to cool. To the mixture was added 2-chloro-5-iodo-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (350 mg, 0.8 mmol), $Pd(dppf)Cl_2$ (114 mg, 0.16 mmol), K_2CO_3 (667 mg, 4.83 mmol) and water (3 mL). The mixture was then heated at 70 °C for a further 2 h. The mixture was cooled and then partitioned between EtOAc and water. The organic layer was washed with brine, dried ($MgSO_4$) and then evaporated in vacuo. The residue was purified by SiO_2 chromatography (eluting with 0-40% acetone/pet. ether) to provide the product (220 mg). MS: $[M+H]^+$ = 481.

[0960] Preparation 141:
4,6-Dichloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine

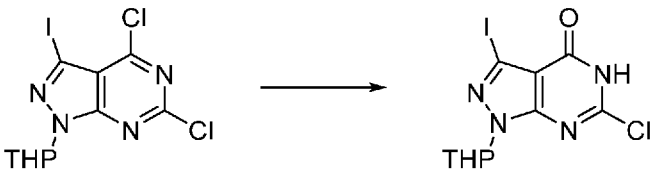
[0961] [Chem.196]



[0962] 4,6-Dichloro-3-iodo-1H-pyrazolo[3,4-d]pyrimidine (4.0 g, 13 mmol), 3,4-dihydro-2H-pyran (3.5 mL, 38 mmol) and p-toluenesulfonic acid monohydrate (0.48 g, 2.5 mmol) were dissolved in THF (60 mL) and heated at 70 °C for 1.5 h. The solvent was removed under vacuum and the solid residue was purified by column chromatography on silica gel (gradient elution, 0-100%, EtOAc/hexane) to give the title compound (3.47 g). MS: $[M+H]^+$ = 399.

[0963] Preparation 142:
6-Chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

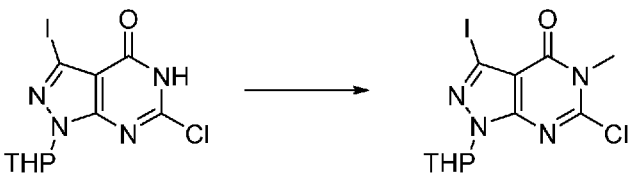
[0964] [Chem.197]



[0965] To a solution of 4,6-dichloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (2.0 g, 5.0 mmol) in THF (20 mL) was added 5 M NaOH (9.0 mL) at r.t. The mixture was stirred at the same temperature for 5 hrs, then THF (10 ml) was added to the mixture. The mixture was stirred at RT overnight. The mixture was acidified with 6 M HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the the title compound (1.87 g). MS: $[M+H]^+$ = 381.

[0966] Preparation 143:
6-Chloro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0967] [Chem.198]

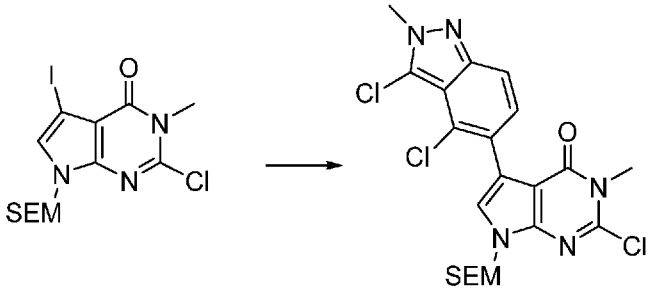


[0968] To a mixture of

6-chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (28.5 g, 74.9 mmol) and K_2CO_3 (12.4 g, 90.0 mmol) in DMF (270 mL) was added iodomethane (11.7 g, 82.4 mmol) in DMF (15 ml) at RT. The mixture was stirred at RT for 4 h, then diluted with water. After stirring for 4 h, The precipitate was collected by filtration and dried in vacuo to give the title compound (27.8 g). MS: $[M+H]^+$ = 395.

[0969] Preparation 144:
2-Chloro-5-(3,4-dichloro-2-methyl-indazol-5-yl)-3-methyl-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-4-one

[0970] [Chem.199]

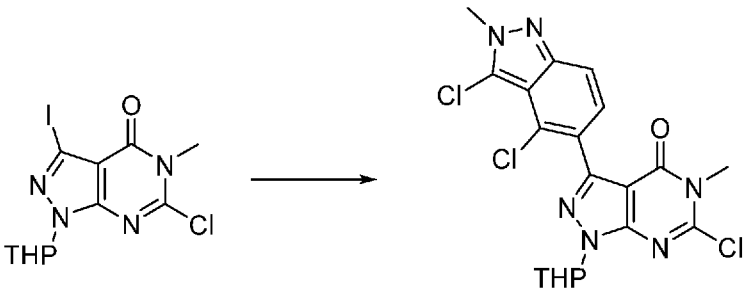


[0971] A mixture of
2-chloro-5-iodo-3-methyl-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-4-one (107 mg, 0.244 mmol),
3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (107 mg, 0.326 mmol), K_3PO_4 (108 mg, 0.506 mmol),
bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (18 mg, 0.026 mmol), 1,4-dioxane (1.2 mL) and water (0.24 mL) was stirred at 70 °C for 5 h and cooled to RT. The mixture was purified by column chromatography on silica gel (gradient elution, 0 - 60% EtOAc/hexane) to give the title compound (113 mg). MS: $[M+H]^+$ = 514, 516.

[0972] Preparation 145:
6-Chloro-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0973]

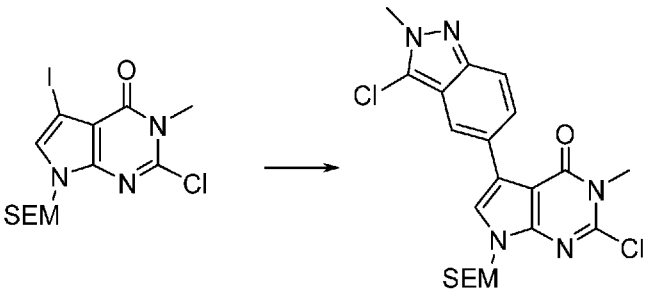
[Chem.200]



[0974] A mixture of 6-chloro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (500 mg, 1.27 mmol), 3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (497 mg, 1.52 mmol), K_3PO_4 (806 mg, 3.80 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (103 mg, 0.127 mmol), 1,4-dioxane (5.0 mL) and water (1.25 mL) was stirred at 90 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (413 mg). MS: $[M+H]^+$ = 467, 469.

[0975] Preparation 146:
2-Chloro-5-(3-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0976] [Chem.201]

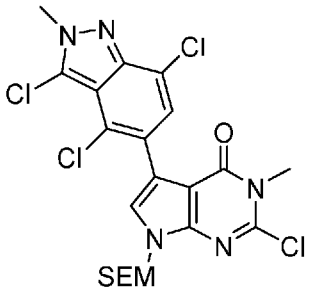


[0977] 2-Chloro-5-iodo-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (362.7 mg, 0.8248 mmol), 3-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (289.1 mg, 0.9881 mmol), $Pd(Amphos)_2Cl_2$ (34.7 mg, 0.0490 mmol) and K_3PO_4 (263.3 mg, 1.240 mmol) were mixed in vessel. To the mixture was added THF (10 mL) and Water (1 mL). The mixture was degassed under reduced pressure and purged with N_2 gas.

After stirring for 5 hours at 75 °C, the mixture was cooled to RT. The mixture was poured into water and extracted with EtOAc. The extract was washed by 9% aq. of $NaHCO_3$. To the extract was added Na_2SO_4 and SH-silica gel (Fuji Silysia). After stirring at RT for 1 hour, the solid was removed by filtration, and the filtrate was concentrated. The residue was purified with silica gel column chromatography (Biotage SNAP Ultra HP-Sphere, 25 g), eluting with hexane / EtOAc to give the titled compound (279.8 mg) as an off-white solid. MS: $[M+H]^+ = 478$.

[0978] Preparation 147:
2-Chloro-3-methyl-5-(3,4,7-trichloro-2-methyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

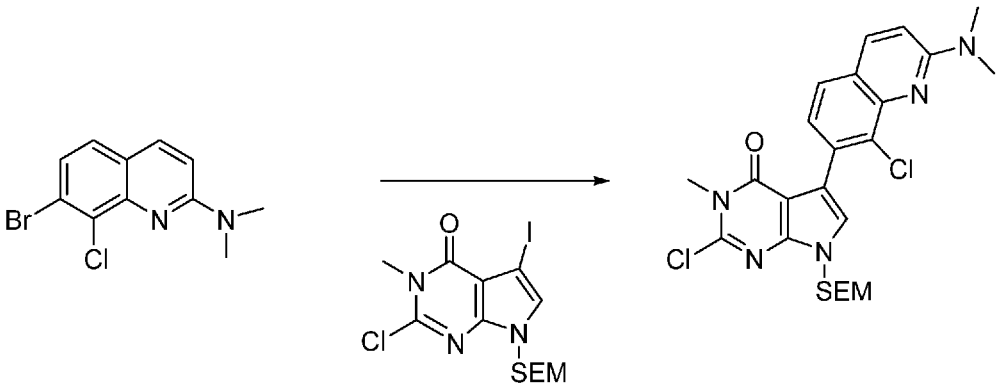
[0979] [Chem.202]



[0980] 2-Chloro-3-methyl-5-(3,4,7-trichloro-2-methyl-2H-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one was prepared in the manner similar to preparation 146, except using (3,4,7-trichloro-2-methyl-2H-indazol-5-yl)boronic acid instead of 3-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole. MS: $[M+H]^+ = 546$.

[0981] Preparation 148:
2-Chloro-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

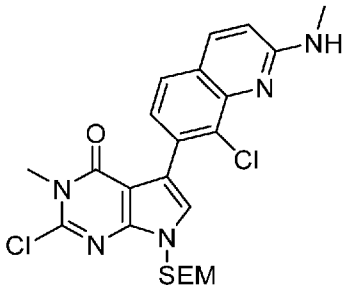
[0982] [Chem.203]



[0983] 7-Bromo-8-chloro-N,N-dimethylquinolin-2-amine (390 mg, 1.36 mmol), bis(pinacolato)diboron (520mg, 2.04 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (150 mg, 0.2 mmol) and potassium acetate (650 mg, 6.8 mmol) were combined in a 30 mL microwave tube, sealed, evacuated and backfilled with nitrogen (x2). 1,4-Dioxane (8 mL) was added and the tube backfilled again (x2) before heating to 90 °C for 2 h. After cooling, 2-chloro-5-iodo-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one (590 mg, 1.36 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (150 mg, 0.2 mmol), potassium carbonate (1.12 g, 8.16 mmol) and water (2 mL) were added. The reaction was resealed, backfilled with nitrogen (x2) and heated to 70 °C for 2 h. After cooling, the reaction was diluted with water and extracted with EtOAc (3x). Combined organics were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (gradient elution, 0-100%, EtOAc/petrol), to give the title compound (426 mg). MS: $[M+H]^+ = 518$.

[0984] Preparation 149: 2-Chloro-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

[0985] [Chem.204]

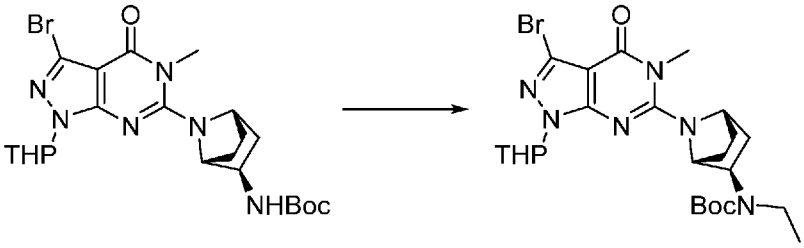


[0986] Starting with 7-bromo-8-chloro-N-methylquinolin-2-amine, the title compound was prepared using procedures similar to those described 2-chloro-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one. MS: $[M+H]^+ = 504$.

[0987] Preparation 150: tert-Butyl ((1R,2R,4S)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(ethyl)carbamate

[0988]

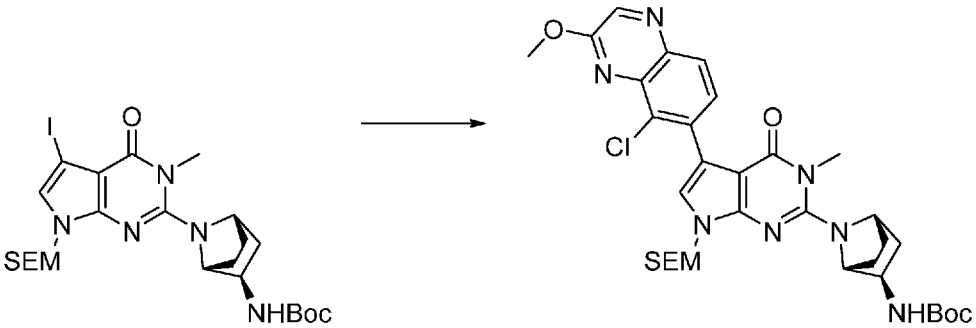
[Chem.205]



[0989] To a solution of tert-butyl ((1R,2R,4S)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (500 mg, 0.955 mmol) in THF (5.00 mL), NaH (60% in mineral oil, 76.4 mg, 1.91 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 15 min. To the mixture, iodoethane (0.153 mL, 1.91 mmol) was added at 0 °C. The mixture was stirred at r.t. overnight. To the mixture, NaH (60% in mineral oil, 57.3 mg, 1.43 mmol) and iodoethane (0.115 mL, 1.43 mmol) were added at 0 °C. The mixture was stirred at r.t.for 6 h. The mixture was poured into sat. NH_4Cl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 10 - 40% EtOAc/hexane) to give the title compound (335 mg). MS: $[M+H]^+$ = 551, 553.

[0990] General procedure 6: tert-Butyl ((1R,2R,4S)-7-(5-(5-chloro-3-methoxyquinoxalin-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0991] [Chem.206]

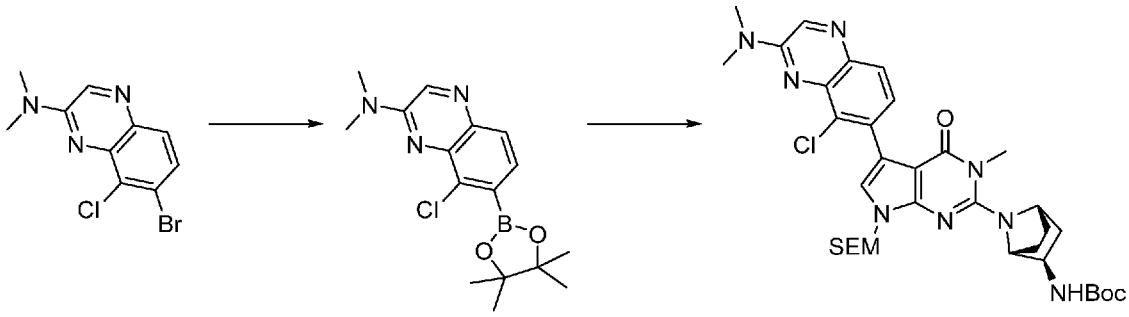


[0992] The mixture of tert-butyl ((1R,2R,4S)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (75.0 mg, 0.122 mmol), 8-chloro-2-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (46.9 mg, 0.146 mmol), K_3PO_4 (38.8 mg, 0.183 mmol),

bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (64.8 mg, 0.0794 mmol), 1,4-dioxane (1.5 mL) and water (0.15 mL) was stirred at 80 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (58.0 mg). MS: $[M+H]^+$ = 682, 684.

[0993] General procedure 7: tert-Butyl ((1R,2R,4S)-7-(5-(5-chloro-3-(dimethylamino)quinoxalin-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate

[0994] [Chem.207]



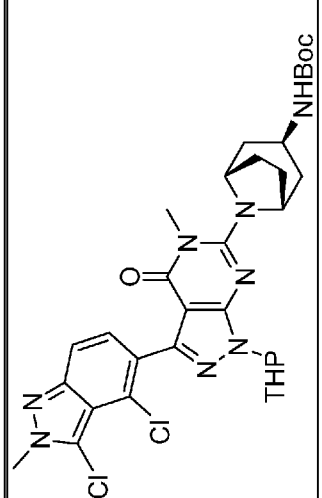
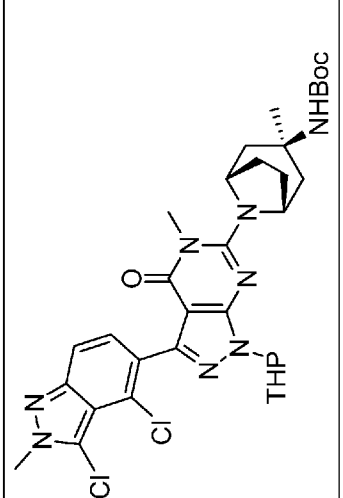
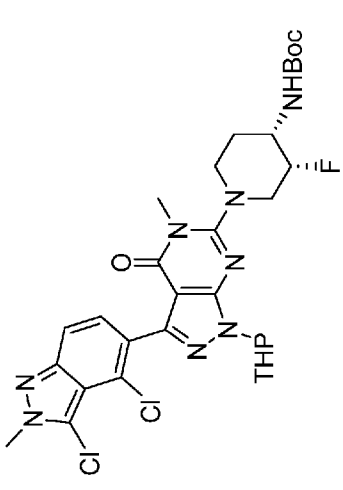
[0995] The mixture of 7-bromo-8-chloro-N,N-dimethylquinoxalin-2-amine (200 mg, 0.698 mmol), bis(pinacolato)diboron (354 mg, 1.40 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (57.0 mg, 0.0698 mmol) and potassium acetate (137 mg, 1.40 mmol) in 1,4-dioxane (2.0 mL) was degassed, purged with nitrogen, and stirred at 100 °C for 6 h. The reaction was cooled to RT, filtered through a pad of Celite, and washed with EtOAc. The filtrate was concentrated in vacuo. The crude residue was used in the next step without further purification. MS: $[M+H]^+$ = 334, 336.

[0996] The mixture of tert-butyl ((1R,2R,4S)-7-(5-iodo-3-methyl-4-oxo-7-((2-trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate (75.0 mg, 0.122 mmol), 8-chloro-N,N-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline-2-amine (48.8 mg, 0.146 mmol), K_3PO_4 (38.8 mg, 0.183 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (64.8 mg, 0.0794 mmol), 1,4-dioxane (1.5 mL) and water (0.15 mL) was stirred at 80 °C for 2 h, cooled to RT, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, 0 - 100% EtOAc/hexane) to give the title compound (60.3 mg). MS: $[M+H]^+$ = 695, 697.

[0997] Compounds of Table 13 below were prepared using procedures analogous to that described in general procedure 1 starting from the appropriate substituted protected pyrrolopyrimidinone or pyrazolopyrimidinone and varying the amine (synthesised as described above with any significant variations indicated below.

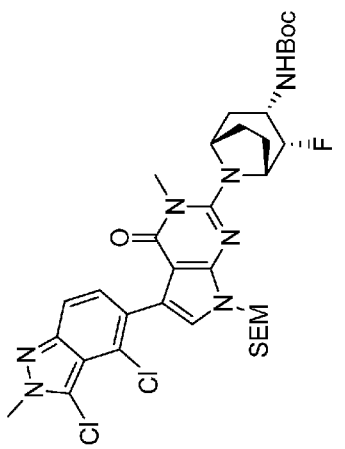
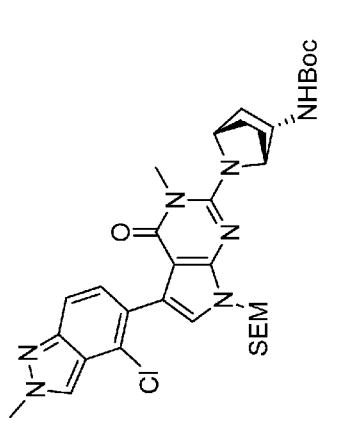
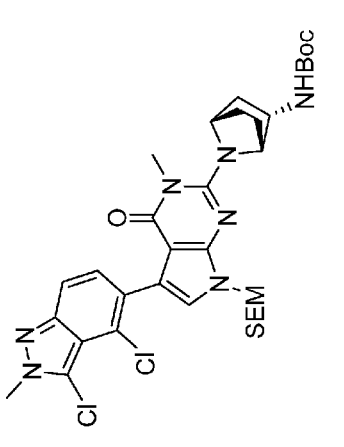
[0998] [Table 13-1]

Table 13

Compound	Compound name	MS: $[M+H]^+$ m/z	Procedure
	*tert*-butyl (*endo*-8-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate	657, 659	Prepared as general procedure 1 above using 6-chloro-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl (*endo*-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-butyl (*endo*-8-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate	671, 673	Prepared as general procedure 1 above using 6-chloro-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl *N*-(*endo*-3-methyl-8-azabicyclo[3.2.1]octan-3-yl)carbamate
	*tert*-butyl ((3*R*,4*S*)-1-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-3-fluoropiperidin-4-yl)carbamate	649, 651	Prepared as general procedure 1 above using 6-chloro-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl *N*-[(3*R*,4*S*)-3-fluoropiperidin-4-yl]carbamate

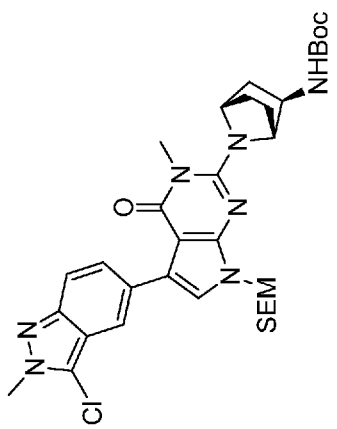
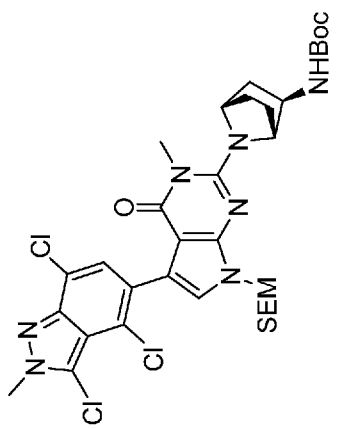
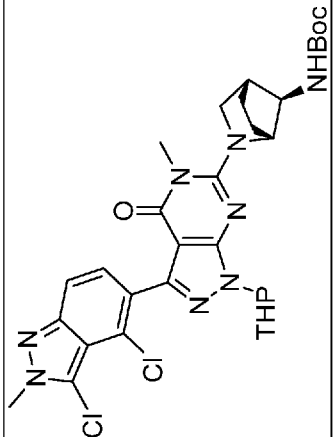
[0999]

[Table 13-2]

	*tert*-butyl ((1*R*,2*S*,3*S*,5*S*)-8-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)carbamate	720, 722	Prepared as general procedure 1 above using 2-chloro-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *N*-[(1*S*,2*R*,3*S*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate
	*tert*-butyl (*rac*-(1*R*,2*S*,4*S*)-7-(5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	654, 656	Prepared as general procedure 1 above using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *rac*-(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptan-2-ylcarbamate hydrochloride
	*tert*-butyl (*rac*-7-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	688, 690	Prepared as general procedure 1 above using 2-chloro-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *rac*-(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptan-2-ylcarbamate hydrochloride

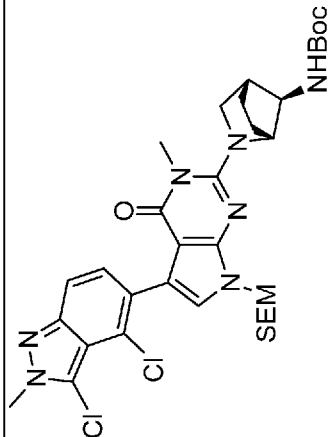
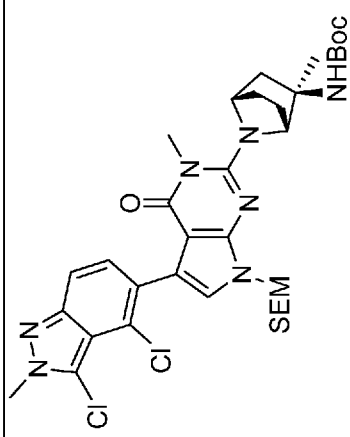
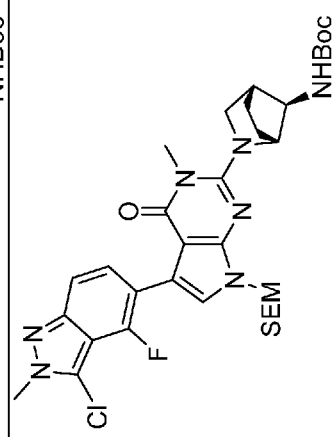
[1000]

[Table 13-3]

	*tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-(3-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	654	Prepared as general procedure 1 above using 2-chloro-5-(3-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	*tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-methyl-4-oxo-5-(3,4,7-trichloro-2-methyl-2*H*-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	722, 724	Prepared as general procedure 1 above using 2-chloro-3-methyl-5-(3,4,7-trichloro-2-methyl-2*H*-indazol-5-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one and *tert*-butyl ((1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate
	*tert*-butyl ((1*R*,4*R*,7*R*)-2-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	643, 645	Prepared as general procedure 1 above using 6-chloro-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,4*R*,7*R*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

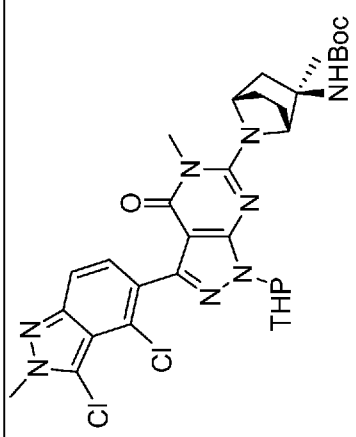
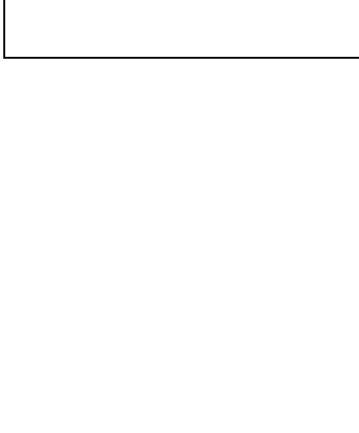
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[Table 13-4]

	*tert*-butyl ((1*R*,4*R*,7*R*)-2-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	688, 690	Prepared as general procedure 1 above using 2-chloro-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,4*R*,7*R*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate
	*rac-tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	702, 704	Prepared as general procedure 1 above using 2-chloro-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl ((1*R*,2*R*,4*S*)-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl)carbamate oxalate
	*tert*-butyl ((1*R*,4*R*,7*R*)-2-(5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate	672, 674	Prepared as general procedure 1 above using 2-chloro-5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl ((1*R*,4*R*,7*R*)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

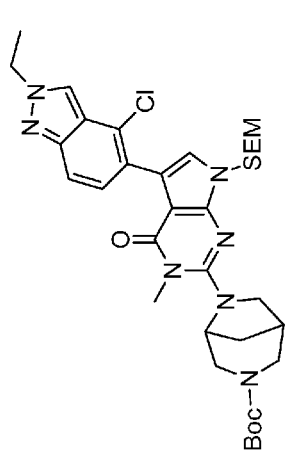
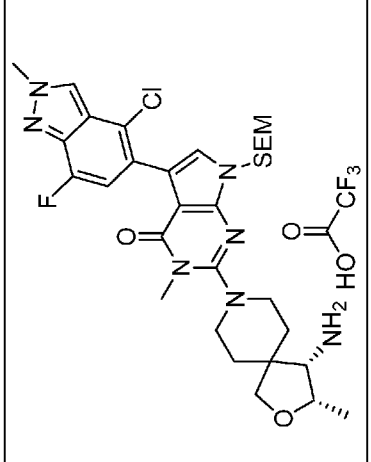
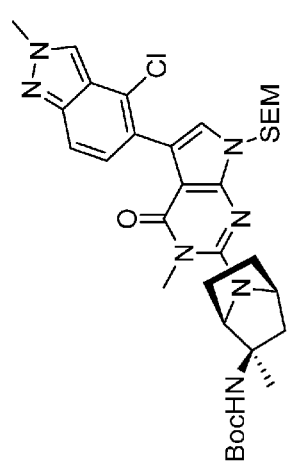
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[Table 13-5]

	*rac-tert*-butyl ((1*R*,2*R*,4*S*)-7-(3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	657, 659	Prepared as general procedure 1 above using 6-chloro-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and *rac-tert*-butyl ((1*R*,2*R*,4*S*)-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl)carbamate oxalate
	*rac-tert*-butyl 3-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-3,6-diazabicyclo[3.2.1]octane-6-carboxylate	668	Prepared using general procedure 1 using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4H-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl 3,6-diazabicyclo[3.2.1]octane-6-carboxylate, purified by normal phase chromatography on silica gel.

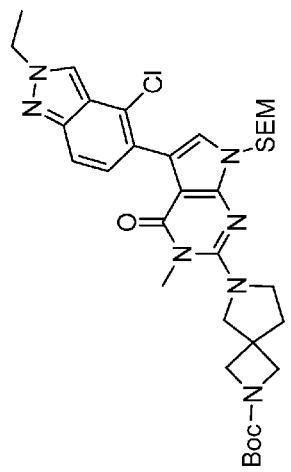
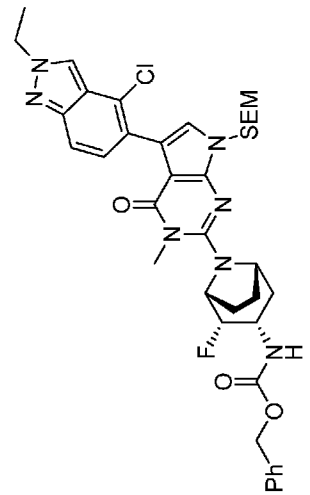
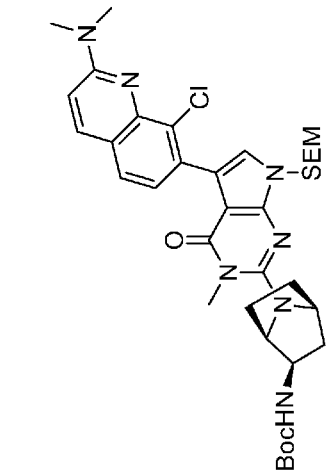
[1003]

[Table 13-6]

	*rac-tert*-butyl 6-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-3,6-diazabicyclo[3.2.1]octane-3-carboxylate	669	Prepared using general procedure 1 using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl 3,6-diazabicyclo[3.2.1]octane-3-carboxylate, purified by normal phase chromatography on silica gel.
	2-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-7-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one; trifluoroacetate	630	Starting from 4-chloro-7-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole, the title compounds was prepared using methods similar to those described for Example 72. Purified by reverse phase chromatography on C18 silica gel.
	*rac-tert*-butyl *N*-[*endo*-7-[5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl]carbamate	668	Prepared as general procedure 1 using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl *N*-[*endo*-2-methyl-7-azabicyclo[2.2.1]heptan-2-yl]carbamate (ChemExpress HY-23145). Purified by normal phase chromatography on NH silica gel.

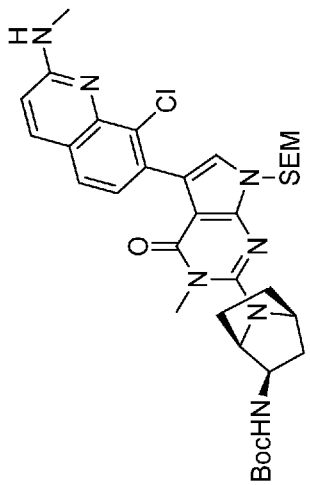
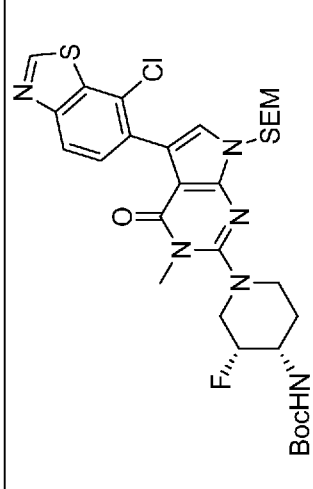
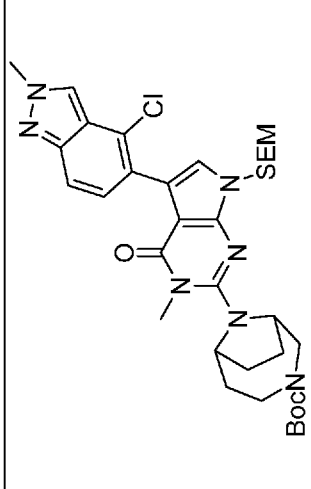
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[Table 13-7]

	*rac-tert*-butyl 6-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2,6-diazaspiro[3.4]octane-2-carboxylate	668.7	Prepared using general procedure 1 using 2-Chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac-tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate, purified by normal phase chromatography on silica gel.
	benzyl *N*-[(1*R*,2*S*,3*S*,5*S*)-8-[5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate	734	Prepared using general procedure 1 using 2-chloro-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and benzyl *N*-[(1*R*,2*R*,3*S*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl]carbamate hydrochloride, purified by normal phase chromatography on silica gel.
	*tert*-butyl *N*-[(1*R*,2*R*,4*S*)-7-{5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}-7-azabicyclo[2.2.1]heptan-2-yl]carbamate	694	Prepared as general procedure 1, using 2-chloro-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *N*-[(1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl]carbamate heating at 120°C for 7h, purified on KP-NH column.

[1005]

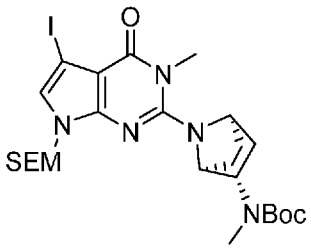
[Table 13-8]

	*tert*-butyl N-[(1*R*,2*R*,4*S*)-7-{5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}-7-azabicyclo[2.2.1]heptan-2-yl]carbamate	694	Prepared as general procedure 1, using 2-chloro-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *N*-[(1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptan-2-yl]carbamate heating at 120°C for 7h, purified on KP-NH column.
	2-((3*R*,4*S*)-4-amino-3-fluoropiperidin-1-yl)-5-(7-chlorobenzo[*d*]thiazol-6-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	663	Prepared using general procedure 1 using 2-chloro-5-(7-chloro-1,3-benzothiazol-6-yl)-3-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *tert*-butyl *N*-[(3*R*,4*S*)-3-fluoropiperidin-4-yl]carbamate
	*rac*-*tert*-butyl 9-[5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-{[2-(trimethylsilyl)ethoxy]methyl}-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]-3,9-diazabicyclo[4.2.1]nonane-3-carboxylate	668	Prepared using general procedure 1 using 2-chloro-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and *rac*-*tert*-butyl 3,9-diazabicyclo[4.2.1]nonane-3-carboxylate

[1006] Preparation 151: tert-Butyl ((1S,2S,4R)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate

[1007]

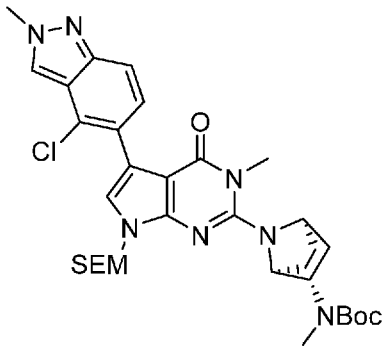
[Chem.208]



[1008] tert-Butyl ((1S,2S,4R)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate was prepared in the manner similar to preparation 93 and 94, except using tert-butyl ((1S,2S,4R)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate instead of tert-butyl ((1R,2R,4S)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate. MS: $[M+H]^+ = 630$.

[1009] Preparation 152: tert-Butyl ((1S,2S,4R)-7-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate

[1010] [Chem.209]

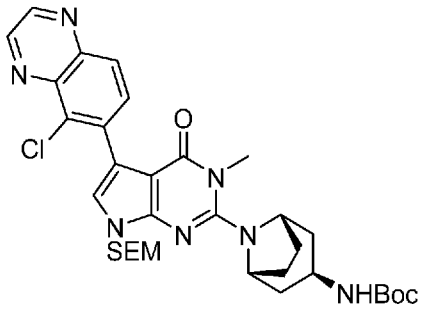


[1011] tert-Butyl ((1S,2S,4R)-7-(5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate was prepared in the manner similar to general procedure 2, except using tert-butyl ((1S,2S,4R)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(methyl)carbamate and 4-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole, MS: $[M+H]^+ = 668, 670$.

[1012] Preparation 153: tert-Butyl (endo-8-(5-(5-chloroquinoxalin-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)met

hyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate

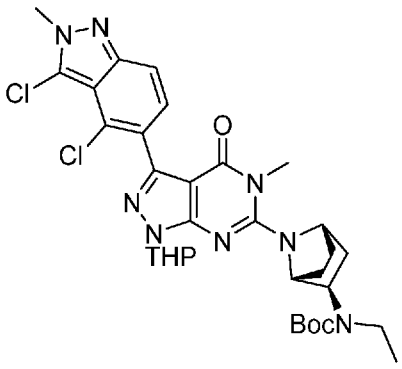
[1013] [Chem.210]



[1014] tert-Butyl (endo-8-(5-(5-chloroquinoxalin-6-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate was prepared in the manner similar to general procedure 2, except using tert-butyl (endo-8-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate and (5-chloroquinoxalin-6-yl)boronic acid and MS: $[M+H]^+$ = 666, 668.

[1015] Preparation 154: tert-Butyl ((1R,2R,4S)-7-(3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(ethyl)carbamate

[1016] [Chem.211]



[1017] tert-Butyl ((1R,2R,4S)-7-(3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(ethyl)carbamate was prepared in a similar manner to general procedure 3 except using tert-butyl ((1R,2R,4S)-7-(3-bromo-5-methyl-4-oxo-1-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1

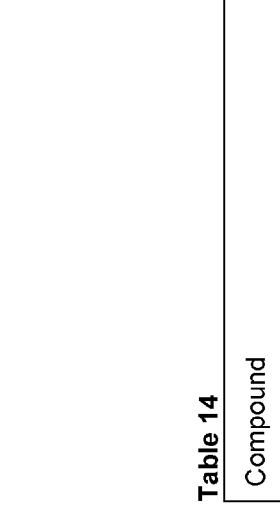
H-pyrazolo[3,4-d]pyrimidin-6-yl)-7-azabicyclo[2.2.1]heptan-2-yl)(ethyl)carbamate and
3,4-dichloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole, MS : $[M+H]^+$ = 671, 673.

[1018] Compounds of Table 14 below were prepared using procedures analogous to that described in general procedure 2 starting from the appropriate substituted protected pyrrolopyrimidinone and varying the boronate or boronic acid (synthesised as described above with any significant variations indicated below).

[1019]

[Table 14]

Table 14

Compound	Compound name	MS: m/z $[M+H]^+$	Procedure
	*tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-(4-chloro-2-(2-methoxyethyl)-2*H*-indazol-5-yl)-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate	698, 700	Prepared as general procedure 2 above using *tert*-butyl ((1*R*,2*R*,4*S*)-7-(5-iodo-3-methyl-4-oxo-7-((2-(trimethylsilyl)ethoxy)methyl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-7-azabicyclo[2.2.1]heptan-2-yl)carbamate and 4-chloro-2-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole

[1020]

[Table 15-1]

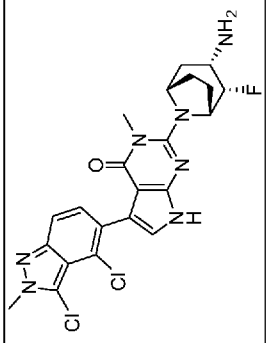
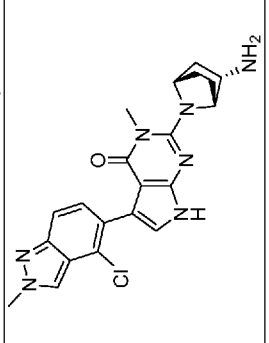
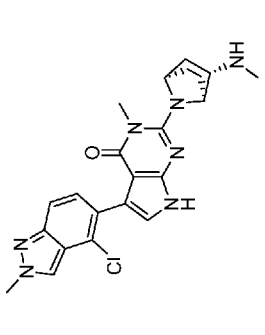
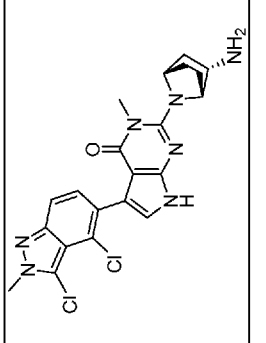
Table 15: Examples 160-178

By following methods similar and/or analogous to those described for general procedures for preparations of compounds of Formula (I) (methods 1-3), the compounds set out in Table 15 were prepared, with any significant variations indicated. The title compounds were either isolated directly as the free base or as the appropriate salt without further purification, or purified for example using mass-directed preparative HPLC, chromatography, crystallization or trituration and converted to the appropriate salt.

Example	Structure	Name	NMR data	MS: $[M+H]^+$ m/z	Method
160	HCl	6-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, hydrochloride salt	^{1}H-NMR (DMSO-d_6) δ: 13.40 (1H, s), 7.95 (3H, s), 7.59 (1H, *J* = 9.2 Hz, d), 7.29 (1H, *J* = 9.2 Hz, d), 4.28 (2H, s), 4.14 (3H, s), 3.48-3.40 (1H, m), 3.37 (3H, s), 2.53-2.48 (2H, m), 2.12-2.06 (2H, m), 1.84-1.78 (2H, m), 1.72-1.65 (2H, m).	473, 475	3 (given without purification)
161		6-(*endo*-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.58 (1H, *J* = 8.8 Hz, d), 7.29 (1H, *J* = 8.8 Hz, d), 4.18-4.13 (2H, m), 4.14 (3H, s), 3.36 (3H, s), 2.31-2.25 (2H, m), 1.89-1.82 (4H, m), 1.62-1.55 (2H, m), 1.06 (3H, s).	487, 489	3
162		6-((3*R*,4*S*)-4-amino-3-fluoropiperidin-1-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 8.45 (3H, s), 7.60 (1H, *J* = 8.8 Hz, d), 7.30 (1H, *J* = 8.8 Hz, d), 5.05 (1H, *J* = 48.8 Hz, d), 4.14 (3H, s), 3.92-3.81 (1H, m), 3.72-3.64 (1H, m), 3.35 (3H, s), 3.32-3.16 (1H, m), 3.01-2.93 (1H, m), 2.13-2.01 (1H, m), 1.59-1.58 (1H, m).	465, 467	3

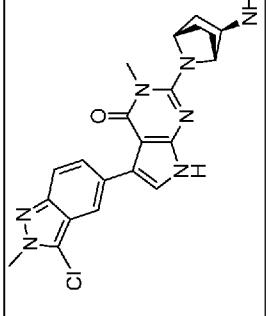
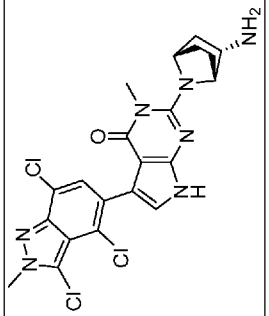
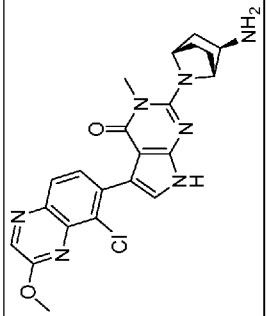
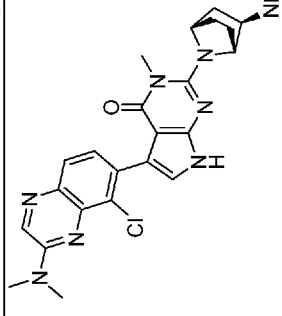
[1021]

[Table 15-2]

163		2-((1*R*,2*S*,3*S*,5*S*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, s), 7.51 (1H, *J* = 8.8 Hz, d), 7.33 (1H, *J* = 8.8 Hz, d), 6.99 (1H, s), 4.57-4.39 (2H, m), 4.15 (3H, s), 3.45 (3H, s), 3.04-2.92 (1H, m), 2.09-1.94 (2H, m), 1.90-1.80 (1H, m), 1.75-1.56 (4H, m).	490, 492	2
164		2-(*rac*-(1*R*,2*S*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.59 (1H, s), 8.38 (1H, s), 7.47 (1H, *J* = 8.8 Hz, d), 7.32 (1H, *J* = 8.8 Hz, d), 6.92 (1H, s), 4.24-4.21 (1H, m), 4.18 (3H, s), 3.95 (1H, *J* = 4.6 Hz, d), 3.46 (3H, s), 2.98-2.91 (1H, m), 1.91-1.54 (5H, m), 1.52-1.44 (1H, m), 1.38-1.28 (2H, m).	424, 426	2
165		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-2-((1*S*,2*S*,4*R*)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, s), 8.38 (1H, s), 7.47 (1H, *J* = 8.8 Hz, d), 7.31 (1H, *J* = 2.2 Hz, d), 6.94 (1H, *J* = 8.8 Hz, d), 4.25-4.14 (2H, m), 4.18 (3H, s), 3.40 (3H, s), 3.16-3.09 (1H, m), 2.27-2.19 (1H, m), 2.24 (3H, s), 2.08-2.01 (1H, m), 1.93-1.85 (1H, m), 1.74-1.64 (1H, m), 1.48-1.41 (1H, m), 0.96-0.89 (1H, m).	438, 440	2
166		2-((1*R*,2*S*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 7.49 (1H, *J* = 8.8 Hz, d), 7.32 (1H, *J* = 8.8 Hz, d), 6.95 (1H, s), 4.26-4.19 (1H, m), 4.13 (3H, s), 3.97-3.92 (1H, m), 3.46 (3H, s), 2.99-2.91 (1H, m), 1.90-1.70 (5H, m), 1.52-1.43 (1H, m), 1.37-1.26 (2H, m).	458, 460	2

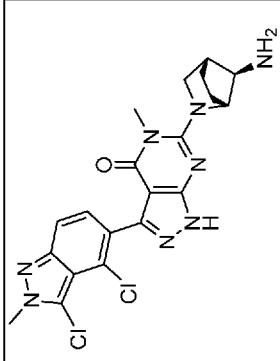
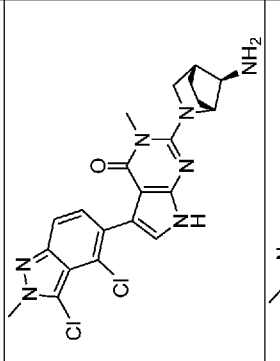
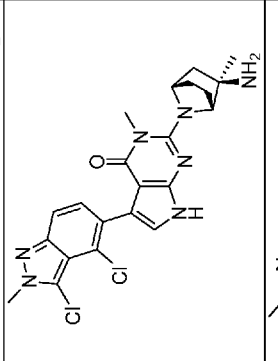
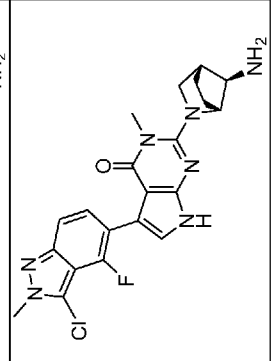
[1022]

[Table 15-3]

167		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, s), 8.44 (1H, s), 7.74 (1H, *J* = 9.3, 1.2 Hz, dd), 7.50 (1H, *J* = 9.3 Hz, d), 7.25 (1H, s), 4.13-4.08 (1H, m), 4.12 (3H, s), 4.02-3.99 (1H, m), 3.46 (3H, s), 2.31-2.04 (3H, m), 1.95-1.85 (1H, m), 1.71-1.62 (1H, m), 1.52-1.44 (1H, m), 0.92-0.84 (1H, m).	424, 426	2
168		2-((1*R*,2*S*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-5-(3,4,7-trichloro-2-methyl-2*H*-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, s), 7.47 (1H, s), 7.04 (1H, s), 4.17 (3H, s), 4.14-4.10 (1H, m), 4.03-3.96 (1H, m), 3.50-3.42 (2H, m), 3.39 (3H, s), 2.30-2.21 (1H, m), 2.20-2.10 (1H, m), 1.92-1.84 (1H, m), 1.71-1.60 (1H, m), 1.51-1.44 (1H, m), 0.92-0.83 (1H, m).	492, 494	2
169		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-methoxyquinoxalin-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.84 (1H, br s), 8.66 (1H, s), 7.94 (1H, d, *J* = 8.6 Hz), 7.76 (1H, d, *J* = 8.6 Hz), 7.17 (1H, s), 4.19-4.17 (1H, m), 4.13 (3H, s), 4.05-4.03 (1H, m), 3.52-3.47 (1H, m), 3.43 (3H, s), 2.34-2.26 (1H, m), 2.24-2.18 (1H, m), 2.05-1.68 (3H, m), 1.56-1.50 (1H, m), 0.93-0.88 (1H, m).	452, 454	2
170		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-(dimethylamino)quinoxalin-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.72 (1H, br s), 8.69 (1H, s), 7.69 (1H, d, *J* = 8.5 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 7.06 (1H, s), 4.15-4.13 (1H, m), 4.01-3.99 (1H, m), 3.48-3.43 (1H, m), 3.40 (3H, s), 3.32 (3H, s), 3.28 (3H, s), 2.30-2.23 (1H, m), 2.21-2.15 (1H, m), 1.94-1.88 (1H, m), 1.70-1.64 (2H, m), 1.52-1.46 (1H, m), 0.89-0.83 (1H, m).	465, 467	2

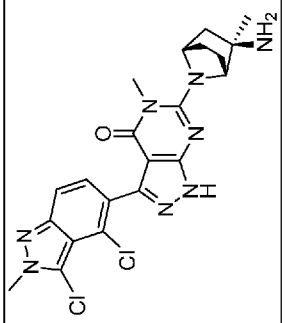
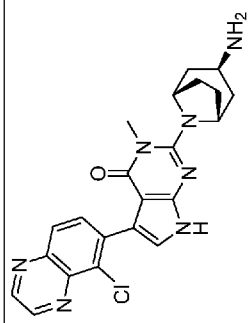
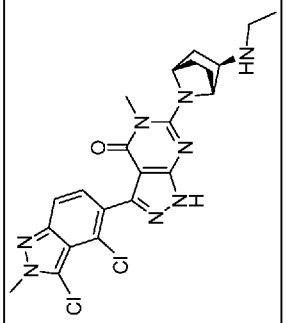
[1023]

[Table 15-4]

171		6-((1*R*,4*R*,7*R*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 7.60 13.20 (1H, br s), (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 4.16 (3H, s), 3.95-3.93 (1H, m), 3.79-3.75 (1H, m), 3.28 (3H, s), 3.26-3.24 (1H, m), 3.07 (1H, d, *J* = 9.2 Hz), 2.19-2.14 (1H, m), 2.02-1.84 (3H, m), 1.40-1.33 (1H, m).	459, 461	3
172		2-((1*R*,4*R*,7*R*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 7.49 (1H, d, *J* = 9.0 Hz), 7.32 (1H, d, *J* = 9.0 Hz), 6.90 (1H, s), 4.13 (3H, s), 3.85-3.83 (1H, m), 3.73-3.68 (1H, m), 3.28 (3H, s), 3.25-3.22 (1H, m), 3.01 (1H, d, *J* = 9.0 Hz), 2.18-2.14 (1H, m), 2.00-1.84 (3H, m), 1.40-1.33 (1H, m).	458, 460	2
173		*rac*-2-((1*R*,2*R*,4*S*)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 7.49 (1H, d, *J* = 9.3 Hz), 7.32 (1H, d, *J* = 9.2 Hz), 6.95 (1H, s), 4.20-4.17 (1H, m), 4.13 (6H, s), 3.78-3.75 (1H, m), 3.41 (3H, s), 2.24-2.17 (1H, m), 1.90-1.81 (2H, m), 1.75-1.66 (1H, m), 1.53-1.46 (1H, m), 1.23 (3H, s), 1.18-1.14 (1H, m).	472, 474	2
174		2-((1*R*,4*R*,7*R*)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3-chloro-4-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 7.66-7.62 (1H, m), 7.36 (1H, d, *J* = 9.0 Hz), 6.98 (1H, s), 4.12 (3H, s), 3.87-3.84 (1H, m), 3.73-3.68 (1H, m), 3.32 (3H, s), 3.26-3.23 (1H, m), 3.05-3.03 (1H, m), 2.18-2.13 (1H, m), 1.99-1.85 (3H, m), 1.42-1.32 (1H, m).	442, 444	2

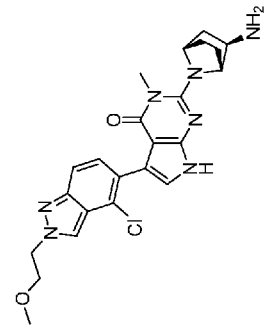
[1024]

[Table 15-5]

175		*rac*-6-((1*R*,2*R*,4*S*)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-5-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.38 (1H, br s), 7.61 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 4.31-4.27 (1H, m), 4.17 (3H, s), 3.88-3.84 (1H, m), 3.41 (3H, s), 2.28-2.20 (1H, m), 1.91-1.69 (3H, m), 1.57-1.49 (1H, m), 1.26-1.18 (4H, m).	473, 475	3
176		2-(*endo*-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(5-chloroquinoxalin-6-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.76 (1H, s), 9.06 (1H, d, J = 1.8 Hz), 9.00 (1H, d, J = 1.8 Hz), 8.03-7.94 (2H, m), 7.22 (1H, s), 4.12 (2H, s), 3.43 (3H, s), 2.34-2.21 (3H, m), 2.18-2.10 (2H, m), 2.00-1.92 (2H, m), 1.58 (2H, d, *J* = 13.2 Hz).	436, 438	2
177		3-(3,4-dichloro-2-methyl-2*H*-indazol-5-yl)-6-((1*R*,2*R*,4*S*)-2-(ethylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.61 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 4.29-4.23 (2H, m), 4.17 (3H, s), 3.39 (3H, s), 3.27-3.23 (1H, m), 2.48-2.44 (2H, m), 2.26-2.20 (1H, m), 2.12-2.07 (1H, m), 1.90-1.84 (1H, m), 1.72-1.65 (1H, m), 1.52-1.46 (1H, m), 1.02 (3H, t, *J* = 7.2 Hz), 0.98-0.93 (1H, m).	487, 489	3

[1025]

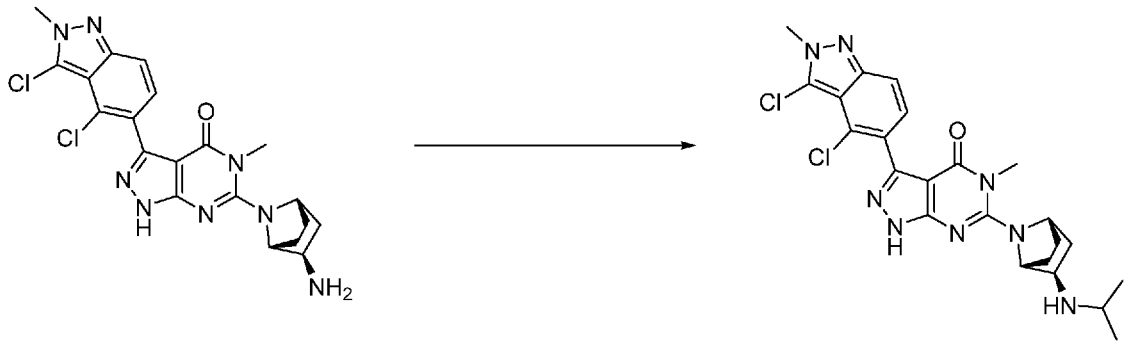
[Table 15-6]

178		2-((1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-(2-methoxyethyl)-2*H*-indazol-5-yl)-3-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.40 (1H, d, *J* = 0.6 Hz), 7.49 (1H, dd, *J* = 8.9, 0.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.94 (1H, s), 4.61 (2H, t, *J* = 5.2 Hz), 4.13 (1H, t, *J* = 4.9 Hz), 4.00 (1H, t, *J* = 5.3 Hz), 3.48-3.44 (1H, m), 3.39 (3H, s), 3.24 (3H, s), 2.29-2.23 (1H, m), 2.19-2.14 (1H, m), 1.94-1.87 (1H, m), 1.71-1.64 (1H, m), 1.52-1.46 (1H, m), 0.88 (1H, dd, *J* = 11.9, 4.6 Hz).	468, 470	2

[1026] Example 179 :

3-(3,4-Dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(isopropylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[1027] [Chem.212]

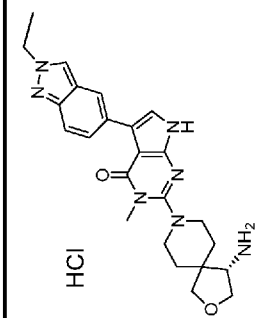


[1028] To a solution of 6-[(1S,3R,4R)-3-amino-7-azabicyclo[2.2.1]heptan-7-yl]-3-(3,4-dichloro-2-methyl-indazol-5-yl)-5-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-one (20.0 mg, 0.0435 mmol) in DCM (0.400 mL), acetone (0.0320 mL, 0.435 mmol) and $NaBH(OAc)_3$ (27.7 mg, 0.131 mmol) were added at r.t. . The mixture was stirred at r.t. for 18h. The reaction solution was then vacuum-concentrated, and the residue was purified by column chromatography on silica gel (gradient elution, 0 - 10% MeOH/$CHCl_3$) to give the title compound (14.1 mg). MS: $[M+H]^+$ = 501, 503. ^{1}H-NMR (DMSO-d_6) δ: 13.39 (1H, s), 7.61 (1H, d, J = 8.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 4.26-4.22 (2H, m), 4.17 (3H, s), 3.39 (3H, s), 2.72-2.66 (1H, m), 2.30-2.23 (1H, m), 2.13-2.06 (1H, m), 1.89-1.67 (3H, m), 1.54-1.48 (1H, m), 1.02-0.92 (7H, m).

[1029] Compounds of Table 16 below were prepared using procedures similar to those described for Example 150. The prerequisite substituted indazoles required were prepared using methods similar to those described above.

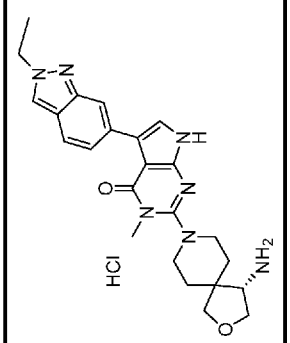
[Table 16-1]

Table 16

Example	Structure	Name	NMR Data	MS: $[M+H]^+$ m/z	Comment
180		2-[(4*S*)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.69 - 11.65 (m, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.67 (dd, J = 9.0, 1.6 Hz, 1H), 7.56 - 7.27 (m, 4H), 7.22 (d, J = 2.1 Hz, 1H), 4.43 (q, J = 7.3 Hz, 2H), 4.07 (dd, J = 10.0, 6.0 Hz, 1H), 3.81 - 3.73 (m, 2H), 3.68 (dd, J = 10.1, 3.6 Hz, 1H), 3.47 (s, 4H), 3.37 (d, J = 13.2 Hz, 1H), 3.29 (s, 1H), 2.92 (t, J = 11.2 Hz, 1H), 2.82 (t, J = 11.6 Hz, 1H), 1.92 - 1.78 (m, 2H), 1.66 (t, J = 14.2 Hz, 2H), 1.51 (t, J = 7.3 Hz, 3H).	448	Prepared using 5-bromo-1*H*-indazole
181		2-[(4*S*)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-4-fluoro-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.76 (br s, 1H), 8.52 (s, 1H), 7.72 (br s, 3H), 7.56 (dd, J = 8.9, 7.3 Hz, 1H), 7.38 (dd, J = 8.8, 0.9 Hz, 1H), 7.07 (s, 1H), 4.47 (q, J = 7.3 Hz, 2H), 4.09 (dd, J = 10.2, 5.9 Hz, 1H), 3.86 - 3.69 (m, 3H), 3.55 (dd, J = 6.0, 3.4 Hz, 1H),3.41 - 3.31 (m, 2H), 3.33 (s, 3H), 2.93 (t, J = 11.6 Hz, 1H), 2.82 (t, J = 11.7 Hz, 1H), 1.86 (m, 2H), 1.68 (t, J = 13.9 Hz, 2H), 1.52 (t, J = 7.3 Hz, 3H).	466	prepred starting from 5-bromo-4-fluoro-1*H*-indazole
182		2-[(4*S*)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(7-chloro-2-ethyl-2*H*-indazol-6-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-d]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.78 (d, J = 2.4 Hz, 1H), 8.47 (s, 1H), 8.41 (d, J = 5.5 Hz, 3H), 7.57 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 4.49 (q, J = 7.3 Hz, 2H), 4.09 (dd, J = 10.3, 6.0 Hz, 1H), 3.86 - 3.75 (m, 3H), 3.60 - 3.52 (m, 4H), 3.40 - 3.36 (m, 1H), 3.34 - 3.27 (m, 1H), 2.93 (t, J = 11.8 Hz, 1H), 2.81 (t, J = 11.8 Hz, 1H), 1.95 - 1.82 (m, 2H), 1.75 - 1.64 (m, 2H), 1.52 (t, J = 7.3 Hz, 3H).	482	Using 4-bromo-3-chloro-2-fluorobenzaldehyde as starting material

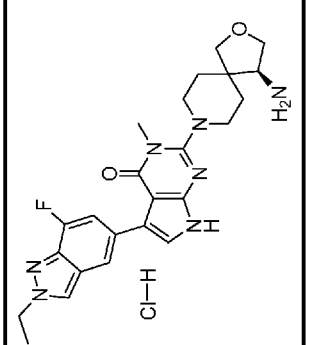
[1030]

[Table 16-2]

183		2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2*H*-indazol-6-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-d]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.76 (d, *J* = 2.6 Hz, 1H), 8.50 - 8.38 (m, 4H), 8.33 (s, 1H), 7.61 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.52 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.31 (d, *J* = 2.5 Hz, 1H), 4.44 (q, *J* = 7.3 Hz, 2H), 4.09 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.86 - 3.76 (m, 3H), 3.55 (m, 1H), 3.48 (s, 3H), 3.43 – 3.37 (m, 1H), 3.36 - 3.30 (m, 1H), 2.93 (t, *J* = 11.8 Hz, 1H), 2.81 (t, *J* = 11.8 Hz, 1H), 1.85 - 1.65 (m, 2H), 1.50-1.25 (m, 2H), 1.52 (t, *J* = 7.3 Hz, 3H).	448	Prepared using 6-bromo-1*H*-indazole
184		2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2*H*-indazol-6-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-d]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, Methanol-d_4) δ : 8.36 (d, *J* = 2.8 Hz, 1H), 7.49 (s, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 4.54 (q, *J* = 7.3 Hz, 2H), 4.20 (dd, J = 10.7, 5.5 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.85 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.66 - 3.61 (m, 1H), 3.57 (s, 3H), 3.52 - 3.42 (m, 2H), 3.10 - 3.01 (m, 1H), 3.01 - 2.93 (m, 1H), 2.03 - 1.94 (m, 2H), 1.89 - 1.76 (m, 2H), 1.63 (t, *J* = 7.3 Hz, 3H). The 4 exchangeable protons of the salt were not observed.	466	Using 4-bromo-2,3-difluorobenzaldehyde as starting material
185		2-[(*endo*)-3-amino-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-d]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 12.56 (s, 1H), 8.16 (s, 1H), 7.33 (br s, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.89 (t, *J* = 6.9 Hz, 1H), 6.69 (td, *J* = 7.3, 1.1 Hz, 1H), 4.68 (d, *J* = 6.3 Hz, 2H), 3.96 - 3.83 (m, 2H), 3.19 (dq, *J* = 7.2, 3.6 Hz, 1H), 2.81 (t, J = 6.4 Hz, 2H), 2.33 (m, 2H), 2.22 - 1.90 (m, 6H), 1.67 (m, , 2H).	488	Using N-[(*endo*)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-3-yl]-2-methylpropane-2-sulfinamide as the required amine

[1031]

[Table 16-3]

186		2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (500 MHz, DMSO-d_6) δ : 12.56 (s, 1H), 8.16 (s, 1H), 7.33 (br s, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.89 (t, *J* = 6.9 Hz, 1H), 6.69 (td, *J* = 7.3, 1.1 Hz, 1H), 4.68 (d, *J* = 6.3 Hz, 2H), 3.96 - 3.83 (m, 2H), 3.19 (dq, *J* = 7.2, 3.6 Hz, 1H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.33 (m, 2H), 2.22 - 1.90 (m, 6H), 1.67 (m, 2H).	466	Using from 5-bromo-2,3-difluorobenzaldehyde as starting material.

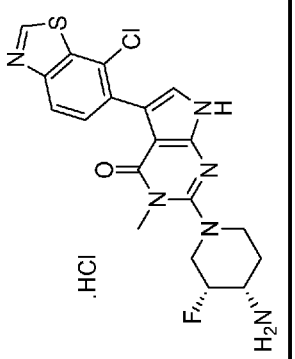
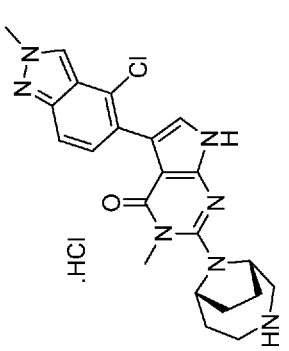
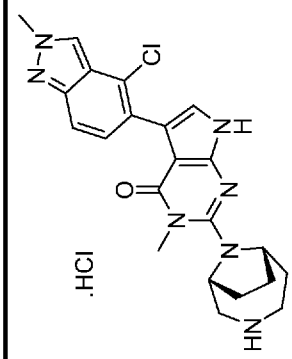
[1032] The compounds shown in Table 17 were prepared using methods similar to those

described in Method 1-9. The compounds could be isolated directly, by trituration/ precipitation from solution, or were purified (e.g. using mass-directed preparative HPLC, chromatography, crystallization). In some cases, the compound was isolated as the hydrochloride salt; by treating a solution of the final compound (e.g. in MeOH) with excess HCl (2N HCl in Et_2O) and then evaporating to dryness.

[1033]

[Table 17]

Table 17

Example	Structure	Name	NMR Data	MS: m/z [M+H]+	Comment
187		2-[(3*R*,4*S*)-4-amino-3-fluoropiperidin-1-yl]-5-(7-chloro-1,3-benzothiazol-6-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.92 (1H, d), 9.46 (1H, s), 8.38 (3H, d), 8.04 (1H, d), 7.65 (1H, d), 7.14 (1H, d), 5.07 (1H, d), 3.86-3.76 (1H, m), 3.67-3.50 (2H, m), 3.42 (3H, s), 3.27-3.13 (1H, m), 3.00-2.89 (1H, m), 2.13-2.04 (1H, m), 1.98-1.90 (1H, m).	433	Method 9
188		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(1*S*,6*R*)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.72 (1H, d), 9.63-9.52 (1H, m), 9.13-9.01 (1H, m), 8.41 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.02 (1H, d), 4.85-4.77 (1H, m), 4.32-4.24 (1H, m), 4.20 (3H, s), 3.50 (3H, s), 3.44-3.28 (2H, m), 3.20-3.04 (2H, m), 2.38-2.27 (2H, m), 2.11-1.95 (2H, m), 1.80-1.71 (2H, m).	438	Method 9
189		5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-2-[(1*R*,6*S*)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.72 (1H, d), 9.64-9.53 (1H, m), 9.15-9.01 (1H, m), 8.41 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.02 (1H, d), 4.85-4.77 (1H, m), 4.33-4.25 (1H, m), 4.20 (3H, s), 3.50 (3H, s), 3.45-3.24 (2H, m), 3.20-3.04 (2H, m), 2.38-2.27 (2H, m), 2.10-1.91 (2H, m), 1.83-1.67 (2H, m).	438	Method 9

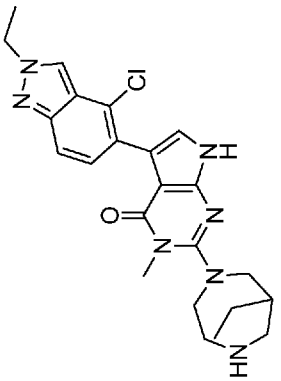
[1034] The compounds shown in Table 18 were prepared using methods similar to those

described in Method 1-9. The compounds could be isolated directly, by trituration/ precipitation from solution, or were purified (e.g. using mass-directed preparative HPLC, chromatography, crystallization). In some cases, the compound was isolated as the hydrochloride salt; by treating a solution of the final compound (e.g. in MeOH) with excess HCl (2N HCl in Et_2O) and then evaporating to dryness.

[1035]

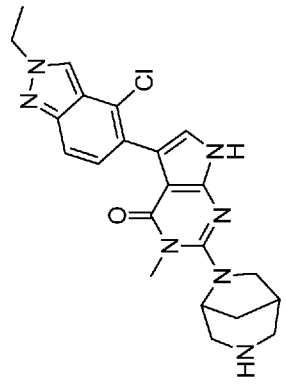
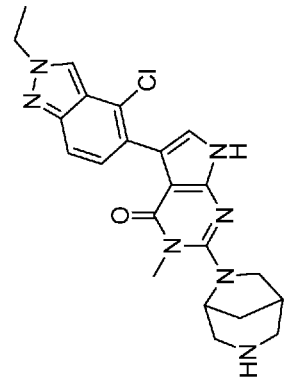
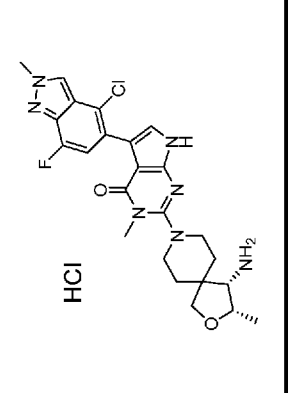
[Table 18-1]

Table 18

Example	Structure	Name	NMR Data	MS: [M+H]+ m/z	Comment
190		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-[3,6-diazabicyclo[3.2.1]octan-3-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (1H, d), 9.66 (1H, s), 9.07 (1H, s), 8.46 (1H, s), 7.52 (1H, dd), 7.32 (1H, d), 7.07 (1H, d), 4.49 (2H, q), 4.15-4.07 (1H, m), 3.55-3.48 (5H, m), 3.43-3.35 (1H, m), 3.34-3.16 (2H, m), 2.81 (1H, d), 2.75-2.69 (1H, m), 1.98 (1H, d), 1.94-1.86 (1H, m), 1.53 (3H, t).	438	Method 2, then purified by reverse phase chromatography on C18 silica gel. Further purification by chiral SFC (45% isocratic MeOH+0.1% DEA, AD column, gave the title compound as the faster eluting enantiomer
191		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-[3,6-diazabicyclo[3.2.1]octan-3-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (1H, d), 9.84 (1H, s), 9.16 (1H, s), 8.46 (1H, s), 7.51 (1H, d), 7.32 (1H, d), 7.06 (1H, d), 4.49 (2H, q), 4.14-4.07 (1H, m), 3.56-3.45 (5H, m), 3.45-3.34 (1H, m), 3.34-3.17 (2H, m), 2.81 (1H, d), 2.75-2.69 (1H, m), 1.97 (1H, d), 1.95-1.85 (1H, m), 1.53 (3H, t).	438.	Method 2, then purified by reverse phase chromatography on C18 silica gel. Further purification by chiral SFC (45% isocratic MeOH+0.1% DEA, AD column, gave the title compound as the slower eluting enantiomer

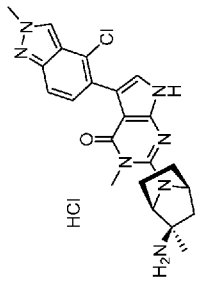
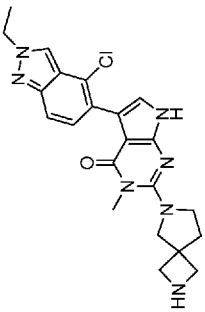
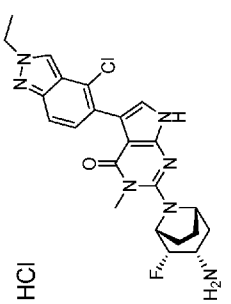
[1036]

[Table 18-2]

192		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-{3,6-diazabicyclo[3.2.1]octan-6-yl}-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (1H, d), 9.79 (1H, d), 8.76 (1H, br. s), 8.45 (1H, s), 7.51 (1H, dd), 7.32 (1H, d), 6.95 (1H, d), 4.65-4.58 (1H, m), 4.49 (2H, q), 3.75-3.60 (3H, m), 3.47 (3H, s), 3.17 (2H, s), 3.11-3.01 (1H, m), 2.72 (1H, s), 1.95 (1H, d), 1.93-1.84 (1H, m), 1.53 (3H, t).	438	Method 2, then purified by reverse phase chromatography on C18 silica gel. Further purification by chiral SFC (40% isocratic EtOH+0.1% DEA, AD column provided the title compound as the faster eluting enantiomer.
193		5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-{3,6-diazabicyclo[3.2.1]octan-6-yl}-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (1H, d), 9.57 (1H, d), 8.67 (1H, br. s), 8.45 (1H, s), 7.51 (1H, dd), 7.32 (1H, d), 6.96 (1H, d), 4.63-4.59 (2H, m), 4.52-4.46 (2H, m), 3.79-3.66 (2H, m), 3.61 (1H, d), 3.47 (3H, s), 3.21-3.18 (1H, m), 3.13-2.99 (1H, m), 2.74 (1H, s), 2.00-1.85 (2H, m), 1.54 (3H, t).	438	Method 2, then purified by reverse phase chromatography on C18 silica gel. Further purification by chiral SFC (40% isocratic EtOH+0.1% DEA, AD column provided the title compound as the slower eluting enantiomer.
194		2-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-7-fluoro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (1H, d), 8.56 (1H, d), 8.09 (3H, br. s), 7.18 (1H, d), 7.12 (1H, d), 4.26-4.20 (4H, m), 3.88 (1H, d), 3.67 (1H, d), 3.53-3.42 (4H, m), 3.42-3.28 (2H, m), 2.94-2.77 (2H, m), 2.00-1.87 (2H, m), 1.78 (1H, d), 1.66 (1H, d), 1.25 (3H, d)	500	Method 2, purified by reverse phase chromatography on C18 silica gel.

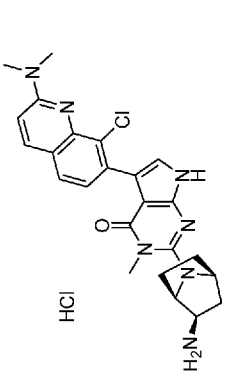
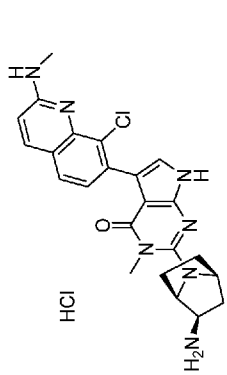
[1037]

[Table 18-3]

195		2-[(*endo*)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl]-5-(4-chloro-2-methyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73 (1H, d), 8.51 (3H, s), 8.40 (1H, s), 7.49 (1H, dd), 7.32 (1H, d), 6.99 (1H, d), 4.34 (1H, t), 4.20 (3H, s), 4.14 (1H, d), 3.43 (3H, s), 2.21-2.10 (1H, m), 2.05-1.98 (1H, m), 1.96-1.87 (1H, m), 1.86-1.76 (1H, m), 1.75-1.69 (1H, m), 1.65 (1H, d), 1.46 (3H, s).	438	Method 9, purified by prep SFC (50% MeOH + 0.1% diethylamine)
196		*rac*-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-2-[2,6-diazaspiro[3.4]octan-6-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one	^{1}H NMR (400 MHz, Me-d3-OD) δ: 8.31 (1H, s), 7.52 (1H, dd), 7.45 (1H, d), 6.95 (1H, s), 4.53 (2H, q), 3.80 (2H, d), 3.76-3.61 (4H, m), 3.58 (2H, t), 3.50 (3H, s), 2.24 (2H, t), 1.64 (3H, t).	438	Method 2. Purified by reverse phase chromatography on C18 silica gel and then by preparative HPLC.
197		2-[(1*R*,2*S*,3*S*,5*S*)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-ethyl-2*H*-indazol-5-yl)-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.68 (1H, d), 8.45 (1H, s), 8.30 (3H, br s), 7.51 (1H, dd), 7.31 (1H, d), 6.98 (1H, d), 4.96-4.79 (1H, m), 4.60-4.53 (1H, m), 4.49 (2H, q), 4.31-4.23 (1H, m), 3.76-3.60 (1H, m), 3.46 (3H, s), 2.29-2.19 (1H, m), 2.14-2.00 (2H, m), 1.97-1.88 (1H, m), 1.78-1.67 (2H, m), 1.53 (3H, t).	470	Method 2 followed by Method 5. Purified by reverse phase chromatography on C18 silica gel and then by preparative HPLC.

[1038]

[Table 18-4]

198		2-[(1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.22 (1H, d), 7.72 (1H, d), 7.40 (1H, d), 7.27 (1H, d), 7.11 (1H, s), 4.37 (1H, s), 4.28 (1H, s), 3.83-3.67 (1H, m), 3.40 (3H, s), 3.31 (7H, s), 1.95 (2H, s), 1.88-1.71 (1H, m), 1.65 (1H, d), 1.36 (1H, dd).	464	Method 9
199		2-[(1*R*,2*R*,4*S*)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (1H, s), 8.53-8.32 (1H, m), 7.84 (1H, s), 7.53 (1H, d), 7.23 (2H, s), 4.39 (1H, s), 4.30 (1H, s), 3.41 (3H, s), 3.13 (3H, s), 1.96 (2H, s), 1.83 (1H, d), 1.66 (1H, s), 1.38 (1H, dd).	450	Method 9

[1039] BIOLOGICAL ASSAYS

SHP2 Biochemical Assay

SHP2 activity was monitored by measuring the conversion of the surrogate substrate 6,8-difluoromethylumbelliferyl phosphate (DiFMUP) to the fluorescent product, 6,8-difluoromethylumbelliferone (DiFMU).

[1040] SHP2 was pre-incubated with test compounds and the activating peptide pIRS1 (H_2 N-LN(pY)IDLDLV-$(PEG)_8$-LST(pY)ASINFQK-amide) for 30 min, prior to addition of the 6,8-difluoromethylumbelliferyl phosphate (DiFMUP), (Thermo Fisher D6567). Final assay concentrations were 10 pM SHP2, 0.25 μM pIRS1 peptide,50 μM DiFMUP, 25mM Bis-Tris propane, pH 7.0, 150 mM NaCl, 0.05 % (v/v) Tween-20, 0.5 mM TCEP and 5 % (v/v) DMSO. Rates of reaction were then measured over 30 min by monitoring fluorescence on a BMG Pherastar reader at excitation 360nm/emission 450nm. IC_{50} values were calculated in singlicate from the normalized dose-response plots using four parameter logistic curve fit. The Experiment for each compound was carried out in one time or multiple times, and the IC_{50} values were shown as a single value (for a compound measured in a single experiment) or an average value (for a compound measured in multiple experiments).

[1041] Results were shown in the Table 19 and 20.

[1042] Cellular pERK Inhibition Assay

Method A:

pERK levels were determined using the In-Cell Western assay. HCC827 cells (ATCC, Manassas, USA) were seeded into 384-well plates at a density of 1 x 10^4 cells/ well in RPMI1640 medium supplemented with 10% FBS and incubated 24h. Compounds were diluted first in DMSO and then into serum-free medium, before being added to cells in quadruplicate to give a final concentration of 0.2% DMSO. Plates were incubated at 37°C for the indicated time in a humidified atmosphere of 5% CO_2 in air.

[1043] Following compound treatment, cells were fixed with formalin neutral buffer solution for 20 minutes at room temperature. Plates were washed three times with 0.1% Triton-X in PBS and cells were blocked for 1 hour with Odyssey blocking buffer (LI-COR, #927-40000). After shaking out blocking buffer, cells were incubated with phospho-p44/42 ERK antibody (Cell Signalling Technology, #4370, 1:200) diluted in Odyssey blocking buffer at 4 °C overnight. Plates were washed again and cells were incubated for 1 hour with Goat anti-Rabbit IR Dye 800CW (LI-COR, #926-32211, 1:800) diluted in Odyssey blocking buffer. After washing and removing wash solution completely using a centrifuge machine, cells were scanned on the Odyssey (LI-COR), following the manufacturer's instructions. The average signal from blank wells (no cells added) was subtracted from the signals from each sample well. Levels of pERK were then expressed as percent of control, using DMSO treated samples as control. The relative IC_{50} values werecaluculated in quadruplicate from the normalized dose-

response plots using four parameter logistic curve fit. The Experiment for each compound was carried out in one time or multiple times, and the IC_{50} values were shown as a single value (for a compound measured in a single experiment) or an average value (for a compound measured in multiple experiments).

[1044] Results were shown in the Table 19 and 20.

[1045] Method B:

HCC827 cells (ATCC, Manassas, USA) were seeded into 96-well plates at a density of 1 x 10^5 cells/well in RPMI medium supplemented with 10% FBS and incubated 24h. Compounds were diluted first in DMSO and then into serum-free medium, before being added to cells in triplicate to give a final concentration of 0.1% DMSO. Plates were incubated at 37°C for the indicated time in a humidified atmosphere of 5% CO_2 in air.

[1046] Following compound treatment, medium was removed and cells were lysed by adding 50 μL of lysis buffer (Cell Signalling Technology, Beverly, USA) to each well. Plates were then incubated at room temperature for 25 minutes with shaking. pERK levels were measured in lysates using the PathScan(Registered Trademark) phospho-p44/42 MAPK (Thr202/Tyr204) sandwich ELISA (Cell Signalling Technology, Beverly, USA) as per kit instructions. Briefly, 50 μL of cell lysate was added to 50 μL of ELISA sample diluent in a 96-well ELISA plate and incubated overnight at 4°C. Following washing, 100 μL of detection antibody was added per well and the plates incubated for 1 hour at 37°C. Plates were washed again and incubated at 37°C for 30 minutes with 100μl of HRP-linked secondary antibody per well. After final washing, 100 μL per well of TMB substrate was added and plates incubated at 37°C to develop colour. Colour development was stopped by the addition of 100 μL per well of stop solution. Plates were read at 450nm on a SpectraMax Gemini reader (Molecular Devices, Uckfield, UK).

[1047] The average signal from blank wells (no cells added) was subtracted from the signals from each sample well. Levels of pERK were then expressed as “percent of control”, using DMSO treated samples as control. Dose response curves were generated using GraphPad Prism Version 6 (GraphPad Software, La Jolla, USA) and fitted using the four parameter logistic curve fit.

[1048] Results were shown in the Table 19 and 20.

[1049]

[Table 19-1]

Table 19

Example	SHP2 (IC50, μM)	pERK (IC50, μM)	pERK (IC50, μM)
		Method A	Method B
1	0.014	0.14	
2	0.014	0.13	
3	0.015	0.21	
4	0.0075	0.12	
5	0.0075	0.16	
6	0.0065	0.58	
7	0.0090	0.17	
8	0.011	0.095	
9	0.094	1.2	
10	0.0085	0.17	
11	0.0063	0.053	
12	0.011	0.12	
13	0.019	0.34	
14	0.024	0.31	
15	0.017	0.50	
16	0.011	0.11	
17	0.043	0.80	
18	0.23		
19	0.35		
20	0.76		
21	0.011	0.32	
22	0.014	2.2	
23	0.12	4.1	
24	0.018	0.14	
25	0.035	0.43	
26	0.011	0.088	
27	0.0070	0.046	
28	0.019	0.68	
29	0.22	2.4	
30	0.0097	0.22	
31	0.040	1.0	
32	0.017	0.92	
33	0.047	0.48	
34	0.16	2.3	
35	0.038	1.0	

[1050]

[Table 19-2]

36	0.0055	0.35	
37	0.012	0.97	
38	0.074	1.4	
39	0.066	0.70	
40	0.096	4.5	
41	0.057	1.8	
42	0.078		
43	0.035	0.72	
44	0.055	1.5	
45	0.11	1.5	
46	0.033	0.42	
47	0.032	0.38	
48	0.085	1.0	
49	0.0045	0.021	
50	0.25	4.7	
51	0.012	0.061	
52	0.18	1.9	
53	0.33	3.1	
54	0.11	1.8	
55	0.074	1.1	
56	0.073	1.1	
57	0.12	2.9	
58	0.099	>10	
59	0.0055	0.048	
60	0.082	3.8	
61	0.098	1.8	
62	0.023	0.36	
63	0.11	4.3	
64	0.042	1.5	
65	0.033	0.43	
66	0.0082	0.082	
67	0.34	3.4	
68	0.041	0.67	
69	0.12	3.0	
70	0.029	0.19	
71	0.26	5.0	
72	0.099	1.9	
73	0.87	>10	
74	0.17	5.4	
75	0.028	2.1	
76	0.031	0.18	
77	0.040	1.9	

[1051] [Table 19-3]

78	0.0060	0.13	
79	0.0055	0.16	
80	0.011	0.27	
81	0.014	0.78	
82	0.014	0.91	
83	0.011	0.19	
84	0.018	0.55	
85	0.013	0.64	
86	0.059	5.2	
87	0.068	0.58	
88	0.052	4.5	
89	0.014	0.54	
90	0.012	0.74	
91	0.012	0.34	
92	0.0033	0.032	
93	0.0020	0.021	
94	0.0050	0.072	
95	0.0025	0.068	
96	0.0028	0.030	
97	0.0077	0.082	
98	0.010	0.19	
99	0.0045	0.057	
100	0.0060	0.095	
101	0.0015	0.046	
102	0.0090	0.088	
103	0.0020	0.026	
104	0.0027	0.084	
105	0.0050	0.16	
106	0.0050	0.10	
107	0.0070	0.27	
108	0.0040	0.090	
109	0.0065	0.12	
110	0.014	1.7	
111	0.026	0.41	
112	0.013	0.26	
113	0.0045	0.078	
114	0.0055	0.073	
115	0.046	0.49	
116	0.0090	0.10	
117	0.025	0.64	
118	0.049	1.1	
119	0.017	0.29	

[1052] [Table 19-4]

120	0.029	0.55	
121	0.016	0.21	
122	0.0080	0.14	
123	0.018	0.17	
124	0.019	0.43	
125	0.017	0.26	
126	0.013	0.084	
127	0.0037	0.063	
128	0.011	0.16	
129	0.069	0.98	
130	0.063	0.80	
131	0.028	0.46	
132	0.015	0.25	
133	0.0067	0.046	
134	0.0040	0.083	
135	0.048	0.95	
136	0.03		2.7
137	0.059		45% at 3.0μM
138	0.019		1.6
139	0.02		0.097
140	0.017		0.48
141	0.043		64% at 10μM
142	0.017		0.11
143	0.022		0.081
144	0.019		0.21
145	0.15		
146	0.057		3.8
147	0.012		0.034
148	0.024		0.025
149	0.29		
150	0.012		0.013
151	0.023		0.52
152	0.029		0.66
153	0.026		0.52
154	0.021		0.92
155	0.0040		
156	0.25		
157	0.0037	0.022	
158	0.25	2.0	
159	0.0035	0.15	

[1053]

[Table 20]

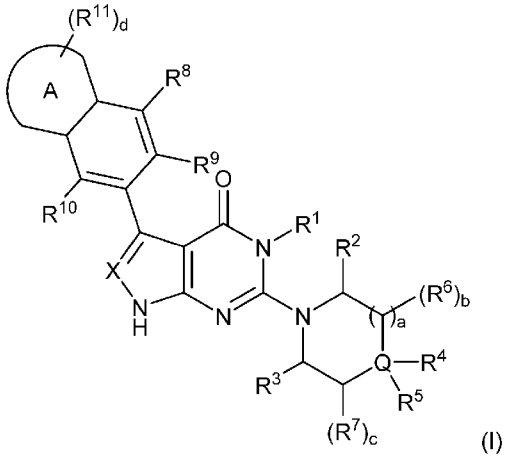
Table 20

Example	SHP2 (IC50, μM)	pERK (IC50, μM) Method A	pERK (IC50, μM) Method B
160	0.0085	0.23	
161	0.012	0.26	
162	0.042	0.81	
163	0.002	0.012	
164	0.17	6.3	
165	0.084	1.4	
166	0.053		
167	0.013		
168	0.007		
169	0.0033	0.073	
170	0.003	0.016	
171	0.0026	0.02	
172	0.0015	0.016	
173	0.0025	0.14	
174	0.003	0.021	
175	0.012	0.22	
176	0.077	0.66	
177	0.095	1.4	
178	0.005	0.071	
179	0.15	2.1	
180	0.034		0.85
181	0.023		0.21
182	0.036		2.2
183	0.14		
184	0.07		1.1
185	0.18		
186	0.036		
187	0.051		0.8
188	0.041		0.56
189	0.019		0.23
190	0.045		3.3
191	0.092		60% at 10uM
192	0.067		0.99
193	0.26		
194	0.016		0.043
195	0.016		0.045
196	0.032		
197	0.012		0.032
198	0.013		0.066
199	0.014		0.11

Claims

[Claim 1] A compound of formula (I):

[Chem.1]



(I)

or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is $-CH_3$;

R^2 and R^3 are independently selected from hydrogen and C_{1-4}alkyl;

Q is C or N;

wherein when Q is C then either:

(i) R^4 is amino, aminoC_{1-4}alkyl or monoC_{1-4}alkylamino;

R^5 is hydrogen, C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;

; or

(ii) R^4 and R^5 together with Q form a four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, S, NH, C(O) and $S(O)_m$, and said ring formed by R^4 and R^5 can be unsubstituted or substituted with 1 to 4 groups independently selected from amino, halogen, haloC_{1-4}alkyl, hydroxyl, methoxy, methylamino, and C_{1-4}alkyl, and m is selected from 1 and 2; and

wherein when Q is N then:

R^4 is absent; and

R^5 is hydrogen;

R^6 and R^7 are independently selected from halogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl and hydroxyl provided that when Q is N then R^6 or R^7 are not halogen or hydroxyl;

Or, any two groups selected from R^2, R^3, R^6 and R^7 together form a one- to three-membered bridge group selected from C_{1-3}alkylene, C_{2-3} alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen and C_{1-4}alkyl;

Or, R^4 and R^7 form a four- to six-membered ring containing a N atom;

Or, R^5 and R^7 form a three- to six-membered ring;

Or, R^6 and R^7 form a direct bond;

a is selected from 0, 1 and 2;

b is selected from 0, 1 and 2;

c is selected from 0, 1 and 2;

Or, Q is C, c is 2, R^4 is hydrogen and the two R^7 join to form a 4 to 6 membered nitrogen containing ring;

Ring A is either:

(i) a five-membered nitrogen-containing heterocyclic ring wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S, or

(ii) a six-membered aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N, O and S; or

(iii) a six-membered non-aromatic nitrogen-containing heterocyclic ring, wherein the heterocyclic ring optionally contains one or two additional heteroatoms selected from N and S;

R^8 is selected from hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl and halogen;

R^9 is selected from hydrogen and halogen;

R^{10} is selected from haloC_{1-4}alkyl, C_{1-4}alkyl, halogen, hydrogen or C_{1-4} alkoxy;

R^{11} are independently selected from halogen, cyano, cyanoC_{1-4}alkyl, hydroxyl, oxo (=O), C_{1-4}alkyl optionally substituted with five- or six-membered heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxylC_{1-4}alkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{1-4}alkylsulfone, amino, monoC_{1-4}alkylamino, diC_{1-4} alkylamino, aminoC_{1-4}alkyl, -C_{1-4}alkylene-C(=O)$NH_{(2-q)}(C_{1-6}alkyl)_q$), -$C_{1-4}$alkylene-NHC(=O)$C_{1-6}$alkyl, sulfonamide, sulfonamideC_{1-4}alkyl, 3 to 6 membered cycloalkyl, C_{1-4}alkyl substituted with 3 to 6 membered cycloalkyl, five- or six-membered unsaturated heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, N, or S, and op-

tionally substituted four- to six-membered saturated heterocyclic group containing 1 or 2 heteroatoms selected from O, N, or S where the optional substituent is selected from C_{1-4}alkyl;
q is selected from 0, 1 or 2; and
d is selected from 0, 1 and 2.

[Claim 2] A compound according to claim 1 or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein:
Ring A is a five-membered or six-membered nitrogen-containing heteroaromatic ring wherein the ring optionally contains one or two additional heteroatoms selected from N, O and S.

[Claim 3] A compound according to claim 1 or 2, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein any two groups selected from R^2, R^3, R^6 and R^7 together form a one- to three-membered bridge group selected from C_{1-3}alkylene, C_{2-3}alkenylene, methylene-NR^q-methylene and methylene-O-methylene, wherein the bridge group is optionally substituted by a group selected from C_{1-4}alkyl, hydroxyl and halogen and R^q is selected from hydrogen and C_{1-4}alkyl.

[Claim 4] A compound according to any one of claims 1 to 3, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein
Q is C.

[Claim 5] A compound according to any one of claims 1 to 4, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein
R^4 is amino, aminoC_{1-4}alkyl or monoC_{1-4}alkylamino;
R^5 is hydrogen, C_{1-4}alkyl, halogen, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl

[Claim 6] A compound according to any one of claims 1 to 4, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein
R^4 and R^5 together with Q form a four- to six-membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, O, S, NH, C(O) and $S(O)_m$, and said ring formed by R^4 and R^5 can be unsubstituted or substituted with 1 to 4 groups independently selected from amino, halogen, halo$_{C1-4}$alkyl, hydroxyl, methoxy, methylamino, and C_{1-4}alkyl, and m is selected from 1 and 2

[Claim 7] A compound according to any one of claims 1 to 5, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein Q is N.

[Claim 8] A compound according to any one of claims 1 to 7, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein X is CH.

[Claim 9] A compound according to any one of claims 1 to 7, or a tautomer or a

solvate or a pharmaceutically acceptable salt thereof, wherein X is N.

[Claim 10] A compound according to claim 1, or a tautomer or a solvate or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(4-amino-4-methylpiperidin-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(2-(tert-butyl)-4-chloro-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(exo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

(R)-2-(1-amino-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

(S)-2-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(endo-3-(methylamino)-8-azabicyclo[3.2.1]octan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(hydroxymethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-(3-(2-hydroxyethyl)piperazin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(7-amino-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-8-amino-3-azabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol

-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(2,5-diazabicyclo[2.2.2]octan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(exo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-9-azabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,8-diazaspiro[4.5]decan-8-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(piperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,7-diazabicyclo[4.2.0]octan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,9-diazaspiro[5.5]undecan-9-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(1,7-diazaspiro[3.5]nonan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-aminopyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(3-methylpipera

zin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,4R)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-(2-methylpiperazin-1-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-amino-3,3-difluoropyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-amino-3-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3R,4R)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
,
2-((3R,4S)-3-amino-4-methylpyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
,
2-(3-amino-3-(hydroxymethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(R)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

2-(1-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
(S)-2-(3-(aminomethyl)pyrrolidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-methoxypiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-methyl-5-(2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-ethylbenzo[d]oxazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6,7-difluoro-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(6-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-methoxy-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-(2-hydroxy-2-methylpropyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrol

o[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2,7-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(1H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
3-(5-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(6-(2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-7-chlorobenzo[d]thiazol-2-yl)-N,N-dimethylacetamide,
2-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylacetamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,

3-(5-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-3,4-dichloro-2H-indazol-2-yl)-N,N-dimethylpropanamide,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2,3-dimethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-methoxy-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,

3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-(fluoromethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-3-methyl-2-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-5-(7-chlorobenzo[d]thiazol-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-3-(difluoromethyl)-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-ethyl-3-(hydroxymethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(3,9-diazabicyclo[3.3.1]nonan-9-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(7-chloro-2-methylbenzo[d]thiazol-6-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-6-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-ethyl-2H-indazol-5-yl)-5-methyl-6-((1R,2R,4S)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[

2,3-d]pyrimidin-4-one,
2-((1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,3R,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1S,2S,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(7-chlorobenzo[d]thiazol-6-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,4S,7S)-7-(methylamino)-2-azabicyclo[2.2.1]heptan-2-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
endo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{3,8-diazabicyclo[3.2.1]octan-8-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R,3S)-1-amino-3-hydroxy-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
exo-6-[3-amino-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-6-{2,7-diazaspiro[3.5]nonan-7-yl}-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1R)-1-amino-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[(1R,3R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-6-{3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl}-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-3-(4-chloro-2-ethyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
6-[(1S,2R,3S,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-3-(4-chloro-2-methyl-2H-indazol-5-yl)-5-methyl-1H,4H,5H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-(1,4-diazepan-1-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-[(1R,2R,5R)-2-amino-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-(4-aminoazepan-1-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1S,4S,7S)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rel-2-((1S,4S,7S)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(4-chloro

-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-chloro-2-ethyl-2H-indazole-3-carbonitrile,
6-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-(endo-3-amino-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
6-((3R,4S)-4-amino-3-fluoropiperidin-1-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-(rac-(1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-2-((1S,2S,4R)-2-(methylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2S,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-3-methyl-5-(3,4,7-trichloro-2-methyl-2H-indazol-5-yl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-methoxyquinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(5-chloro-3-(dimethylamino)quinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,

6-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-2-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-5-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
2-((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)-5-(3-chloro-4-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-6-((1R,2R,4S)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl)-3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-(endo-3-amino-8-azabicyclo[3.2.1]octan-8-yl)-5-(5-chloroquinoxalin-6-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(ethylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)-5-(4-chloro-2-(2-methoxyethyl)-2H-indazol-5-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one,
3-(3,4-dichloro-2-methyl-2H-indazol-5-yl)-6-((1R,2R,4S)-2-(isopropylamino)-7-azabicyclo[2.2.1]heptan-7-yl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-4-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(7-chloro-2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(endo)-3-amino-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-

d]pyrimidin-4-one,
2-[(4S)-4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(2-ethyl-7-fluoro-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(3R,4S)-4-amino-3-fluoropiperidin-1-yl]-5-(7-chloro-1,3-benzothiazol-6-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1S,6R)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-methyl-2H-indazol-5-yl)-2-[(1R,6S)-3,9-diazabicyclo[4.2.1]nonan-9-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1R,5R)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{(1S,5S)-3,6-diazabicyclo[3.2.1]octan-3-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1S,5R)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one
,
5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-[(1R,5S)-3,6-diazabicyclo[3.2.1]octan-6-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-(4-chloro-7-fluoro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(endo)-2-amino-2-methyl-7-azabicyclo[2.2.1]heptan-7-yl]-5-(4-chloro-2-methyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
rac-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-2-{2,6-diazaspiro[3.4]octan-6-yl}-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(1R,2S,3S,5S)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octan-8-yl]-5-(4-chloro-2-ethyl-2H-indazol-5-yl)-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one,
2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(dimethylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one, and
2-[(1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl]-5-[8-chloro-2-(methylamino)quinolin-7-yl]-3-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one.

[Claim 11] A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

[Claim 12] A pharmaceutical composition according to claim 11 for the pro-

phylaxis or treatment of a disease or condition mediated by SHP2.

[Claim 13] A compound according to any one of claims 1 to 10 for use in therapy.

[Claim 14] A compound according to any one of claims 1 to 10 for use in the prophylaxis or treatment of a disease or condition mediated by SHP2.

[Claim 15] A use of a compound according to any one of claims 1 to 10 for the manufacture of a medicament for use in the prophylaxis or treatment of a disease or condition mediated by SHP2.

[Claim 16] A method for the prophylaxis or treatment of a disease or condition mediated by SHP2 comprising administering to a patient a compound according to any one of claims 1 to 10.

[Claim 17] A pharmaceutical composition of claims 11 and 12, a compound of claims 13 and 14, a use of claim 15 or a method of claim 16, wherein the subject of therapy or the disease or condition mediated by SHP2 is cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2019/028822

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. C07D519/00(2006.01)i, A61K31/519(2006.01)i, A61P35/00(2006.01)i, A61P43/00(2006.01)i, C07D451/02(2006.01)i, C07D487/04(2006.01)i

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)

Int.Cl. C07D519/00, A61K31/519, A61P35/00, A61P43/00, C07D451/02, C07D487/04

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

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2019
Registered utility model specifications of Japan 1996-2019
Published registered utility model applications of Japan 1994-2019

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

JSTPlus/JMEDPlus/JST580 (JDreamIII), CAplus/REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/203404 A1 (NOVARTIS AG) 2016.12.22, THE WHOLE DOCUMENT & US 2019/0185475 A1 & EP 3310779 A1	1-17
A	WO 2018/130928 A1 (NOVARTIS AG) 2018.07.19, THE WHOLE DOCUMENT & AU 2018207464 A	1-17
A	WO 2017/156397 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 2017.09.14, THE WHOLE DOCUMENT (PATENT FAMILY:NONE)	1-17
P,A	WO 2019/165073 A1 (RELAY THERAPEUTIC, INC.) 2019.08.29, THE WHOLE DOCUMENT (PATENT FAMILY:NONE)	1-17

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01.10.2019	08.10.2019

Name and mailing address of the ISA/JP	Authorized officer	
Japan Patent Office	Koji ITO	4P 9450
3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	Telephone No. +81-3-3581-1101 Ext. 3492	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2019/028822

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2019/118909 A1 (REVOLUTION MEDICINES, INC.) 2019.06.20, THE WHOLE DOCUMENT (PATENT FAMILY:NONE)	1-17

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WO2020/022323 EN 2020.01.30
(71)申请人 大鹏药品工业株式会社
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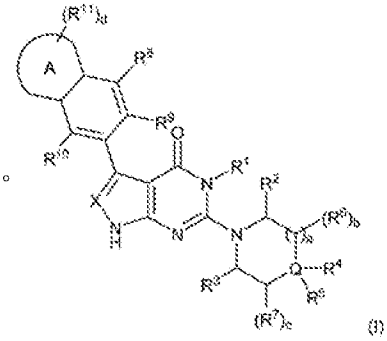
权利要求书13页 说明书282页

(54)发明名称

抑制SHP2活性的杂环化合物

(57)摘要

式(I)化合物,其中环A、Q、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、X、a、b、c和d如说明书中所定义。

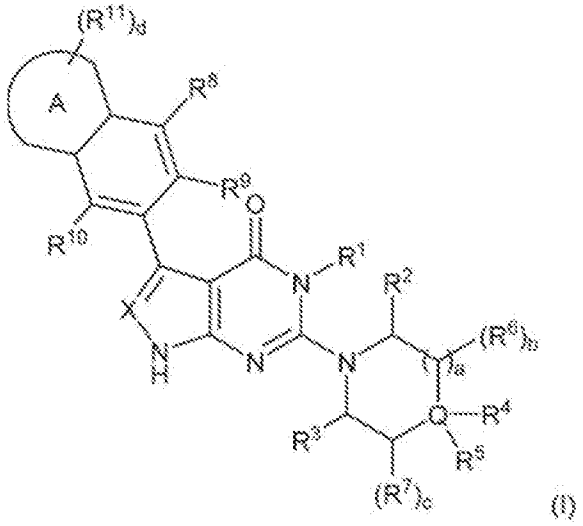


(I)

CN 112513050 A

1.式(I)化合物：

[化学式1]



(I)

或其互变异构体或溶剂合物或药学上可接受的盐，其中：

X是CH或N；

R^1是$-CH_3$；

R^2和R^3独立选自氢和C_{1-4}烷基；

Q是C或N；

其中当Q是C时，则：

(i)R^4是氨基、氨基C_{1-4}烷基或者单C_{1-4}烷基氨基；

R^5是氢、C_{1-4}烷基、卤素、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基或C_{1-4}烷氧基C_{1-4}烷基；

或者

(ii)R^4和R^5与Q一起形成4-6元环，所述环可任选地含有独立选自N、O、S、NH、C(O)和$S(O)_m$的1-3个杂原子或基团，并且R^4和R^5形成的所述环可以是未取代的或被1-4个基团取代，所述基团独立选自：氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基和C_{1-4}烷基，并且m选自1和2；和

其中当Q是N时，则：

R^4不存在；且

R^5是氢；

R^6和R^7独立选自卤素、C_{1-4}烷基、羟基C_{1-4}烷基和羟基，前提是当Q是N时，则R^6或R^7不是卤素或羟基；

或者，选自R^2、R^3、R^6和R^7的任何两个基团一起形成1-3元桥接基团，该桥接基团选自C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基$-NR^q-$亚甲基和亚甲基-O-亚甲基，其中所述桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且Rq选自氢和C_{1-4}烷基；

或者，R^4和R^7形成含有N原子的4-6元环；

或者，R^5和R^7形成3-6元环；

或者，R^6和R^7形成直接键；

a选自0、1和2；

b选自0、1和2；

c选自0、1和2；

或者，Q是C，c是2，R^4是氢，并且两个R^7连接形成4-6元含氮环；

环A是：

(i)五元含氮杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

(ii)六元含氮芳香杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

(iii)六元含氮非芳香杂环，其中所述杂环任选地含有选自N和S的1个或2个另外的杂原子；

R^8选自氢、C_{1-4}烷基、卤代C_{1-4}烷基和卤素；

R^9选自氢和卤素；

R^{10}选自卤代C_{1-4}烷基、C_{1-4}烷基、卤素、氢或C_{1-4}烷氧基；

R^{11}独立地选自卤素，氰基，氰基C_{1-4}烷基，羟基，氧代(=O)，任选地被含有选自O、N或S的1或2个杂原子的5-或6-元杂环基取代的C_{1-4}烷基，卤代C_{1-4}烷基，C_{1-4}烷氧基，羟基C_{1-4}烷基，C_{1-4}烷氧基C_{1-4}烷基，C_{1-4}烷基砜，氨基，单C_{1-4}烷基氨基，二C_{1-4}烷基氨基，氨基C_{1-4}烷基，-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$，-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基，磺酰胺，磺酰胺C_{1-4}烷基，3-6元环烷基，被3-6元环烷基取代的C_{1-4}烷基，含有选自O、N或S的1、2、3或4个杂原子的5-或6-元不饱和杂环基，以及含有选自O、N或S的1或2个杂原子的任选取代的4-6元饱和杂环基，其中所述任选的取代基选自C_{1-4}烷基；

q选自0、1或2；且

d选自0、1和2。

2.根据权利要求1所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中：

环A是五元或六元含氮杂芳环，其中所述环任选地含有选自N、O和S的1个或2个另外的杂原子。

3.根据权利要求1或2所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中选自R^2、R^3、R^6和R^7的任何两个基团一起形成1-3元桥接基团，该桥接基团选自C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基-NRq-亚甲基和亚甲基-O-亚甲基，其中所述桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且Rq选自氢和C_{1-4}烷基。

4.根据权利要求1-3中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

Q是C。

5.根据权利要求1-4中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

R^4是氨基、氨基C_{1-4}烷基或单C_{1-4}烷基氨基；

R^5是氢、C_{1-4}烷基、卤素、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基或C_{1-4}烷氧基C_{1-4}烷基。

6.根据权利要求1-4中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

R^4和R^5与Q一起形成4-6元环，所述环可任选地含有独立选自N、O、S、NH、C(O)和$S(O)_m$的1-3个杂原子或基团，并且R^4和R^5形成的所述环可以是未取代的或被1-4个基团取代，所述基团独立选自氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基和C_{1-4}烷基，并且m选自1和2。

7.根据权利要求1-5中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中Q是N。

8.根据权利要求1-7中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中X是CH。

9.根据权利要求1-7中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中X是N。

10.根据权利要求1所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中所述化合物选自：

2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(4-(氨基甲基)-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(4-氨基-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(2-(叔丁基)-4-氯-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(R)-2-(1-氨基-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(S)-2-(4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(羟基甲基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(2-羟基乙基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1S,4S)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(7-氨基-3-氧杂-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,4R)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(exo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

rac-2-((1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,8-二氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,6-二氮杂二环[3.1.1]庚烷-6-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,6-二氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(2,5-二氮杂二环[2.2.2]辛烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(exo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-

3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(5-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(exo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,8-二氮杂螺[4.5]癸烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(3,7-二氮杂二环[4.2.0]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,9-二氮杂螺[5.5]十一烷-9-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,7-二氮杂螺[3.5]壬烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(S)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(R)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1S,2S,4R)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((3R,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((3S,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(4-氨基-3,3-二氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

(S)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(R)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((3R,4R)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((3R,4S)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3-氨基-3-(羟基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(R)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(1-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(6-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

(S)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(4-(氨基甲基)-4-甲氧基哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(4-(氨基甲基)-4-氟哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-甲基-5-(2-甲基-2H-吲唑-5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6,7-二氟-1-甲基-1H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-甲氧基-2-甲基-2H-吲唑-5-

基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-(2-羟基-2-甲基丙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2,7-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(1H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺，

3-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺，

2-(6-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-7-氯苯并[d]噻唑-2-基)-N,N-二甲基乙酰胺，

2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺，

2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺，

3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺，

2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2,3-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-甲氧基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-(氟甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(7-氯苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-3-(二氟甲基)-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-(羟基甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(4-氯-2-乙基-2H-吲唑-

5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(7-氯苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

2-((1R,2S,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,2R,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1S,2S,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

rac-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,4S,7S)-7-(甲基氨基)-2-氮杂二环[2.2.1]庚烷-2-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

endo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{3,8-二氮杂二环[3.2.1]辛烷-8-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(1R,3S)-1-氨基-3-羟基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

exo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{2,7-二氮杂螺[3.5]壬烷-7-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(1R)-1-氨基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(1R,3R)-1-氨基-3-氟-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-2-(1,4-二氮杂环庚烷-1-基)-3-甲基-3H,4H,7H-吡

咯并[2,3-d]嘧啶-4-酮，

rac-2-[(1R,2R,5R)-2-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

rac-2-(4-氨基氮杂环庚烷-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2-乙基-2H-吲唑-3-甲腈，

6-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

6-((3R,4S)-4-氨基-3-氟哌啶-1-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

2-((1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-(rac-(1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,2S,4R)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-5-(3,4,7-三氯-2-甲基-2H-吲唑-5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-甲氧基喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-(二甲基氨基)喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

6-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

rac-2-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

rac-6-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(5-氯喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(乙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-(2-甲氧基乙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(异丙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-4-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(7-氯-2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(endo)-3-氨基-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(3R,4S)-4-氨基-3-氟哌啶-1-基]-5-(7-氯-1,3-苯并噻唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1S,6R)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1R,5R)-3,6-二氮杂二环[3.2.1]辛烷-3-基}-

3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1S,5S)-3,6-二氮杂二环[3.2.1]辛烷-3-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1S,5R)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1R,5S)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-7-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(endo)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

rac-5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{2,6-二氮杂螺[3.4]辛烷-6-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(二甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,和

2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮。

11.药物组合物,其包含权利要求1-10中任何一项所述的化合物和药学上可接受的载体。

12.根据权利要求11所述的药物组合物,其用于预防或治疗SHP2介导的疾病或病症。

13.根据权利要求1-10中任何一项所述的化合物,其用于治疗。

14.根据权利要求1-10中任何一项所述的化合物,其用于预防或治疗SHP2介导的疾病或病症。

15.根据权利要求1-10中任何一项所述的化合物在制备用于预防或治疗SHP2介导的疾病或病症的药物中的用途。

16.预防或治疗SHP2介导的疾病或病症的方法,其包括向患者施用权利要求1-10中任何一项所述的化合物。

17.权利要求11和12的药物组合物、权利要求13和14的化合物、权利要求15的用途或权利要求16的方法,其中治疗对象或SHP2介导的疾病或病症是癌症。

抑制SHP2活性的杂环化合物

技术领域

[0001] 本发明涉及抑制SHP2活性的新杂双环化合物，包含所述化合物的药物组合物，以及所述化合物的用途。

背景技术

[0002] 包含Src同源区2(SH2)的蛋白酪氨酸磷酸酶2(SHP2)是由PTPN11基因编码的广泛表达的蛋白酪氨酸磷酸酶。SHP2包含两个N末端纵排的SH2域(N-SH2，C-SH2)、催化磷酸酶(PTP)域和具有2个酪氨酸磷酸化位点的C末端尾部。

[0003] 由于N-SH2和PTP域之间的自抑制相互作用，SHP2在“开放”活性形式和“封闭”非活性形式之间切换。当双酪氨酰磷酸化肽与N-SH2结构域结合，并且SHP2采用“开放”构象时，释放所述天然存在的自抑制作用，致使酶活化和用于底物识别和催化的PTP结构域暴露。

[0004] PTPN11突变与包括癌症的几种人类疾病有关。种系PTPN11突变与诸如Noonan综合征和豹皮综合症的发育障碍相关，而体细胞突变发生在几种恶性血液病中例如JMML，并且在实体瘤中较罕见地发生。

[0005] SHP2是受体酪氨酸激酶(例如EGFR、ALK、PDGFR)信号传导下游所必需的，并且在调控许多细胞过程例如响应生长因子和细胞因子刺激的增殖中起积极作用。先前的研究表明SHP2作用于Ras的上游，并且SHP2是MAPK通路完全、持续活化所必需的。RTK失调通常会引发多种癌症，这使SHP2成为RTK激活的癌症的重要靶标。还报道因为基于免疫受体酪氨酸的抑制性基序(ITIM)结合至SHP2的SH2结构域，以介导负信号，所以SHP2通过介导免疫检查点通路(例如PD-1)而在调控免疫应答中起作用。

[0006] 已报道在小鼠异种移植模型中，某些SHP2抑制剂化合物对体外癌细胞的增殖和肿瘤体积的增加具有抑制作用(Nature(2016)535:148-152)。

[0007] 引文列表

[0008] 非专利文献

[0009] NPL 1:Nature(2016)535:148-152

[0010] 发明概述

[0011] 技术问题

[0012] 本发明的目的是提供选择性抑制SHP2并可用于治疗SHP2介导的疾病或病症的一系列新化合物。

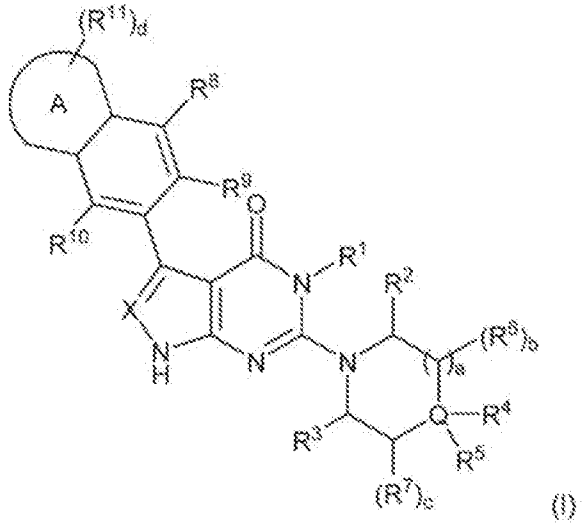
[0013] 解决方案

[0014] 本发明人进行了广泛研究，以实现上述目的，并由此发现下式(I)所示的化合物组显示优异的SHP2抑制活性，并可用作治疗SHP2介导的疾病例如癌症的药物制剂。因此，完成了本发明。

[0015] 本发明包括以下各项。

[0016] 第1项.式(I)化合物：

[0017] [化学式1]

[0018] 

(I)

[0019] 或其互变异构体或溶剂合物或药学上可接受的盐，其中：

[0020] X是CH或N；

[0021] R^1是-CH_3；

[0022] R^2和R^3独立选自H和C_{1-4}烷基；

[0023] Q是C或N；

[0024] 其中当Q是C时，则：

[0025] (i)R^4是氨基、氨基C_{1-4}烷基或者单C_{1-4}烷基氨基；

[0026] R^5是氢、C_{1-4}烷基、卤素、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基或C_{1-4}烷氧基C_{1-4}烷基；

[0027] 或者

[0028] (ii)R^4和R^5与Q一起形成4-6元环，所述环可任选地含有独立选自N、O、S、NH、C(O)和$S(O)_m$的1-3个杂原子或基团，并且R^4和R^5形成的所述环可以是未取代的或被1-4个基团取代，所述基团独立选自：氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基和C_{1-4}烷基，并且m选自1和2；知

[0029] 其中当Q是N时，则：

[0030] R^4不存在；且

[0031] R^5是氢；

[0032] R^6和R^7独立选自卤素、C_{1-4}烷基、羟基C_{1-4}烷基和羟基，前提是当Q是N时，则R^6或R^7不是卤素或羟基；

[0033] 或者，选自R^2、R^3、R^6和R^7的任何两个基团一起形成1-3元桥接基团，该桥接基团选自C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基-NR^q-亚甲基和亚甲基-O-亚甲基，其中所述桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且R^q选自氢和C_{1-4}烷基；

[0034] 或者，R^4和R^7形成含有N原子的4-6元环；

[0035] 或者，R^5和R^7形成3-6元环；

[0036] 或者，R^6和R^7形成直接键(direct bond)；

[0037] a选自0、1和2；

[0038] b选自0、1和2；

[0039] c选自0、1和2；

[0040] 或者，Q是C，c是2，R^4是氢，并且两个R^7连接形成4-6元含氮环；

[0041] 环A是：

[0042] (i)五元含氮杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

[0043] (ii)六元含氮芳香杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

[0044] (iii)六元含氮非芳香杂环，其中所述杂环任选地含有选自N和S的1个或2个另外的杂原子；

[0045] R^8选自氢、C_{1-4}烷基、卤代C_{1-4}烷基和卤素；

[0046] R^9选自氢和卤素；

[0047] R^{10}选自卤代C_{1-4}烷基、C_{1-4}烷基、卤素、氢或C_{1-4}烷氧基；

[0048] R^{11}独立地选自卤素，氰基，氰基C_{1-4}烷基，羟基，氧代(=O)，任选地被含有选自O、N或S的1或2个杂原子的5-或6-元杂环基取代的C_{1-4}烷基，卤代C_{1-4}烷基，C_{1-4}烷氧基，羟基C_{1-4}烷基，C_{1-4}烷氧基C_{1-4}烷基，C_{1-4}烷基砜，氨基，单C_{1-4}烷基氨基，二C_{1-4}烷基氨基，氨基C_{1-4}烷基，-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$，-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基，磺酰胺，磺酰胺C_{1-4}烷基，3-6元环烷基，被3-6元环烷基取代的C_{1-4}烷基，含有选自O、N或S的1、2、3或4个杂原子的5-或6-元不饱和杂环基，以及含有选自O、N或S的1或2个杂原子的任选取代的4-6元饱和杂环基，其中任选的取代基选自C_{1-4}烷基；

[0049] q选自0、1或2；且

[0050] d选自0、1和2。

[0051] 第2项.根据第1项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中：

[0052] 环A是五元或六元含氮杂芳环，其中所述环任选地含有选自N、O和S的1个或2个其他杂原子。

[0053] 第3项.根据第1项或第2项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中选自R^2、R^3、R^6和R^7的任何两个基团一起形成1-3元桥接基团，该桥接基团选自C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基-NR^q-亚甲基和亚甲基-O-亚甲基，其中所述桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且R^q选自氢和C_{1-4}烷基。

[0054] 第4项.根据第1-3项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

[0055] Q是C。

[0056] 第5项.根据第1-4项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

[0057] R^4是氨基、氨基C_{1-4}烷基或单C_{1-4}烷基氨基；

[0058] R^5是氢、C_{1-4}烷基、卤素、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基或C_{1-4}烷氧基C_{1-4}烷基。

[0059] 第6项.根据第1-4项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中

[0060] R^4和R^5与Q一起形成4-6元环，所述环可任选地含有独立选自N、O、S、NH、C(O)和S

$(O)_m$的1-3个杂原子或基团，并且R^4和R^5形成的所述环可以是未取代的或被1-4个基团取代，所述基团独立选自：氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基和C_{1-4}烷基，并且m选自1和2。

[0061] 第7项.根据第1-5项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中Q是N。

[0062] 第8项.根据第1-7项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中X是CH。

[0063] 第9项.根据第1-7项中任何一项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中X是N。

[0064] 第10项.根据第1项所述的化合物或其互变异构体或溶剂合物或药学上可接受的盐，其中所述化合物选自：

[0065] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0066] 2-(4-(氨基甲基)-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0067] 2-(4-氨基-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0068] 2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0069] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0070] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0071] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0072] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0073] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(2-(叔丁基)-4-氯-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0074] 2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0075] (R)-2-(1-氨基-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0076] (S)-2-(4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0077] 5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0078] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0079] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0080] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0081] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0082] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0083] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(羟基甲基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0084] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(2-羟基乙基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0085] 2-((1S,4S)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0086] 2-(7-氨基-3-氧杂-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0087] 2-((1R,4R)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0088] 2-(exo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0089] 2-(endo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0090] rac-2-((1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0091] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0092] 2-(3,8-二氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0093] 2-(3,6-二氮杂二环[3.1.1]庚烷-6-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0094] 2-(3,9-二氮杂二环[3.3.1]壬烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0095] 2-(3,6-二氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0096] 2-(2,5-二氮杂二环[2.2.2]辛烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0097] 2-(exo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0098] 2-(endo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-

基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0099] 2-(5-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0100] 2-(exo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0101] 2-(endo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0102] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,8-二氮杂螺[4.5]癸烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0103] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0104] 2-(3,7-二氮杂二环[4.2.0]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0105] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,9-二氮杂螺[5.5]十一烷-9-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0106] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,7-二氮杂螺[3.5]壬烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0107] (S)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0108] (R)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0109] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0110] 2-((1S,2S,4R)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0111] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0112] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0113] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0114] 2-((3R,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0115] rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0116] 2-((3S,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0117] 2-(4-氨基-3,3-二氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0118] (S)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0119] (R)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0120] 2-((3R,4R)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0121] 2-((3R,4S)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0122] 2-(3-氨基-3-(羟基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0123] 2-((3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0124] (R)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0125] 2-(1-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0126] 2-(6-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0127] (S)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0128] 2-(4-(氨基甲基)-4-甲氧基哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0129] 2-(4-(氨基甲基)-4-氟哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0130] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0131] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-甲基-5-(2-甲基-2H-吲唑-5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0132] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0133] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0134] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0135] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6,7-二氟-1-甲基-1H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0136] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0137] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-甲氧基-2-甲基-2H-吲

唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0138] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0139] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-(2-羟基-2-甲基丙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0140] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2,7-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0141] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(1H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0142] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0143] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0144] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0145] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0146] 2-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺,

[0147] 3-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺,

[0148] 2-(6-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-7-氯苯并[d]噻唑-2-基)-N,N-二甲基乙酰胺,

[0149] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0150] 2-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺,

[0151] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0152] 3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺,

[0153] 3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺,

[0154] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0155] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0156] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0157] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0158] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2,3-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0159] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0160] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0161] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0162] 5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0163] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0164] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0165] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0166] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-甲氧基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0167] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-(氟甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0168] 5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0169] 5-(7-氯苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0170] 5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0171] 5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0172] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0173] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-3-(二氟甲基)-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0174] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-(羟基甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0175] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0176] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(4-氯-2-乙基-2H-吲

唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0177] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0178] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0179] 6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0180] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0181] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0182] 3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0183] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0184] 3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0185] 3-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0186] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0187] 3-(7-氯苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0188] 3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0189] rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0190] rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0191] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0192] 3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0193] 2-((1R,2S,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0194] 2-((1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0195] 2-((1R,2R,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0196] 2-((1S,2S,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0197] rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0198] rac-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0199] rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,4S,7S)-7-(甲基氨基)-2-氮杂二环[2.2.1]庚烷-2-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0200] endo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0201] 3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{3,8-二氮杂二环[3.2.1]辛烷-8-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0202] 6-[(1R,3S)-1-氨基-3-羟基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0203] 6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0204] exo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0205] 3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{2,7-二氮杂螺[3.5]壬烷-7-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0206] 6-[(1R)-1-氨基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0207] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0208] 6-[(1R,3R)-1-氨基-3-氟-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0209] 3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0210] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0211] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0212] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0213] 6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0214] 2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0215] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-(1,4-二氮杂环庚烷-1-基)-3-甲基-3H,4H,

7H-吡咯并[2,3-d]嘧啶-4-酮，

[0216] rac-2-[(1R,2R,5R)-2-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

[0217] rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

[0218] rac-2-(4-氨基氮杂环庚烷-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮，

[0219] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0220] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0221] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0222] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0223] 5-(2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2-乙基-2H-吲唑-3-甲腈，

[0224] 6-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0225] 6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0226] 6-((3R,4S)-4-氨基-3-氟哌啶-1-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0227] 2-((1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0228] 2-(rac-(1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0229] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,2S,4R)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0230] 2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0231] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0232] 2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-5-(3,4,7-三氯-2-甲基-2H-吲唑-5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0233] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-甲氧基喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0234] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-(二甲基氨基)喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0235] 6-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0236] 2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0237] rac-2-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0238] 2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0239] rac-6-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0240] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(5-氯喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0241] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(乙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0242] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-(2-甲氧基乙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0243] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(异丙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0244] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0245] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-4-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0246] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(7-氯-2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0247] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0248] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0249] 2-[(endo)-3-氨基-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0250] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0251] 2-[(3R,4S)-4-氨基-3-氟哌啶-1-基]-5-(7-氯-1,3-苯并噻唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0252] 5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1S,6R)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0253] 5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0254] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1R,5R)-3,6-二氮杂二环[3.2.1]辛烷-3-

基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0255] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1S,5S)-3,6-二氮杂二环[3.2.1]辛烷-3-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0256] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1S,5R)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0257] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1R,5S)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0258] 2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-7-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0259] 2-[(endo)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0260] Rac-5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{2,6-二氮杂螺[3.4]辛烷-6-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0261] 2-[(1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0262] 2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(二甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,和

[0263] 2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮。

[0264] 第11项.药物组合物,其包含第1-10项中任何一项所述的化合物和药学上可接受的载体。

[0265] 第12项.根据第11项所述的药物组合物,其用于预防或治疗SHP2介导的疾病或病症。

[0266] 第13项.根据第1-10项中任何一项所述的化合物,其用于治疗。

[0267] 第14项.根据第1-10项中任何一项所述的化合物,其用于预防或治疗SHP2介导的疾病或病症。

[0268] 第15项.根据第1-10项中任何一项所述的化合物在制备用于预防或治疗SHP2介导的疾病或病症的药物中的用途。

[0269] 第16项.预防或治疗SHP2介导的疾病或病症的方法,其包含向患者施用第1-10项中任何一项所述的化合物。

[0270] 第17项.第11和12项所述的药物组合物、第13和14项所述的化合物、第15项的用途或第16项的方法,其中治疗对象或SHP2介导的疾病或病症是癌症。

[0271] 应该理解第11-17项所述的药物组合物、化合物、用途或方法中的“化合物”包含相应化合物的互变异构体或溶剂合物或药学上可接受的盐。

[0272] 本文称作化合物152的rac-2-[(1R,2R,5R)-2-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮在第1项的范围之外,可将其为化合物或其互变异构体或溶剂合物或药学上可接受的盐独立地要求保护。可将其中包含、使用或施用化合物152的药物组合物、化合物、用途或方法与第11-17项类似地那样要求保护。

[0273] 发明的有益效果

[0274] 已经显示式(I)化合物或其互变异构体或溶剂合物或药学上可接受的盐具有优异的SHP2抑制活性。因此，本发明的化合物或其衍生物可用作预防和/或治疗SHP2介导的疾病例如癌症的物质。

[0275] 式(I)化合物或其互变异构体或溶剂合物或药学上可接受的盐在某些方面具有优异的性质，所述方面例如功效、选择性、药代动力学诸如ADME性质、口服生物利用度、透过血脑屏障的能力、作用时间、理化特性、hERG活性、QT延长等。

[0276] 实施方案详述

[0277] 本发明式(I)所示化合物是新的吡咯并嘧啶酮或吡唑并嘧啶酮化合物，其包含(i)单环、双环、桥环或螺环的含氮的5-7元饱和杂环基和(ii)含苯并-环的芳香或非芳香稠合环，以及5或6元含氮杂环。

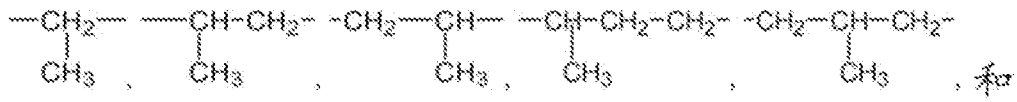
[0278] 在本说明书中，除非另外说明，*表示键合位置。

[0279] 在本说明书中，“卤素”的示例包括氟、氯、溴、碘等，优选氟、氯、溴或碘，并且更优选氟或氯。

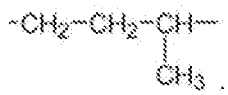
[0280] 在本说明书中，“烷基”可以是直链或支链的。C_{1-6}烷基的示例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、叔戊基和正己基。C_{1-4}烷基的示例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基。

[0281] 在本说明书中，“亚烷基”是二价基团，其中从上述烷基基团中除去一个氢。C_{1-4}亚烷基的示例包括直链C_{1-4}亚烷基，例如亚甲基、亚乙基、亚丙基、亚丁基和支链的C_{1-4}亚烷基，例如

[0282] [化学式2]



[0283]



[0284] 在本说明书中，“杂环”包括包含碳原子和至少一个杂原子的任何单环或多环、饱和或不饱和环系统。“杂环”涵盖芳香族和非芳香族基团。

[0285] 在本说明书中，“C_{2-3}亚烯基”的示例包括亚乙烯基和亚烯丙基。

[0286] 在本说明书中，“3-6元环烷基”包括环丙基、环丁基、环戊基和环己基。

[0287] 在本说明书中，“氨基C_{1-4}烷基”是含有一个氨基基团的上述直链或支链C_{1-4}烷基，并指-C_{1-4}亚烷基-NH_2所示的基团。示例包括-亚甲基-氨基、-亚乙基-氨基、-亚丙基-氨基、-亚丁基-氨基等。

[0288] “单C_{1-4}烷基氨基”的示例包括被直链或支链C_{1-4}烷基单取代的氨基，例如甲基氨基、乙基氨基、正丙基氨基、异丙基氨基、正丁基氨基、异丁基氨基、叔丁基氨基等。

[0289] “二C_{1-4}烷基氨基”的示例包括被相同或不同直链或支链C_{1-4}烷基二取代的氨基，例如二甲基氨基、二乙基氨基、二(正丙基)氨基、二异丙基氨基、二(正丁基)氨基、二异丁基氨基、二(叔丁基)氨基等。

[0290] 在本说明书中，“羟基C_{1-4}烷基”的示例包括含有至少1个羟基基团(例如1个或2个羟基基团)的上述直链或支链烷基基团。具体示例包括羟基甲基、2-羟基乙基、1-羟基乙基、

3-羟基丙基、2-羟基丙基、1-甲基-2-羟基乙基、4-羟基丁基、2,2-二甲基-2-羟基乙基等，优选含有1个羟基基团的羟基烷基。

[0291] 在本说明书中，“C_{1-4}烷氧基”是指上述直链或支链C_{1-4}烷基键合至其的氧基(-O-)。示例包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、叔丁氧基等。

[0292] 在本说明书中，“氰基C_{1-4}烷基”的示例包括含有至少1个氰基基团(例如1个或2个氰基基团)的上述直链或支链C_{1-4}烷基基团。具体示例包括氰基甲基、2-氰基乙基、1-氰基乙基、3-氰基丙基、2-氰基丙基、1-甲基-2-氰基乙基、4-氰基丁基、2,2-二甲基-2-氰基乙基等，优选含有1个氰基基团的氰基烷基。

[0293] 在本说明书中，“卤代C_{1-4}烷基”是含有1-7个卤素原子的上述直链或支链C_{1-4}烷基基团(卤素取代的C_{1-4}烷基)。示例包括氟甲基、二氟甲基、三氟甲基、三氯甲基、氟乙基、1,1,1-三氟乙基、单氟-正丙基、全氟-正丙基和全氟异丙基。

[0294] 在本说明书中，“C_{1-4}烷氧基C_{1-4}烷基”是含有1个上述C_{1-4}烷氧基的上述直链或支链C_{1-4}烷基基团，并指-C_{1-4}亚烷基-C_{1-4}烷氧基(-C_{1-4}亚烷基-O-C_{1-4}烷基)所示的基团。上文列出了C_{1-4}亚烷基、C_{1-4}烷氧基和C_{1-4}烷基的示例。

[0295] 在本说明书中，“C_{1-4}烷基砜”指-SO_2-C_{1-4}烷基所示的基团。示例包括甲基砜、乙基砜、丙基砜、丁基砜等。

[0296] 在本说明书中，“-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$”(其中q是整数0、1或2)的示例包括-C_{1-4}亚烷基-C(=O)NH_2、-C_{1-4}亚烷基-C(=O)NH(C_{1-6}烷基)和-C_{1-4}亚烷基-C(=O)N(C_{1-6}烷基)$_2$。C_{1-4}亚烷基和C_{1-6}烷基的示例在上文中列出。

[0297] 在本说明书中，“-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基”指其中上文所述的C_{1-4}亚烷基和C_{1-6}烷基通过酰胺键(-NHC(=O)-)连接的基团。C_{1-4}亚烷基和C_{1-6}烷基的示例在上文中列出。

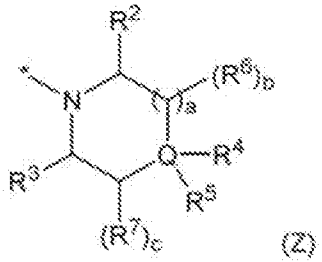
[0298] 在本说明书中，“磺酰胺C_{1-4}烷基”指-C_{1-4}亚烷基-SO_2-NH_2所示的基团。示例包括-SO_2-NH_2、-亚甲基-SO_2-NH_2、-亚乙基-SO_2-NH_2、-亚丙基-SO_2-NH_2、-亚丁基-SO_2-NH_2等。

[0299] 在本发明式(I)所示的化合物中，X表示CH或N。当X表示CH时，式(I)所示的化合物是吡咯并嘧啶酮化合物，而当X表示N时，式(I)所示的化合物是吡唑并嘧啶酮化合物。

[0300] 在本发明式(I)所示的化合物中，R^1表示甲基(-CH_3)。

[0301] 在本发明式(I)所示的化合物中，下述部分(下文称作Z部分(portion))：

[0302] [化学式3]

[0303] 

[0304] 其中Q、R^2、R^3、R^4、R^5、R^6和R^7、a、b和c同上文所定义的；

[0305] 是单环、双环、桥环或螺环的含氮的饱和杂环基。

[0306] 在本发明式(I)所示的化合物中，R^2和R^3独立表示选自氢和C_{1-4}烷基的任何一个。

[0307] 在本发明式(I)所示的化合物中，R^6和R^7独立表示选自卤素、C_{1-4}烷基、羟基C_{1-4}烷基和羟基的任何一个。当Q是N时，则R^6或R^7不代表卤素或羟基，因此代表C_{1-4}烷基。

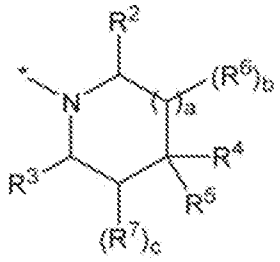
[0308] 在本发明式(I)所示的化合物中，Q表示C或N。

[0309] 在一实施方案中，当Q表示C时，R^4是氨基、氨基C_{1-4}烷基或单C_{1-4}烷基氨基；

[0310] R^5是氢、C_{1-4}烷基、卤素、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基或C_{1-4}烷氧基C_{1-4}烷基。在一实施方案中，当R^4是氨基时，则R^5选自氢、C_{1-4}烷基、羟基C_{1-4}烷基、C_{1-4}烷氧基、卤代C_{1-4}烷基和C_{1-4}烷氧基C_{1-4}烷基。

[0311] 在所述实施方案中，Z部分是单环、含氮的饱和5-7元杂环基，其含有一个氮，由下式表示：

[0312] [化学式4]

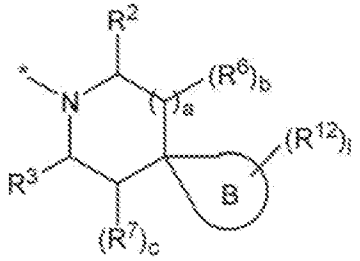
[0313] 

[0314] 其中R^2、R^3、R^4、R^5、R^6和R^7、a、b和c同上文所定义的；

[0315] 在另一实施方案中，当Q表示C时，R^4和R^5与Q一起形成4-6元环，该环可任选地包含独立选自N、O、S、NH、C(O)和$S(O)_m$的1-3个杂原子或基团，并且R^4和R^5形成的所述环可以是未取代的或被1-4个独立地选自下述的基团取代，所述基团选自氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基、C_{1-4}烷基，并且m选自1和2。

[0316] 在所述实施方案中，Z部分是包含8-12个成员(包括Q)的螺环含氮饱和杂环基，所述成员中1-4个为氮，并且所述成员中1-4个任选为选自氧和硫的相同或不同的杂原子。在所述实施方案中，Z部分表示为下式：

[0317] [化学式5]

[0318] 

[0319] 其中R^2、R^3、R^6、R^7、a、b和c同上文所定义的；

[0320] 其中B环是饱和的4-6元环，其可任选地包含1-3个独立选自N、O、S、NH、C(O)和$S(O)_m$的杂原子或基团，

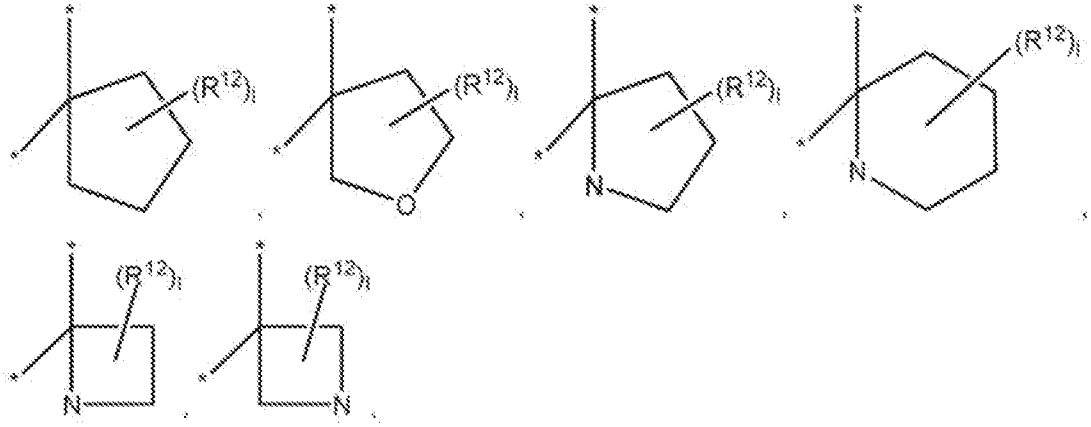
[0321] R^{12}独立选自氨基、卤素、卤代C_{1-4}烷基、羟基、甲氧基、甲基氨基、C_{1-4}烷基，

[0322] l是选自0、1、2、3和4的整数，

[0323] m是选自1和2的整数。

[0324] 可任选包含独立选自N、O、C(O)和$S(O)_m$的1-3个杂原子或基团的4-6元环的示例包括

[0325] [化学式6]

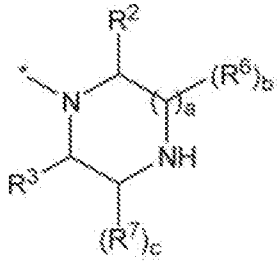
[0326] 

[0327] 其中R^{12}和1同上文定义的。

[0328] 在一实施方案中，当Q表示N时，则R^4不存在，且R^5是氢。

[0329] 在所述实施方案中，可将Z部分表示为下式：

[0330] [化学式7]

[0331] 

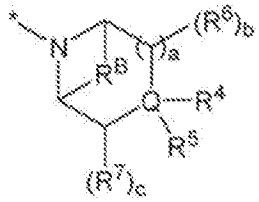
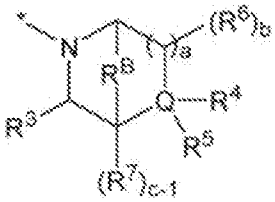
[0332] 其中R^2、R^3、a、b和c同上文所定义的；R^6和R^7独立选自羟基C_{1-4}烷基和C_{1-4}烷基，前提是a不是0；

[0333] 并且是单环含氮的饱和5-7元杂环基，其含有两个氮。

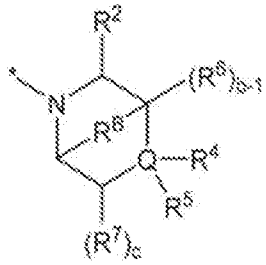
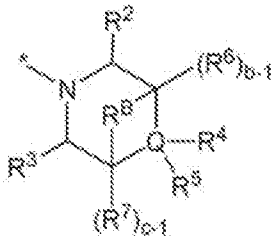
[0334] 在本发明式(I)所示的化合物中，R^2、R^3、R^6和R^7可替代地具有下述结构，其中选自R^2、R^3、R^6和R^7的任何两个基团一起形成1-3元桥接基团，该桥接基团选自C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基-NR^q-亚甲基和亚甲基-O-亚甲基，其中桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且R^q选自氢和C_{1-4}烷基。

[0335] 所述实施方案的示例包括下式中任何一个所示的Z部分：

[0336] [化学式8]

[0337]

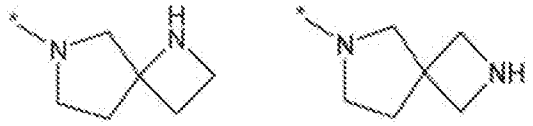



[0338] 其中Q、R^2、R^3、R^4、R^5、R^6和R^7、a、b和c同上文所定义的，前提是在包含“b-1”和/或“c-1”的式中，“b-1”(可称作b′)和“c-1”(可称作c′)独立选自0和1。

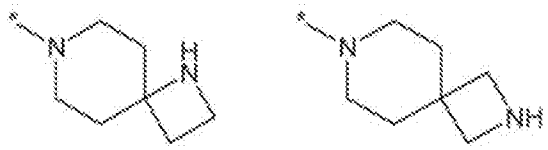
[0339] R^B表示选自直链C_{1-3}亚烷基、C_{2-3}亚烯基、亚甲基-NR^q-亚甲基和亚甲基-O-亚甲基的1-3元桥接基团，其中所述桥接基团任选地被选自C_{1-4}烷基、羟基和卤素的基团取代，并且R^q选自氢和C_{1-4}烷基。

[0340] 在本发明式(I)所示化合物的另一实施方案中，Q是C，c是2，R^4是氢，并且两个R^7连接以形成含氮的4-6元环。所述实施方案的示例包括下式中任何一个所示的Z部分：

[0341] [化学式9]

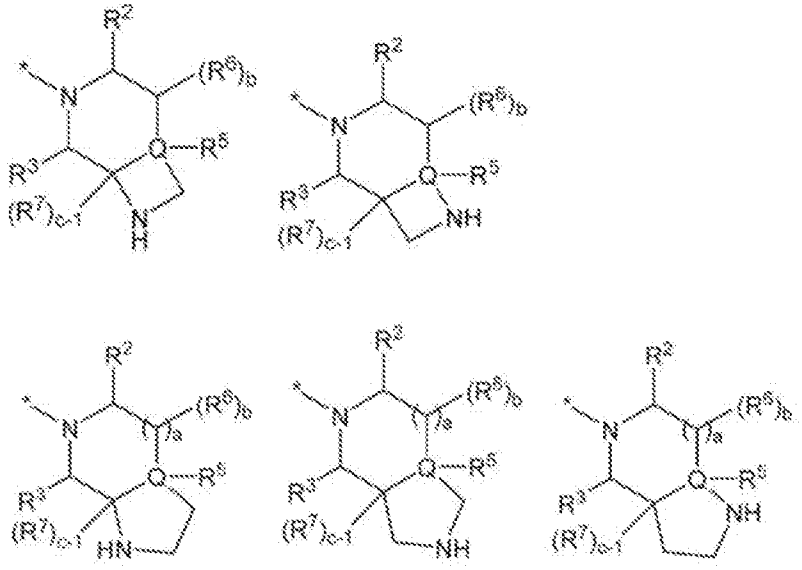


[0342]

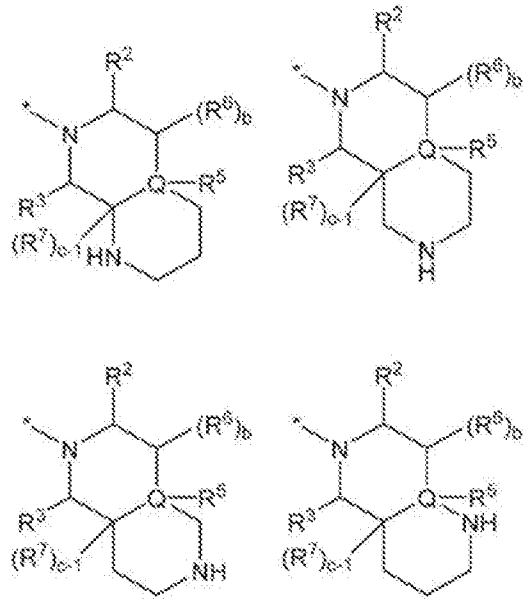


[0343] 在本发明式(I)所示的化合物中，R^4和R^7可替代地形成含有一个N原子的4-6元环。所述实施方案的示例包括下式中任何一个所示的Z部分：

[0344] [化学式10]



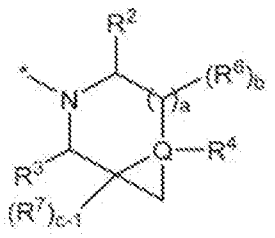
[0345]

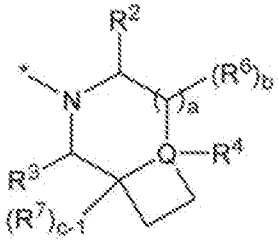


[0346] 其中Q、R^2、R^3、R^5、R^6和R^7、a、b和c同上文所定义的，前提是“c-1”(可称作c′)选自0和1。

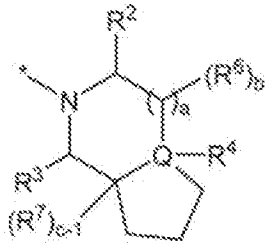
[0347] 在本发明式(I)所示的化合物中，R^5和R^7可替代地形成3-6元环。所示实施方案的示例包括下式中任何一个所示的Z部分：

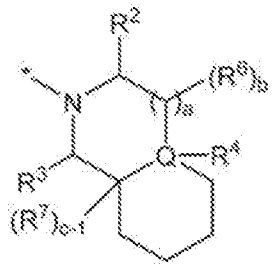
[0348] [化学式11]





[0349]



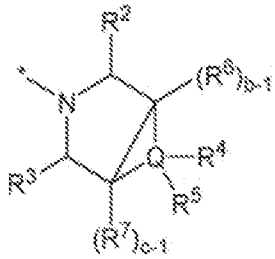


[0350] 其中Q、R^2、R^3、R^4、R^6和R^7、a、b和c同上文所定义的，前提是“c-1”(可称作c′)选自0和1。

[0351] 在一替代实施方案中，R^6和R^7替代地形成直接键。所示实施方案的示例包括下式所示的Z部分：

[0352] [化学式12]

[0353]



[0354] 其中Q、R^2、R^3、R^4、R^5、R^6、R^7、b和c同上文所定义的，前提是“b-1”(可称作b′)和“c-1”(可称作c′)独立选自0和1。

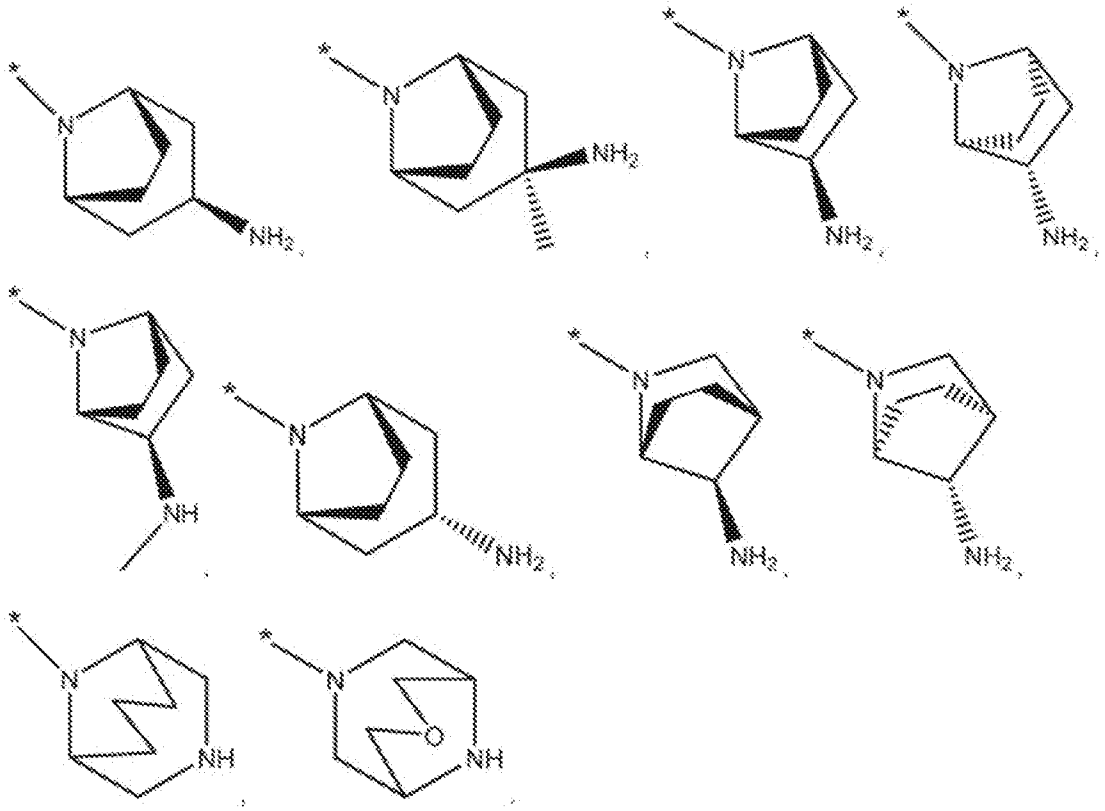
[0355] 在式(I)所示的化合物中，a是选自0、1和2的整数。

[0356] 在式(I)所示的化合物中，b是选自0、1和2的整数。

[0357] 在式(I)所示的化合物中，c是选自0、1和2的整数。

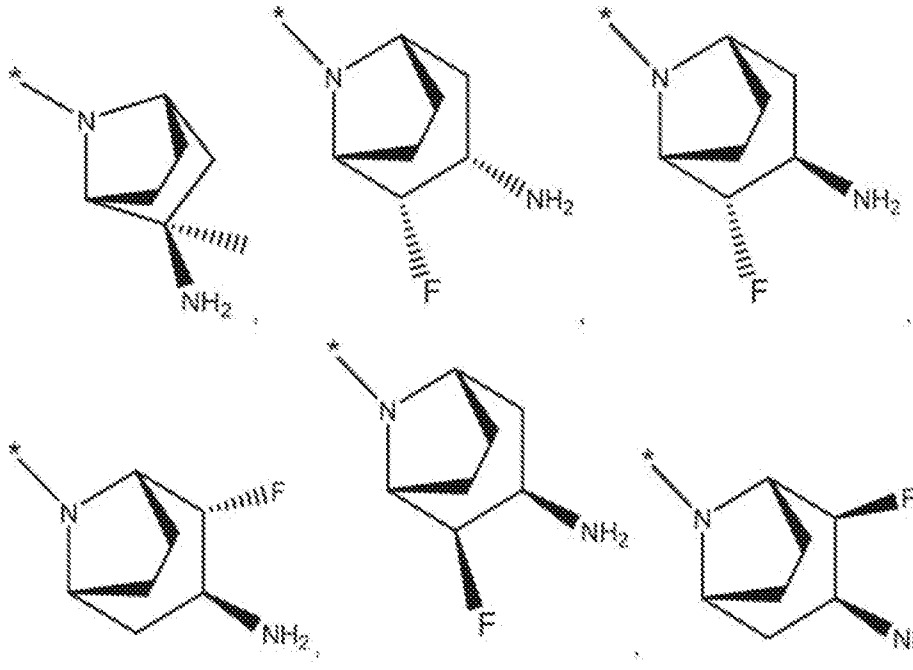
[0358] 优选的实施方案包括下式中任何一个所示的Z部分：

[0359] [化学式13]

[0360] 

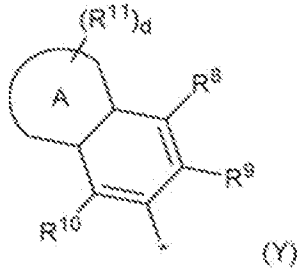
[0361] 另一个优选实施方案包括下式中任何一个所示的Z部分：

[0362] [化学式14]

[0363] 

[0364] 在本发明式(I)所示的化合物中，下述部分(portion)(下文称作Y部分)：

[0365] [化学式15]

[0366] 

[0367] 其中环A、R^8、R^9、R^{10}、R^{11}和d同上文定义的；

[0368] 是含苯并-环的芳香或非芳香稠环，以及5-6元含氮杂环。

[0369] 在式(I)所示的化合物中，下面所示的环A

[0370] [化学式16]

[0371] 

[0372] 与该基团键合的苯并环一起形成5或6元含氮杂环。

[0373] 具体地，环A是：

[0374] (i)五元含氮杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

[0375] (ii)六元含氮芳香杂环，其中所述杂环任选地含有选自N、O和S的1个或2个另外的杂原子，或者

[0376] (iii)六元含氮非芳香杂环，其中所述杂环任选地含有选自N和S的1个或2个另外的杂原子；

[0377] 五元含氮杂环(其中所述杂环任选地包含选自N、O和S的1个或2个另外的杂原子)可以是五元含氮芳香杂环或五元含氮非芳香杂环。所述杂环含有2-4个碳原子(包括与该基团键合的苯并环共享的两个碳原子)、1-3个氮原子，和被氧原子或硫原子替代的不与苯并环共享的碳原子(1个或2个碳原子)。

[0378] 五元含氮芳香杂环的示例包括吡咯、咪唑、吡唑、噁唑、异噁唑、噻唑、异噻唑等。

[0379] 五元含氮非芳香杂环的示例包括吡咯烷、吡唑烷、三唑烷、噁唑烷、异噁唑烷、噻唑烷、异噻唑烷等。

[0380] 六元含氮芳香杂环，其中该杂环任选地包含选自N、O和S的1个或2个另外的杂原子。所述杂环包含2-5个碳原子(包括与该基团键合的苯并环共享的两个碳原子)、1-3个氮原子，和被氧原子或硫原子替代的不与苯并-环共享的碳原子(1个、2个或3个碳原子)。

[0381] 六元含氮芳香杂环的示例包括吡啶、吡嗪、嘧啶、哒嗪、三嗪、噁嗪、噻嗪等。

[0382] 六元含氮非芳香杂环，其中该杂环任选地包含选自N和S的1个或2个另外的杂原子。所述杂环包含2-5个碳原子(包括与该基团键合的苯并-环共享的两个碳原子)、1-3个氮原子，和被硫原子替代的不与苯并环共享的碳原子(1个、2个或3个碳原子)。

[0383] 六元含氮非芳香杂环的示例包括哌啶、哌嗪、吗啉等。

[0384] 在式(I)所示的化合物中，R^8表示选自氢、C_{1-4}烷基、卤代C_{1-4}烷基和卤素中的1个。

[0385] 在式(I)所示的化合物中，R^9表示选自氢和卤素中的1个。

[0386] 在式(I)所示的化合物中，R^{10}表示选自卤代C_{1-4}烷基、C_{1-4}烷基、卤素、氢和C_{1-4}烷氧

基中的1个。

[0387] 在式(I)所示的化合物中，R^{11}各自独立地表示选自下述基团之一：卤素，氰基，氰基C_{1-4}烷基，羟基，氧代(=O)，C_{1-4}烷基(其任选地被含有选自O、N或S的1或2个杂原子的5-或6-元杂环基取代)，卤代C_{1-4}烷基，C_{1-4}烷氧基，羟基C_{1-4}烷基，C_{1-4}烷氧基C_{1-4}烷基，C_{1-4}烷基砜，氨基，单C_{1-4}烷基氨基，二C_{1-4}烷基氨基，氨基C_{1-4}烷基，-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$，-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基，磺酰胺，磺酰胺C_{1-4}烷基，3-6元环烷基，被3-6元环烷基取代的C_{1-4}烷基，含有选自O、N或S的1、2、3或4个杂原子的5-或6-元不饱和杂环基，以及含有选自O、N或S的1或2个杂原子的任选取代的4-6元饱和杂环基，其中任选的取代基选自C_{1-4}烷基；

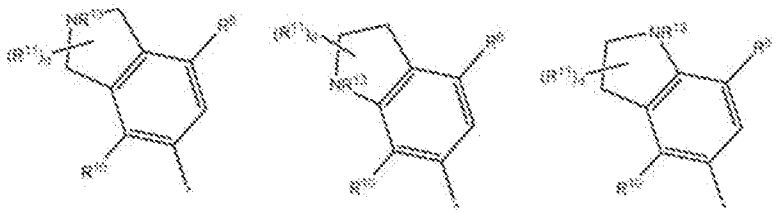
[0388] 当R^{11}是氧代(=O)时，R^{11}和环A之间的原子键是双键。在R^{11}是单价基团的其他情况下，R^{11}和环A之间的原子键是单键。

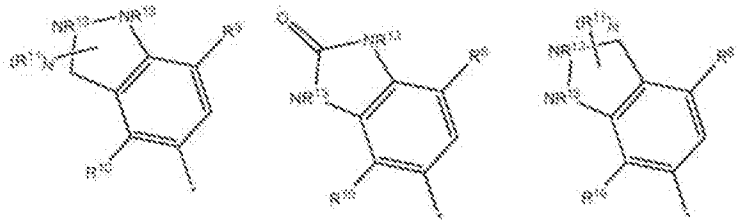
[0389] 在式(I)所示的化合物中，q是选自0、1和2的整数。

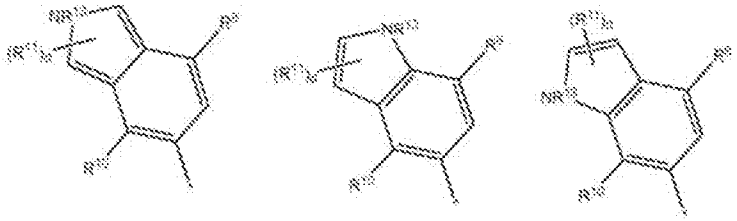
[0390] 在式(I)所示的化合物中，d是选自0、1和2的整数。

[0391] 优选实施方案包括下式中任何一个所示的Y部分：

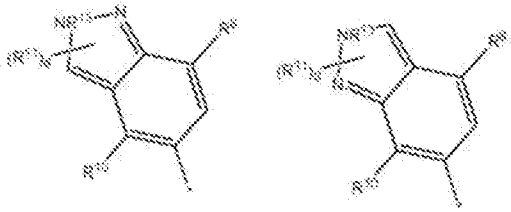
[0392] [化学式17]

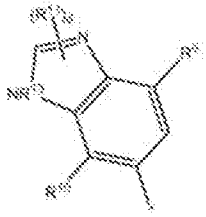
A 

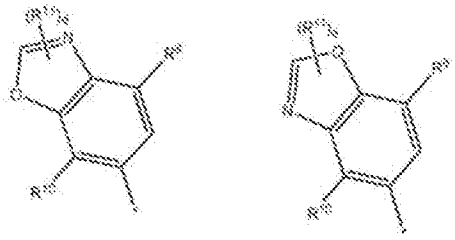
B 

C 

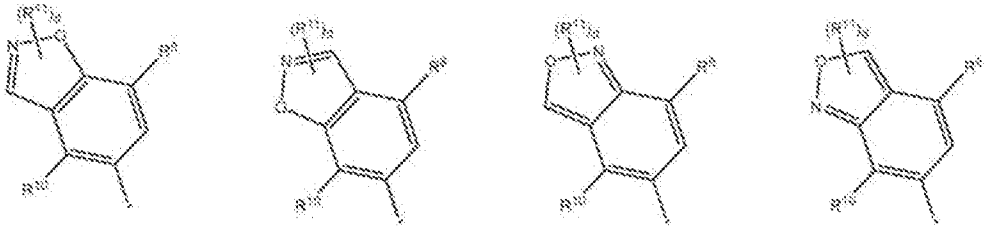
[0393]

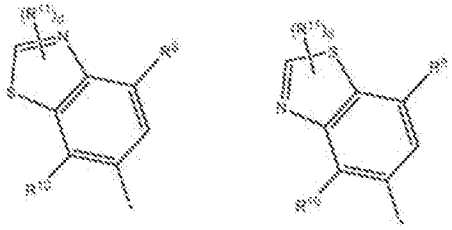
D 

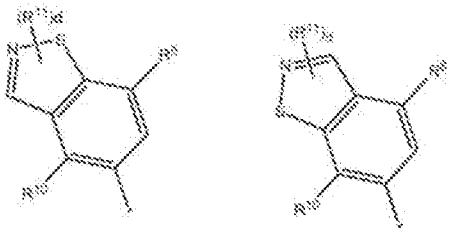
E 

F 

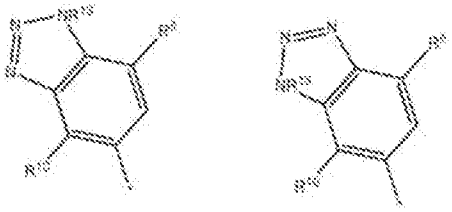
[0394] [化学式18]

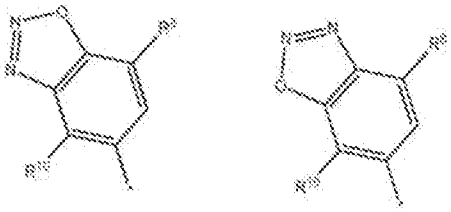
G 

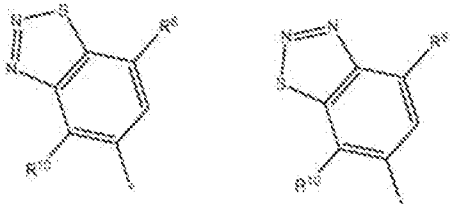
H 

I 

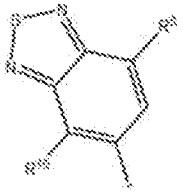
[0395]

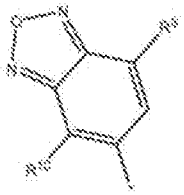
J 

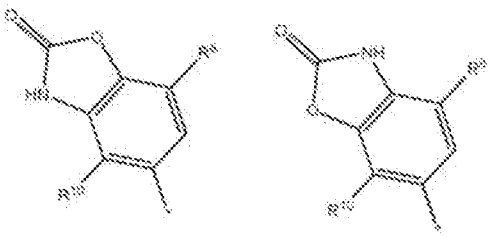
K 

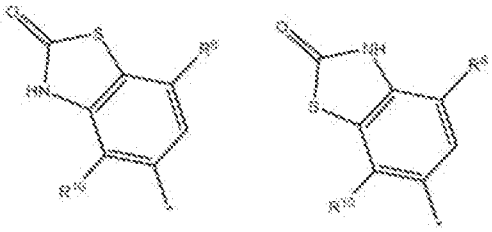
L 

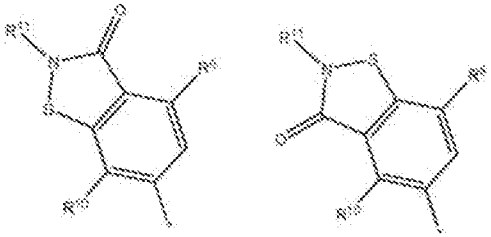
[0396] [化学式19]

M 

N 

[0397] O 

P 

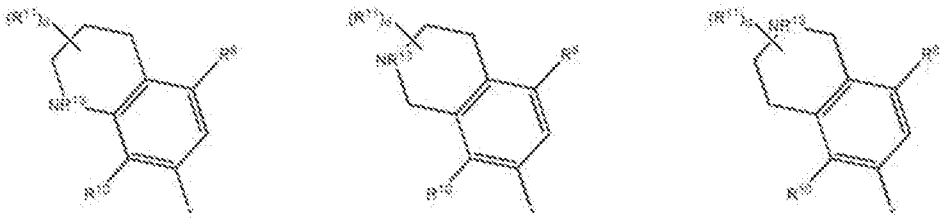
Q 

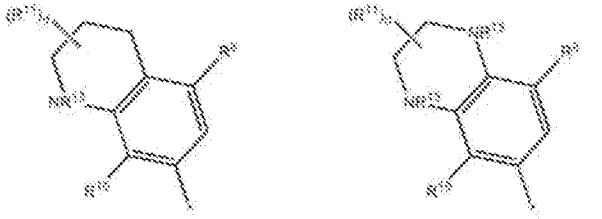
[0398] 其中R^8、R^{10}、R^{11}和d同上文定义的；

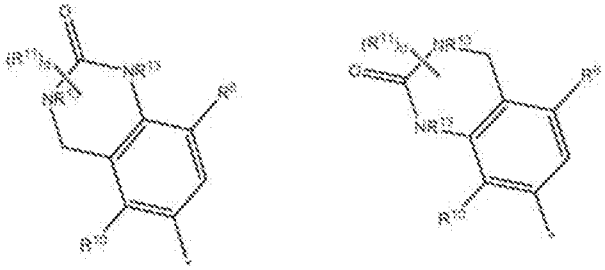
[0399] R^{13}独立选自氢、卤素，氰基，氰基C_{1-4}烷基，C_{1-4}烷基(其任选地被含有选自O、N或S的1或2个杂原子的5-或6-元杂环基取代)，卤代C_{1-4}烷基，C_{1-4}烷氧基，羟基C_{1-4}烷基，C_{1-4}烷氧基C_{1-4}烷基，C_{1-4}烷基砜，氨基C_{2-4}烷基，-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$，-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基，磺酰胺C_{1-4}烷基，3-6元环烷基，被3-6元环烷基取代的C_{1-4}烷基，含有选自O、N或S的1、2、3或4个杂原子的5-或6-元不饱和杂环基，以及含有选自O、N或S的1或2个杂原子的任选取代的4-6元饱和杂环基，其中任选的取代基选自C_{1-4}烷基。

[0400] 其他优选实施方案包括下式中任何一个所示的Y部分：

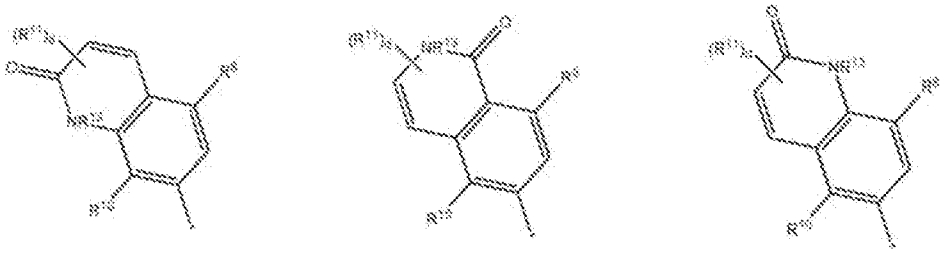
[0401] [化学式20]

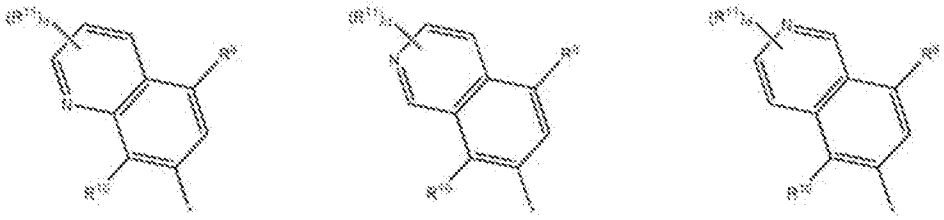
A 

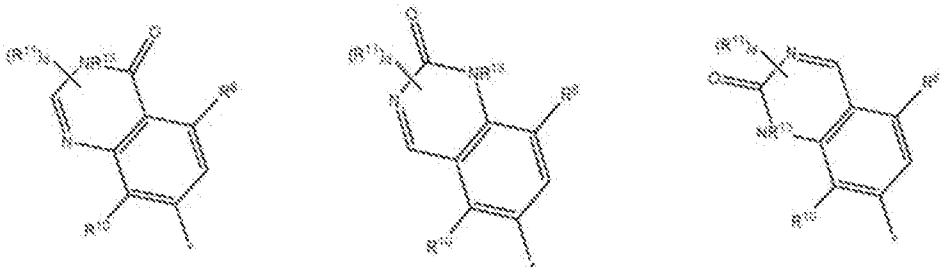
B 

C 

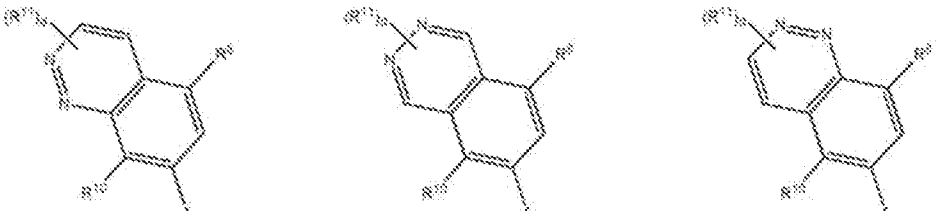
[0402]

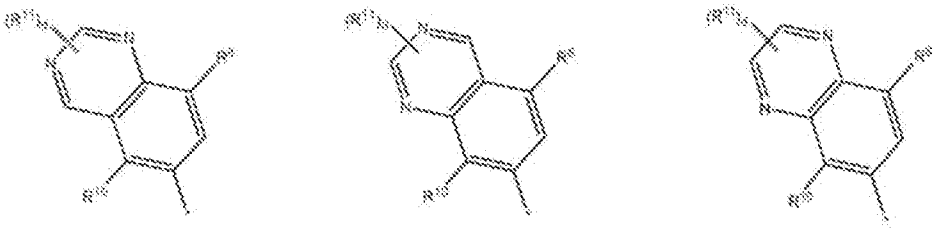
D 

E 

F 

[0403] [化学式21]

[0404] G 

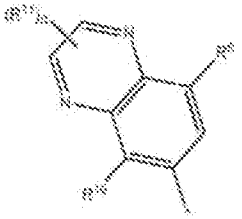
H 

[0405] 其中R^8、R^{10}、R^{11}和d同上文定义的；

[0406] R^{13}独立选自氢，氰基，氰基C_{1-4}烷基，C_{1-4}烷基(其任选地被含有选自O、N或S的1或2个杂原子的5-或6-元杂环基取代)，卤代C_{1-4}烷基，C_{1-4}烷氧基，羟基C_{1-4}烷基，C_{1-4}烷氧基C_{1-4}烷基，C_{1-4}烷基砜，氨基C_{2-4}烷基，-C_{1-4}亚烷基-C(=O)$NH_{(2-q)}$(C_{1-6}烷基)$_q$，-C_{1-4}亚烷基-NHC(=O)C_{1-6}烷基，磺酰胺C_{1-4}烷基，3-6元环烷基，被3-6元环烷基取代的C_{1-4}烷基，含有选自O、N或S的1、2、3或4个杂原子的5-或6-元不饱和杂环基，以及含有选自O、N或S的1或2个杂原子的任选取代的4-6元饱和杂环基，其中任选的取代基选自C_{1-4}烷基。

[0407] 其他优选实施方案包括下式中任何一个所示的Y部分：

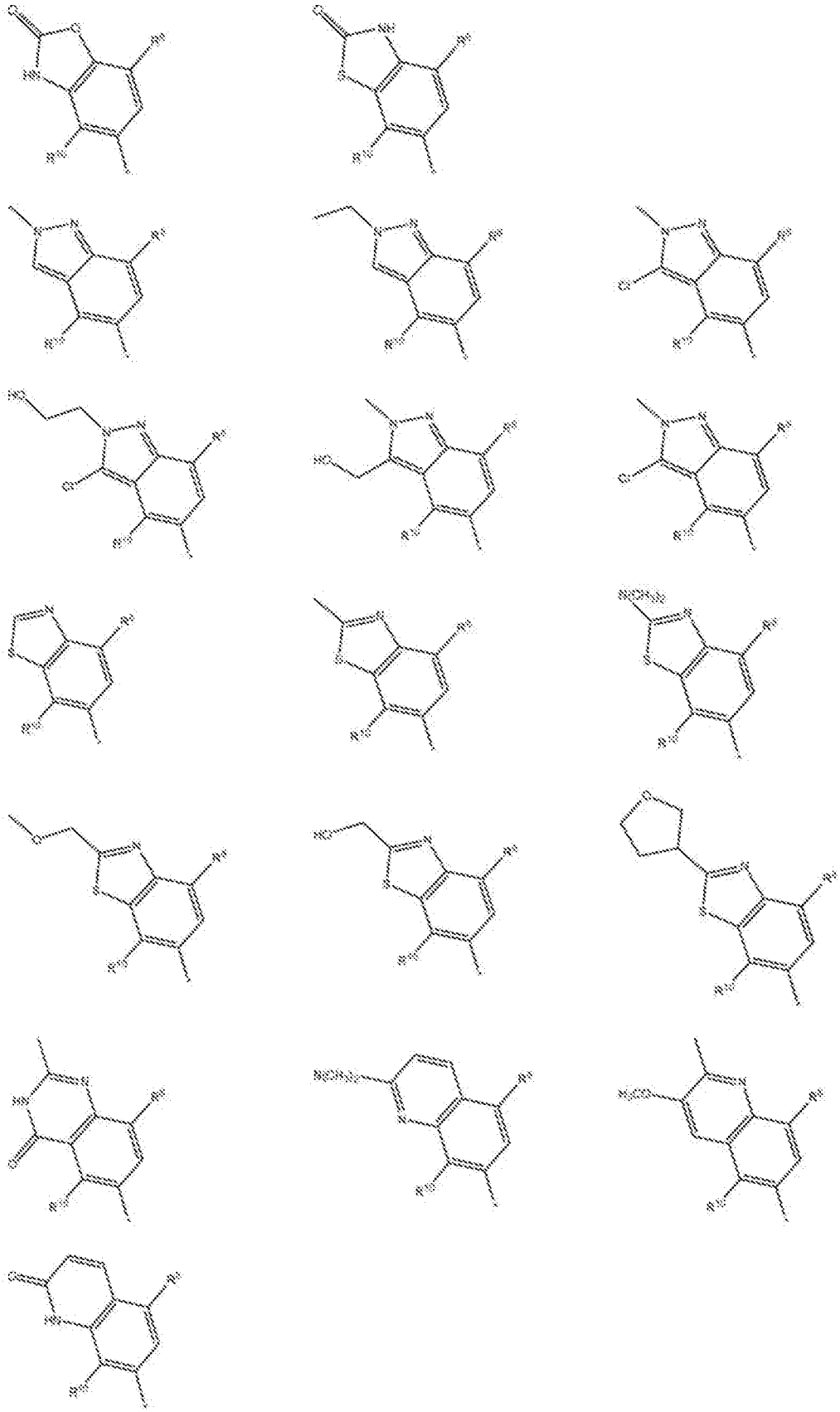
[0408] [化学式22]

[0409] I 

[0410] 其中R^8、R^{10}、R^{11}和d同上文定义的；

[0411] 更优选的实施方案包括下式中任何一个所示的Y部分：

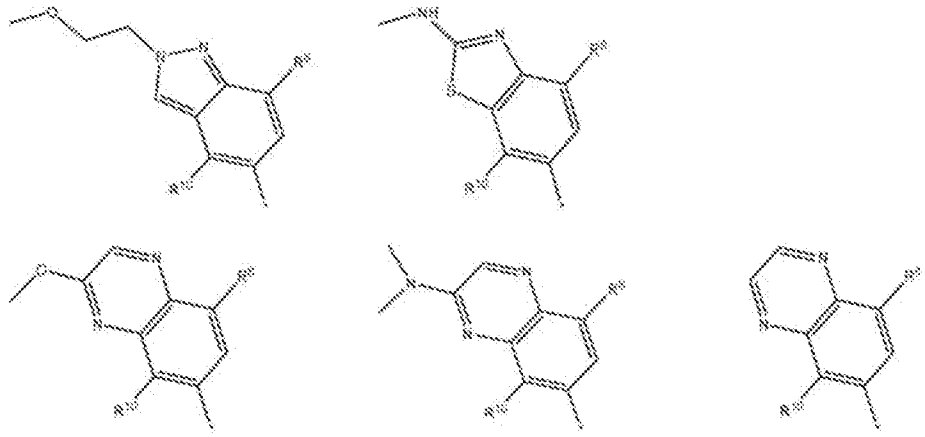
[0412] [化学式23]

[0413] 

[0414] 其中R^8和R^{10}同上文定义的。

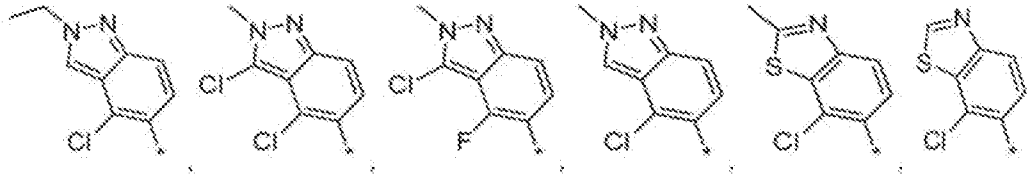
[0415] 更优选的实施方案包括下式中任何一个所示的Y部分：

[0416] [化学式24]

[0417] 

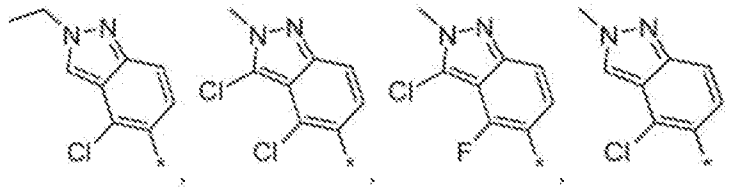
[0418] 更优选的实施方案包括下式中任何一个所示的Y部分：

[0419] [化学式25]

[0420] 

[0421] 特别优选的实施方案包括下式中任何一个所示的Y部分：

[0422] [化学式26]

[0423] 

[0424] 下述是本发明优选化合物的实例：

[0425] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0426] 2-(4-(氨基甲基)-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0427] 2-(4-氨基-4-甲基哌啶-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0428] 2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0429] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0430] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0431] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0432] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0433] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(2-(叔丁基)-4-氯-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0434] 2-(exo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0435] (R)-2-(1-氨基-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0436] (S)-2-(4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0437] 5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0438] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(endo-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0439] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0440] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0441] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0442] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0443] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(羟基甲基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0444] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-(3-(2-羟基乙基)哌嗪-1-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0445] 2-((1S,4S)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0446] 2-(7-氨基-3-氧杂-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0447] 2-((1R,4R)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0448] 2-(exo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0449] 2-(endo-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0450] rac-2-((1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0451] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0452] 2-(3,8-二氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲

基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0453] 2-(3,6-二氮杂二环[3.1.1]庚烷-6-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0454] 2-(3,9-二氮杂二环[3.3.1]壬烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0455] 2-(3,6-二氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0456] 2-(2,5-二氮杂二环[2.2.2]辛烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0457] 2-(exo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0458] 2-(endo-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0459] 2-(5-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0460] 2-(exo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0461] 2-(endo-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0462] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,8-二氮杂螺[4.5]癸烷-8-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0463] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0464] 2-(3,7-二氮杂二环[4.2.0]辛烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0465] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,9-二氮杂螺[5.5]十一烷-9-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0466] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(1,7-二氮杂螺[3.5]壬烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0467] (S)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0468] (R)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0469] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0470] 2-((1S,2S,4R)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0471] (R)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0472] (S)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-(2-甲基哌嗪-1-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0473] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0474] 2-((3R,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0475] rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0476] 2-((3S,4S)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0477] 2-(4-氨基-3,3-二氟吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0478] (S)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0479] (R)-2-(3-氨基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0480] 2-((3R,4R)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0481] 2-((3R,4S)-3-氨基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0482] 2-(3-氨基-3-(羟基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0483] 2-((3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0484] (R)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0485] 2-(1-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0486] 2-(6-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0487] (S)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0488] 2-(4-(氨基甲基)-4-甲氧基哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0489] 2-(4-(氨基甲基)-4-氟哌啶-1-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0490] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0491] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-甲基-5-(2-甲基-2H-吲唑-

5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0492] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0493] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[d]噁唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0494] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0495] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6,7-二氟-1-甲基-1H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0496] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0497] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-甲氧基-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0498] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0499] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-(2-羟基-2-甲基丙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0500] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2,7-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0501] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(1H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0502] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0503] 2-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0504] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0505] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0506] 2-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺，

[0507] 3-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺，

[0508] 2-(6-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-7-氯苯并[d]噻唑-2-基)-N,N-二甲基乙酰胺，

[0509] 2-(3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0510] 2-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基乙酰胺，

[0511] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-苯并[d][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0512] 3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺,

[0513] 3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-3,4-二氯-2H-吲唑-2-基)-N,N-二甲基丙酰胺,

[0514] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0515] 2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0516] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0517] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0518] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2,3-二甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0519] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0520] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0521] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0522] 5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0523] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0524] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0525] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0526] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-甲氧基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0527] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-(氟甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0528] 5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0529] 5-(7-氯苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0530] 5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-

7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0531] 5-(7-氯-2-甲基苯并[d]噻唑-6-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0532] 2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0533] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-3-(二氟甲基)-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0534] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-(羟基甲基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮，

[0535] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0536] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0537] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0538] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0539] 6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0540] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0541] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0542] 3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0543] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0544] 3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0545] 3-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0546] 6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0547] 3-(7-氯苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0548] 3-(7-氯-2-甲基苯并[d]噻唑-6-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0549] rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮，

[0550] rac-6-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0551] 6-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0552] 3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-6-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0553] 2-((1R,2S,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0554] 2-((1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0555] 2-((1R,2R,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0556] 2-((1S,2S,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0557] rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0558] rac-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(7-氯苯并[d]噻唑-6-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0559] rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,4S,7S)-7-(甲基氨基)-2-氮杂二环[2.2.1]庚烷-2-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0560] endo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0561] 3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{3,8-二氮杂二环[3.2.1]辛烷-8-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0562] 6-[(1R,3S)-1-氨基-3-羟基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0563] 6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0564] exo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0565] 3-(4-氯-2-甲基-2H-吲唑-5-基)-6-{2,7-二氮杂螺[3.5]壬烷-7-基}-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0566] 6-[(1R)-1-氨基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0567] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0568] 6-[(1R,3R)-1-氨基-3-氟-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0569] 3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬

烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0570] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0571] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0572] 6-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0573] 6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,

[0574] 2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0575] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-(1,4-二氮杂环庚烷-1-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0576] rac-2-[(1R,2R,5R)-2-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0577] rac-5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0578] rac-2-(4-氨基氮杂环庚烷-1-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0579] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0580] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0581] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0582] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0583] 5-(2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2-乙基-2H-吲唑-3-甲腈,

[0584] 6-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0585] 6-(endo-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0586] 6-((3R,4S)-4-氨基-3-氟哌啶-1-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0587] 2-((1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0588] 2-(rac-(1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0589] 5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-2-((1S,2S,4R)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0590] 2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0591] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0592] 2-((1R,2S,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-5-(3,4,7-三氯-2-甲基-2H-吲唑-5-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0593] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-甲氧基喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0594] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-(二甲基氨基)喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0595] 6-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0596] 2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0597] rac-2-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0598] 2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3-氯-4-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0599] rac-6-((1R,2R,4S)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0600] 2-(endo-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(5-氯喹喔啉-6-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0601] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(乙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0602] 2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-(2-甲氧基乙基)-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮,

[0603] 3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(异丙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮,

[0604] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0605] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-4-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0606] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(7-氯-2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0607] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0608] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-

6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0609] 2-[(endo)-3-氨基-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0610] 2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0611] 2-[(3R,4S)-4-氨基-3-氟哌啶-1-基]-5-(7-氯-1,3-苯并噻唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0612] 5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1S,6R)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0613] 5-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(1R,6S)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0614] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1R,5R)-3,6-二氮杂二环[3.2.1]辛烷-3-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0615] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{(1S,5S)-3,6-二氮杂二环[3.2.1]辛烷-3-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0616] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1S,5R)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0617] 5-(4-氯-2-乙基-2H-吲唑-5-基)-2-[(1R,5S)-3,6-二氮杂二环[3.2.1]辛烷-6-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0618] 2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-7-氟-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0619] 2-[(endo)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基]-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0620] rac-5-(4-氯-2-乙基-2H-吲唑-5-基)-2-{2,6-二氮杂螺[3.4]辛烷-6-基}-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0621] 2-[(1R,2S,3S,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,

[0622] 2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(二甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮,和

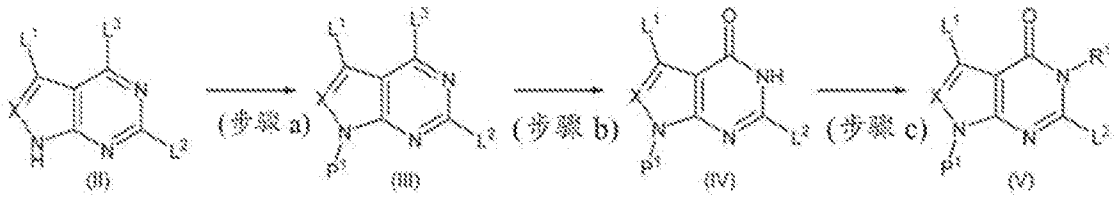
[0623] 2-[(1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮。

[0624] 式(I)化合物的制备方法

[0625] 可根据技术人员公知的合成方法制备式(I)化合物。

[0626] 根据本发明的另一方面,提供制备式(I)化合物或其互变异构体、立体异构体、药学上可接受的盐或溶剂合物的方法,该方法包括:

[0627] [化学式27]

[0628] 

[0629] (其中P^1是保护基，L^1、L^2和L^3是离去基团，R^1和X同上文定义的)。L^1、L^2和L^3可以例如是氯化物、溴化物和碘化物中的任何一种。

[0630] (步骤a)

[0631] 在该步骤中，保护式(II)化合物，以形成式(III)化合物。

[0632] 式(II)化合物是市售的，或利用实施例中所述的类似方法制备。

[0633] 式(III)化合物中P^1所示的保护基的示例包括((2-三甲基硅烷基)乙氧基)甲基(SEM)或四氢-2H-吡喃-2-基(THP)。

[0634] 所述方法通常包含式(II)化合物与((2-三甲基硅烷基)乙氧基)甲基氯(SEMCl)在适当温度下、在适当的溶剂、适当的碱中反应。适当的碱的示例是氢化钠、三乙胺或N,N-二异丙基乙基胺。适当的溶剂的示例是四氢呋喃或N,N-二甲基甲酰胺。对于每摩尔式(II)所示的化合物，SEMCl的用量通常为1-10摩尔，并优选1-5摩尔。对于每摩尔式(II)所示的化合物，碱的用量通常为1-100摩尔，优选为1-10摩尔。

[0635] 所述方法通常包含式(II)化合物与3,4-二氢-2H-吡喃在适当温度下、在适当的溶剂、适当的酸中反应。适当的酸的示例是p-甲苯磺酸一水合物或樟脑磺酸。适当的溶剂的示例是四氢呋喃或二氯甲烷。对于每摩尔式(II)所示的化合物，3,4-二氢-2H-吡喃的用量通常为1-10摩尔，并优选1-5摩尔。对于每摩尔式(II)所示的化合物，酸的用量通常为0.001-100摩尔，优选为0.01-10摩尔。

[0636] 反应温度通常为0-200℃，优选室温至150℃。反应时间通常为5分钟至7天，优选30分钟至4天。

[0637] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(III)化合物进行随后的步骤。

[0638] (步骤b)

[0639] 在该步骤中，将式(III)化合物羟基化，以产生式(IV)化合物。

[0640] 该方法通常包含式(III)化合物与适当的碱在适当温度下、在适当的溶剂中反应。适当的碱的示例是氢氧化钠或氢氧化钾。适当的溶剂的示例是四氢呋喃、1,2-二甲氧基乙烷或1,4-二氧六环与水。

[0641] 对于每摩尔式(III)所示的化合物，碱的用量通常是0.1-100摩尔，并优选1-20摩尔。

[0642] 反应温度通常是0-200℃，优选室温至150℃。反应时间通常是5分钟至7天，优选30min至4天。

[0643] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(IV)化合物进行随后的步骤。

[0644] (步骤c)

[0645] 在该步骤中，式(IV)化合物与烷基化剂例如碘甲烷反应，以产生式(V)化合物。

[0646] 该方法通常包含式(IV)化合物与碘甲烷和适当的碱在适当温度下、在适当的溶剂

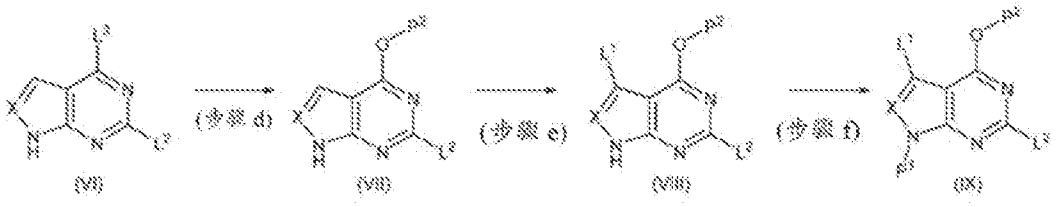
中反应。适当的碱的示例是碳酸钾或碳酸铯。适当的溶剂的示例是N,N-二甲基甲酰胺或N-甲基-2-吡咯烷酮。

[0647] 相对于每摩尔式(IV)所示的化合物,碘甲烷的用量通常为1-100摩尔,并优选为1-20摩尔。相对于每摩尔式(IV)所示的化合物,碱的用量通常为1-100摩尔,并优选为1-20摩尔。

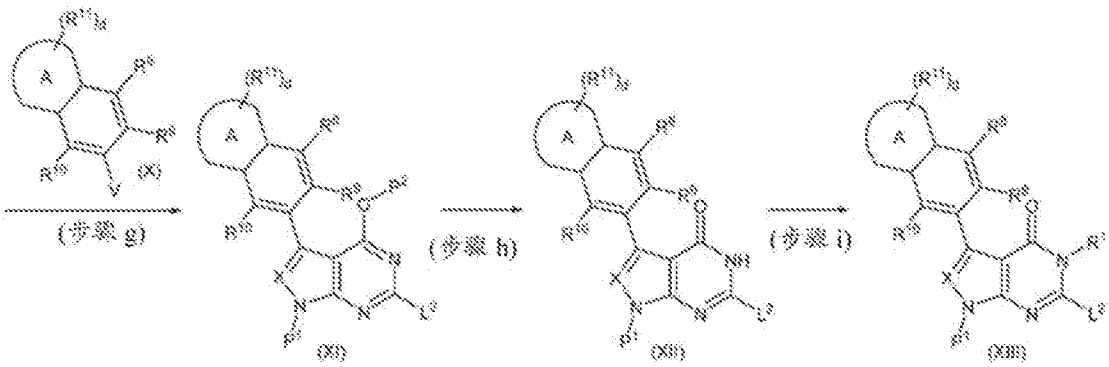
[0648] 反应温度通常是0-200℃,优选0-100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0649] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化,将由此得到的式(V)化合物进行随后的步骤。

[0650] [化学式28]



[0651]



[0652] (其中P^1、P^2是保护基,L^1、L^2和L^3是离去基团,V代表金属或类金属残基(例如硼酸、频哪醇硼酸酯),环A、R^1、R^8、R^9、R^{10}、R^{11}、X和d同上文定义的)。

[0653] (步骤d)

[0654] 在该步骤中,式(VI)化合物与醇P^2-OH反应,以产生式(VII)化合物。

[0655] 式(VI)化合物是市售的或可利用实施例中所述的类似方法制备。

[0656] 该方法通常包含式(VI)化合物与醇例如4-甲氧基苄醇和适当的碱于适当的溶剂中在适当的温度下反应。适当的碱的示例是叔丁醇钾或叔丁醇钠。适当的溶剂的示例是四氢呋喃或1,4-二氧六环。

[0657] 相对于每摩尔式(VI)所示的化合物,醇的用量通常为1-100摩尔,并优选为1-20摩尔。相对于每摩尔式(VI)所示的化合物,碱的用量通常为1-100摩尔,并优选为1-20摩尔。

[0658] 反应温度通常是0-200℃,优选0-100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0659] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化,将由此得到的式(VII)化合物进行随后的步骤。

[0660] (步骤e)

[0661] 在该步骤中,将式(VII)化合物卤化,以产生式(VIII)化合物,其中L^1是卤素。

[0662] 该方法通常包含式(VII)化合物与卤化试剂于适当的溶剂中在适当的温度下反应。卤化试剂的示例是N-溴代琥珀酰亚胺或N-碘代琥珀酰亚胺。适当的溶剂的示例是四氢呋喃或N,N-二甲基甲酰胺。

[0663] 相对于每摩尔式(VII)所示的化合物,卤化试剂的用量通常为1-100摩尔,并优选为1-20摩尔。

[0664] 反应温度通常是-78-100℃,优选-20-100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0665] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化,将由此得到的式(VIII)化合物进行随后的步骤。

[0666] (步骤f)

[0667] 用与步骤a类似的方式完成该步骤。

[0668] (步骤g)

[0669] 在该步骤中,将式(IX)化合物与式(X)化合物进行偶联反应,以产生式(XI)化合物。

[0670] 式(X)化合物是市售的或可利用实施例中所述的类似方法制备。

[0671] 该方法通常包含式(IX)化合物与式(X)化合物和适当的催化剂、适当的碱在适当的温度下、在适当的溶剂中反应。

[0672] 适当的催化剂的示例是[1,1′-双(二苯基膦基)二茂铁]二氯化钯(II)、四三苯基膦钯或具有合适配体(例如三苯基膦、三叔丁基膦、2-二环己基膦基-2′,4′,6′-三异丙基联苯)的三(二亚苄基丙酮)二钯(0)。适当的催化剂的另一个示例是(二-叔丁基(4-二甲基氨基苯基)膦)二氯化钯(ii)。适当的碱的示例是碳酸钠、碳酸钾或磷酸钾。适当的溶剂的示例是四氢呋喃、1,2-二甲氧基乙烷或1,4-二氧六环与水)。

[0673] 相对于每摩尔式(IX)所示的化合物,式(X)化合物的用量通常为1-100摩尔,并优选为1-20摩尔。相对于每摩尔式(IX)所示的化合物,催化剂的用量通常为0.0001-1摩尔,并优选为0.001-0.5摩尔。相对于每摩尔式(IX)所示的化合物,配体的用量通常为0.0001-4摩尔,并优选为0.001-2摩尔。相对于每摩尔式(IX)所示的化合物,碱的用量通常为0.1-10摩尔,并优选为1-5摩尔。

[0674] 反应温度通常是0-200℃,优选室温至150℃。反应时间通常是5分钟至7天,优选30min至4天。

[0675] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化,将由此得到的式(XI)化合物进行随后的步骤。

[0676] (步骤h)

[0677] 在该步骤中,将式(XI)化合物脱保护,以产生式(XII)化合物。

[0678] 该方法通常包含式(XI)化合物与2,3-二氯-5,6-二氰基-p-苯醌于适当溶剂中在适当温度下反应。适当溶剂的示例是二氯甲烷。

[0679] 相对于每摩尔式(XI)所示的化合物,2,3-二氯-5,6-二氰基-p-苯醌的用量通常为1-100摩尔,并优选为1-20摩尔。

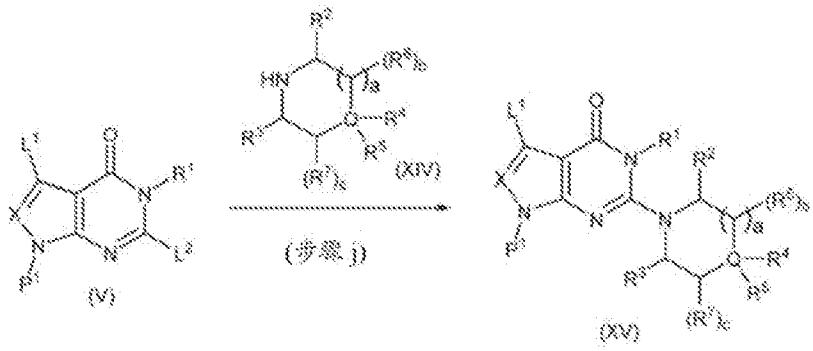
[0680] 反应温度通常是0-200℃,优选室温至100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0681] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(XII)化合物进行随后的步骤。

[0682] (步骤i)

[0683] 用与步骤c中类似的方式完成该步骤。

[0684] [化学式29]

[0685] 

[0686] (其中P^1是保护基，L^1、L^2是离去基团，R^1、R^2、R^3、R^4、R^5、R^6、R^7、Q、X、a、b和c同上文定义的)。

[0687] (步骤j)

[0688] 在所述步骤中，将式(V)化合物与式(XIV)化合物进行偶联反应，以产生式(XV)的化合物。

[0689] 任选地，在活化剂存在下完成所述反应。

[0690] 式(XIV)化合物是市售的或可利用实施例中所述的类似方法制备。

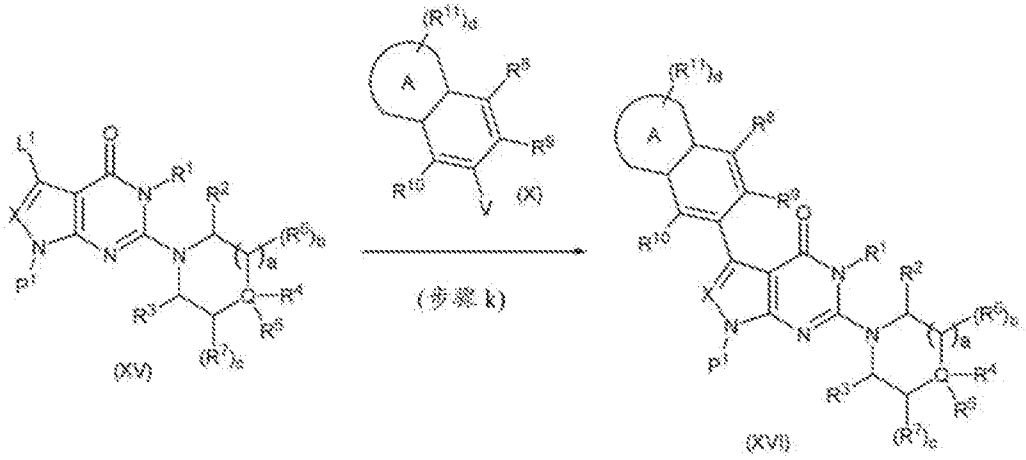
[0691] 该方法通常包含式(V)化合物与式(XIV)化合物和适当的碱在适当溶剂中在适当温度下反应。适当的碱的示例是N,N-二异丙基乙胺。适当的的溶剂的示例是N-甲基-2-吡咯烷酮或N,N-二甲基甲酰胺。

[0692] 相对于每摩尔式(V)所示的化合物，式(XIV)化合物的用量通常为1-100摩尔，并优选为1-10摩尔。相对于每摩尔式(V)所示的化合物，碱的用量通常为1-100摩尔，并优选为1-20摩尔。

[0693] 反应温度通常是室温-200℃，优选室温至150℃。反应时间通常是5分钟至7天，优选30min至4天。

[0694] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(XV)化合物进行随后的步骤。

[0695] [化学式30]

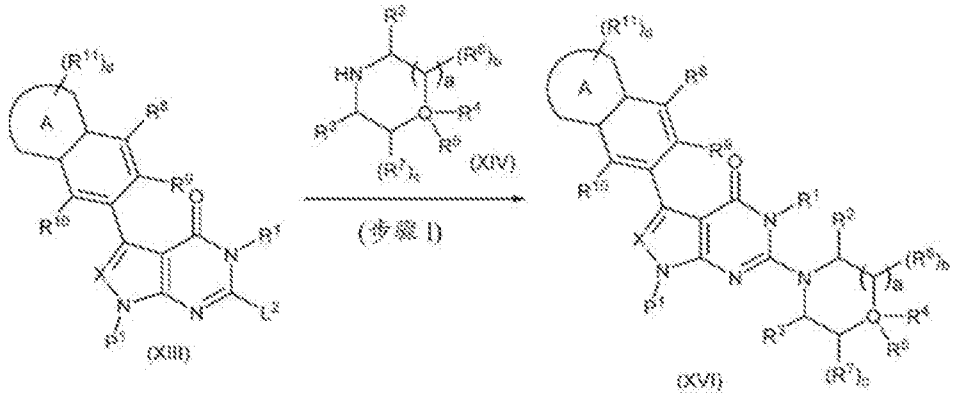
[0696] 

[0697] (其中P^1是保护基，L^1是离去基团，V代表金属或类金属残基(例如硼酸或频哪醇硼酸酯)，环A、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、Q、X、a、b、c和d同上文定义的)。

[0698] (步骤k)

[0699] 可用与步骤g类似的方式完成该步骤。

[0700] [化学式31]

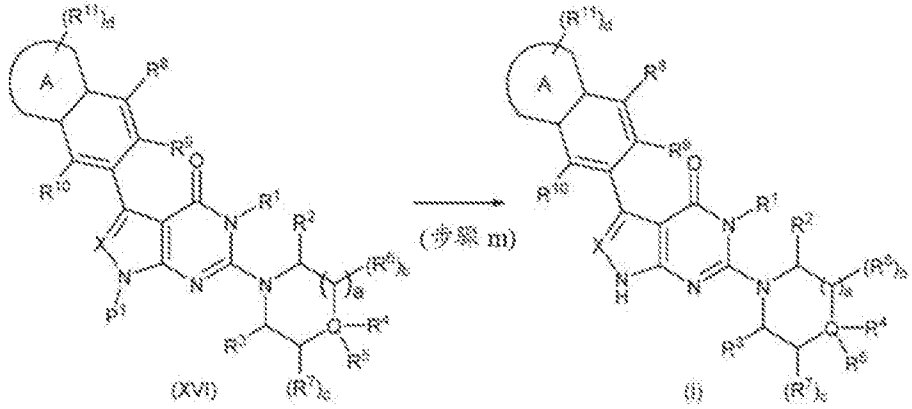
[0701] 

[0702] (其中P^1是保护基，L^2是离去基团，环A、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、Q、X、a、b、c和d同上文定义的)。

[0703] (步骤l)

[0704] 可用与步骤j类似的方式完成该步骤。

[0705] [化学式32]

[0706] 

[0707] (其中P^1是保护基，环A、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、Q、X、a、b、c和d同上文

定义的)。

[0708] (步骤m)

[0709] 在该步骤中,将式(XVI)化合物脱保护,以产生式(I)化合物。

[0710] 所述方法通常包含任何适当的脱保护反应,其条件将取决于保护基的性质。当保护基P^1代表((2-三甲基硅烷基)乙氧基)甲基基团(SEM)时,所述脱保护反应通常包含在适当的溶剂中使用合适的酸,然后用乙二胺或氢氧化钠除去在SEM保护基的酸脱保护期间形成的羟基甲基加合物。例如,酸可以适当地包含三氟乙酸或盐酸,并且溶剂可以适当地包含二氯甲烷、氯仿、N,N-二甲基甲酰胺或甲醇。任选地,可以使用溶剂混合物,例如水和甲醇。第二步涉及真空浓缩,然后将粗物质溶解在适当的溶剂例如甲醇中,并用适当的清除剂例如乙二胺或氢氧化钠处理。

[0711] 相对于每摩尔式(XVI)所示的化合物,酸的用量通常为1-100摩尔,并优选为1-20摩尔。相对于每摩尔式(XVI)所示的化合物,清除剂的用量通常为1-100摩尔,并优选为1-20摩尔。

[0712] 反应温度通常是0-200℃,优选室温至100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0713] 当保护基是四氢-2H-吡喃-2-基基团(THP)时,可在适当的温度下,将强酸例如盐酸用于适当的溶剂例如甲醇中。

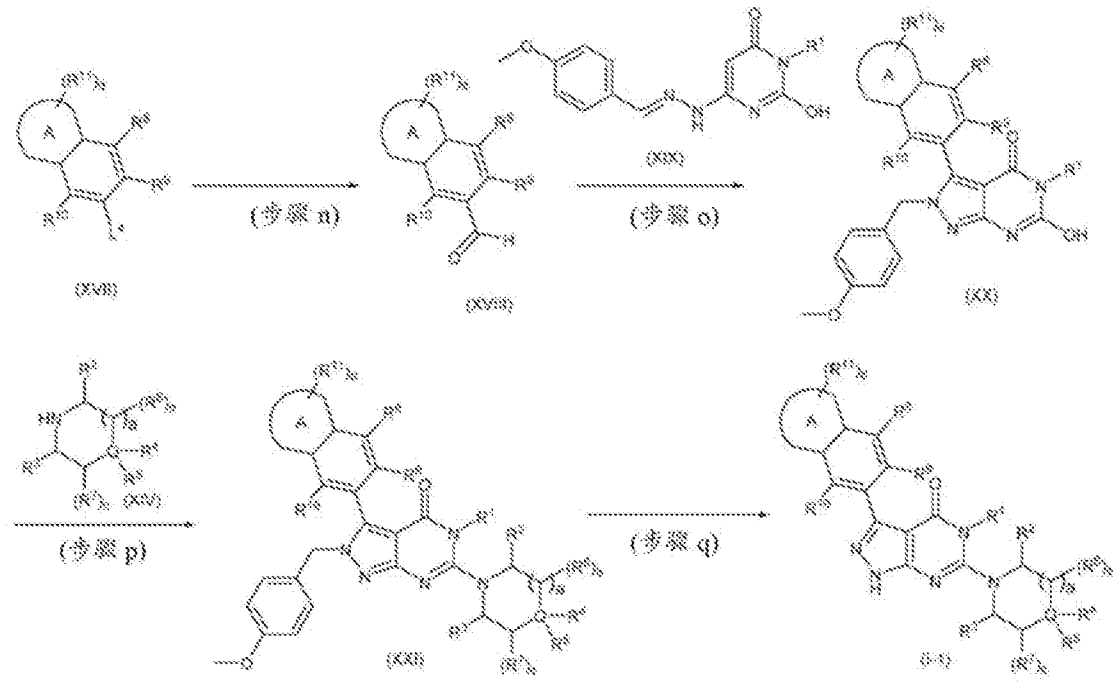
[0714] 相对于每摩尔式(XVI)所示的化合物,酸的用量通常为1-100摩尔,并优选为1-20摩尔。

[0715] 反应温度通常是0-200℃,优选室温至100℃。反应时间通常是5分钟至7天,优选30min至4天。

[0716] 可通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱,将由此得到的式(I)化合物进行分离和纯化。

[0717] 作为制备式(I)化合物的通用方法,可根据本文所述的方法,完成脱保护。

[0718] [化学式33]

[0719] 

[0720] (其中L^4是离去基团，R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、环A、Q、a、b、c和d同上文定义的)。L^4可以是例如溴化物、碘化物和三氟甲磺酸酯中的任何一个。

[0721] (步骤n)

[0722] 在该步骤中，将式(XVII)化合物进行甲酰化，以产生式(XVIII)化合物。

[0723] 该方法通常包含式(XVII)化合物与有机金属试剂例如i-PrMgCl和甲酰化试剂例如N,N-二甲基甲酰胺在合适的溶剂中在适当的温度下反应。合适的溶剂的示例是四氢呋喃。

[0724] 相对于每摩尔式(XVII)所示的化合物，i-PrMgCl的用量通常为1-10摩尔，并优选为1-5摩尔。相对于每摩尔式(XVII)所示的化合物，N,N-二甲基甲酰胺的用量通常为1-20摩尔，并优选为1-10摩尔。

[0725] 反应温度通常是0-100℃，优选0-60℃。反应时间通常是5分钟至7天，优选30min至4天。

[0726] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(XVIII)化合物进行随后的步骤。

[0727] (步骤o)

[0728] 在该步骤中，将式(XVIII)化合物与式(XIX)化合物进行环化反应，以产生式(XX)化合物。

[0729] 该方法通常包含式(XVIII)化合物与式(XIX)化合物和适当的碱在适当的溶剂中在适当的温度下反应。适当的碱的示例是哌啶。适当的溶剂的示例是N,N-二甲基甲酰胺和异丙醇。

[0730] 相对于每摩尔式(XIX)所示的化合物，式(XVIII)化合物的用量通常为1-10摩尔，并优选为1-5摩尔。相对于每摩尔式(XIX)所示的化合物，碱的用量通常为1-10摩尔，并优选为1-5摩尔。

[0731] 反应温度通常是0-100℃，优选0-60℃。反应时间通常是5分钟至7天，优选30min至

4天。

[0732] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(XX)化合物进行随后的步骤。

[0733] 式(XIX)化合物是已知的或者根据文献中所述的类似方法制备。

[0734] (步骤p)

[0735] 在该步骤中，将式(XX)化合物与式(XIV)化合物进行偶联反应，以产生式(XXI)化合物。

[0736] 式(XIV)化合物是市售的或可利用实施例中所述的类似方法制备。

[0737] 所述方法通常包含式(XX)化合物与式(XIV)化合物、活化剂例如PyBOP和适当的碱于适当的溶剂中在适当的温度下反应。适当的碱的示例是DBU或N,N-二异丙基乙胺。适当的溶剂的示例是N-甲基-2-吡咯烷酮或N,N-二甲基甲酰胺。

[0738] 相对于每摩尔式(XX)所示的化合物，式(XVIII)化合物的用量通常为1-10摩尔，并优选为1-5摩尔。相对于每摩尔式(XX)所示的化合物，PyBOP的用量通常为1-10摩尔，并优选为1-5摩尔。相对于每摩尔式(XX)所示的化合物，碱的用量通常为1-20摩尔，并优选为1-10摩尔。

[0739] 反应温度通常是0-100℃，优选0-60℃。反应时间通常是5分钟至7天，优选30min至4天。

[0740] 可在通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱分离或纯化之后或不经分离或纯化，将由此得到的式(XXI)化合物进行随后的步骤。

[0741] (步骤q)

[0742] 在该步骤中，将式(XXI)化合物脱保护，以产生式(I-1)化合物。

[0743] 所述方法通常包含式(XXI)化合物与适当的酸在适当的溶剂中在适当的温度下反应。适当的酸的示例是三氟甲磺酸。适当的溶剂的示例是二氯甲烷或氯仿。

[0744] 相对于每摩尔式(XXI)所示的化合物，三氟甲磺酸的用量通常为1-100摩尔，并优选为1-20摩尔。

[0745] 反应温度通常是0-200℃，优选0-100℃。反应时间通常是5分钟至7天，优选30min至4天。

[0746] 可通过已知的分离和纯化方式例如浓缩、真空浓缩、结晶、溶剂萃取、再沉淀和色谱，将由此得到的式(I-1)化合物分离和纯化。

[0747] 作为式(I-1)化合物制备的通用方法，可根据文中所述的方法，完成脱保护。

[0748] 在上述任何步骤中，可以适当地完成取代基的保护以及保护基的去除或转化。例如，对于氨基、亚氨基、羟基、羧基、羰基和酰氨基等官能团，以及具有活性质子的官能团例如吲哚，可以使用保护剂，或者可以根据通常方法将保护基引入所述官能团。然后，可以在每种生产方法的适当步骤中除去保护基。

[0749] 不特别限定氨基基团的保护基或亚氨基基团的保护基，只要其具有保护功能。所述保护基的示例包括芳烷基，例如苄基、p-甲氧基苄基、3,4-二甲氧基苄基、o-硝基苄基、p-硝基苄基、二苯甲基、三苯甲基和枯基；低级烷酰基基团，例如甲酰基、乙酰基、丙酰基、丁酰基、新戊酰基、三氟乙酰基和三氯乙酰基；苯甲酰基；芳基烷酰基基团，例如苯乙酰基和苯氧乙酰基；低级烷氧基羰基基团，例如甲氧基羰基、乙氧基羰基、丙氧基羰基和叔丁氧羰基；芳

烷基氧羰基基团，例如p-硝基苄氧羰基和苯乙氧羰基；低级烷基硅烷基基团，例如三甲基甲硅烷基和叔丁基二甲基硅烷基；四氢吡喃基；三甲基硅烷基乙氧基甲基；低级烷基磺酰基基团，例如甲磺酰基、乙磺酰基和叔丁基磺酰基；低级烷基亚磺酰基基团，例如叔丁基亚磺酰基；芳基磺酰基基团，例如苯磺酰基和甲苯磺酰基；和亚氨基基团，例如邻苯二甲酰亚氨基。具体地，三氟乙酰基、乙酰基、叔丁氧羰基、苄氧羰基、三甲硅烷基乙氧基甲基、枯基等是优选的。

[0750] 不特别限定羟基基团的保护基，只要其具有保护功能。所述保护基的示例包括低级烷基基团，例如甲基、乙基、丙基、异丙基和叔丁基；低级烷基硅烷基基团，例如三甲基硅烷基和叔丁基二甲基硅烷基；低级烷氧基甲基基团，例如甲氧基甲基和2-甲氧基乙氧基甲基；四氢吡喃基；三甲基硅基乙氧基甲基；芳烷基基团，例如苄基、p-甲氧基苄基、2,3-二甲氧基苄基、o-硝基苄基，p-硝基苄基和三苯甲基；和酰基基团，例如甲酰基、乙酰基和三氟乙酰基。具体地，甲基、甲氧基甲基、四氢吡喃基、三甲基硅基乙氧基甲基、叔丁基二甲基硅烷基和乙酰基是优选的。

[0751] 不特别限定羧基基团的保护基，只要其具有保护功能。所述保护基的示例包括低级烷基基团，例如甲基、乙基、丙基、异丙基和叔丁基；卤代-低级-烷基基团，例如2,2,2-三氯乙基；低级烯基，例如烯丙基；三甲基硅烷基乙氧基甲基；和芳烷基基团，例如苄基、p-甲氧基苄基、p-硝基苄基、二苯甲基和三苯甲基。具体地讲，甲基、乙基、叔丁基、烯丙基、苄基、p-甲氧基苄基、三甲基硅烷基乙氧基甲基等是优选的。

[0752] 不特别限定羰基基团的保护基，只要其具有保护功能。所述保护基的示例包括乙二醇缩酮、三亚甲基缩酮、二甲基缩酮、乙二醇缩醛、三亚甲基缩醛、二甲基缩醛和类似的缩酮类和缩醛类。

[0753] 不特别限定酰氨基的保护基或具有活性质子的官能团例如吲哚的保护基，只要其具有保护功能。所述保护基的示例包括低级烷基基团，例如甲基、乙基、丙基、异丙基和叔丁基；低级烷基硅烷基基团，例如三甲基硅烷基和叔丁基二甲基硅烷基；低级烷氧基甲基基团，例如甲氧基甲基和2-甲氧基乙氧基甲基；四氢吡喃基；三甲基硅基乙氧基甲基；芳烷基基团，例如苄基、p-甲氧基苄基、2,3-二甲氧基苄基、o-硝基苄基、p-硝基苄基和三苯甲基；和酰基基团，例如甲酰基、乙酰基和三氟乙酰基。具体地讲，甲基、甲氧基甲基、四氢吡喃基、三甲基硅烷基乙氧基甲基、叔丁基二甲基硅烷基和乙酰基是优选的。

[0754] 除去所述保护基的方法可根据保护基的类型、目标化合物(I)的稳定性等而变化。例如，可以使用下述方法：根据出版物(Protective Groups in Organic Synthesis，第三版，TW Green，John Wiley&Sons(1999))中公开的方法或类似方法，利用酸或碱进行溶剂分解，即包含与0.01摩尔或大过量的酸(优选三氟乙酸、甲酸或盐酸)或等摩尔至大过量摩尔量的碱(优选氢氧化钾或氢氧化钙)反应的方法；利用金属氢化物络合物等进行化学还原；或利用钯-碳催化剂、兰尼镍催化剂等进行催化还原。

[0755] 可将本发明化合物通过常用的分离和纯化方法容易地进行分离纯化。所述方法的示例包括溶剂萃取、重结晶、制备型反相高效液相色谱法、柱色谱法、制备型薄层色谱法等。

[0756] 当本发明化合物具有异构体例如光学异构体、立体异构体、旋转异构体和互变异构体时，任何异构体及其混合物均包括在本发明化合物的范围内，除非另外说明。例如，当本发明的化合物具有光学异构体时，从外消旋混合物中分离的光学异构体也包括在本发明

化合物的范围内，除非另外说明。通过已知的合成和分离手段(例如浓缩、溶剂萃取和柱色谱、重结晶)，每种所述异构体可作为单一化合物获得。

[0757] 如上所述，除非另外说明，本发明的化合物包括所有的对映异构体及其混合物。本发明化合物可以是R和S对映异构体的混合物。所述混合物可以是包含55％或更多、60％或更多、65％或更多、70％或更多、75％或更多、80％或更多、85％或更多、90％或更多、95％或更多或者99％或更多的R异构体的混合物；包含55％或更多、60％或更多、65％或更多、70％或更多、75％或更多、80％或更多、85％或更多、90％或更多、95％或更多或者99％或更多的S异构体的混合物；等。

[0758] 用于手性拆分的方法包括例如：非对映体方法，其使手性拆分剂作用于本发明化合物以形成盐，并利用所得盐的溶解度差异等拆分其中一种对映异构体；优先结晶方法，其将一种对映异构体添加到外消旋体的过饱和溶液中作为晶种；和柱色谱法，例如利用手性柱的HPLC。可用于非对映体方法的手性拆分剂可适当地选自例如酸拆分剂诸如酒石酸、苹果酸、乳酸、扁桃酸、10-樟脑磺酸及其衍生物；和碱性拆分剂诸如马钱子碱、士的宁、奎宁，以及类似生物碱化合物，氨基酸衍生物，辛可尼丁和α-甲基苄基胺。不仅可以通过以对映体混合物的形式获得本发明化合物，然后如上所述进行手性拆分，来获得单独的本发明化合物的一种对映体，而且可以通过上述的手性拆分或通过其他方法获得本发明化合物的一种对映体，并将其用作本发明化合物的合成原料，而获得单独的本发明化合物的一种对映体。此外，用于获得本发明化合物或其原料化合物的一种对映异构体的方法包括通过在生成不对称碳的反应步骤中调节催化剂等反应条件而优先获得一种对映异构体的方法。

[0759] 可将式(I)化合物任选地转化为药学上可接受的盐。本发明的化合物或其盐可以是晶体形式。单晶和多晶型混合物包括于本发明化合物或其盐的范围内。可根据本领域公知的结晶方法，通过结晶生产所述晶体。本发明化合物或其盐可以是溶剂合物(例如水合物)或非溶剂合物。任何所述形式都包括于本发明化合物或其盐的范围内。用一种或多种同位素(例如^{2}H、^{3}H、^{14}C、^{35}S和^{125}I)标记的化合物也包括于本发明化合物或其盐的范围内。

[0760] 本发明化合物或其中间体的盐是指在有机化学领域中使用的普通盐。所述盐的示例包括当化合物含有羧基时，与羧基的碱加成盐，以及当化合物含有氨基或碱性杂环基时，与氨基或碱性杂环基的酸加成盐。

[0761] 碱加成盐的示例包括碱金属盐例如钠盐和钾盐；碱土金属盐例如钙盐和镁盐；铵盐；和有机胺盐例如三甲基胺盐、三乙胺盐、二环己基胺盐、乙醇胺盐、二乙醇胺盐、三乙醇胺盐、普鲁卡因盐和N,N′-二苄基乙二胺盐。

[0762] 酸加成盐的示例包括无机酸盐例如盐酸盐、硫酸盐、硝酸盐、磷酸盐和高氯酸盐；有机酸盐例如乙酸盐、甲酸盐、马来酸盐、富马酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐和三氟乙酸盐；磺酸盐例如甲磺酸盐、羟乙磺酸盐、苯磺酸盐和p-甲苯磺酸盐。

[0763] 式(I)还包含的是式(I)化合物的任何前药。“前药”是指例如在体内转化为生物活性的式(I)化合物的任何化合物。所述前药可以例如通过用本领域技术人员已知的某些基团代替式(I)化合物中存在的适当官能团来制备。在一实施方案中，某些式(I)化合物本身可作为其他式(I)化合物的前药。在一实施方案中，式(I)不包括在其范围内的式(I)化合物的前药。

[0764] 由于其优异的SHP2抑制活性，本发明化合物或其盐可用作预防或治疗SHP2介导的

疾病或病症的药物制剂。

[0765] “SHP2介导的疾病或病症”的示例包括可以通过消除、压制和/或抑制SHP2功能降低其发病率，以及可消除、缓解和/或完全治愈其症状的疾病或病症。所述疾病可包含其中SHP2活性/存在/状态异常的、与异常的RAS-ERK信号传导通路或受体酪氨酸激酶信号传导通路状态相关的疾病，或其中SHP2活性/存在/状态异常的、与异常的免疫应答状态相关的疾病。“SHP2介导的疾病或病症”的示例包括但不限于恶性肿瘤等。

[0766] 不特别限制待用本发明化合物或其盐治疗的恶性肿瘤的类型。所述恶性肿瘤的示例包括头颈癌、食道癌、胃癌、结肠癌、直肠癌、肝癌、胆囊癌、胆管癌、胆道癌、胰腺癌、肺癌、乳腺癌、卵巢癌、宫颈癌、子宫内膜癌、肾癌、膀胱癌、前列腺癌、睾丸肿瘤、骨肉瘤、软组织肉瘤、白血病、骨髓增生异常综合症、慢性骨髓增生性疾病、恶性淋巴瘤、多发性骨髓瘤、皮肤癌、脑瘤、间皮瘤等。

[0767] 当将本发明化合物或其盐用作药物制剂时，如果需要，可加入药学上可接受的载体，从而根据预防和治疗目的而形成适当的剂型。剂型的示例包括口服制剂、注射剂、栓剂、软膏剂、贴剂等；优选口服制剂。可以通过本领域技术人员常规已知的方法形成所述剂型。

[0768] 作为药学上可接受的载体，可将用作制剂材料的各种常规有机或无机载体材料作为固体制剂中的赋形剂、粘合剂、崩解剂、润滑剂或包衣剂而混入；或作为液体制剂中的溶剂、增溶剂、助悬剂、等渗剂、pH调节剂/缓冲剂或舒缓剂(soothing agent)而混入。并且，如果需要，也可以使用药物制剂添加剂例如防腐剂、抗氧化剂、着色剂、甜味剂和稳定剂。

[0769] 当制备用于口服的固体制剂时，可以向本发明化合物中任选地加入赋形剂、粘合剂、崩解剂、润滑剂、着色剂、甜味剂等；并且可以根据常规方法将得到的混合物配制为片剂、包衣片剂、颗粒剂、散剂、胶囊剂等。

[0770] 当制备注射剂时，可以根据需要向本发明化合物中加入pH调节剂、缓冲剂、稳定剂、等渗剂、局部麻醉剂等；并且，可以根据常规方法将得到的混合物配制为皮下、肌内和静脉注射剂。

[0771] 在每种所述剂量单位形式中，掺入的本发明化合物的量取决于施用化合物的患者的状况、剂型等。通常，对于口服剂、注射剂和栓剂，每剂量单位形式，本发明化合物的量分别优选是0.05-1000mg、0.01-500mg和1-1000mg。

[0772] 施用的活性化合物的量将取决于治疗的哺乳动物、病患或病症的严重性、给药速度、化合物的处置和处方医生的判断力。有效剂量通常为大约0.001至大约100mg/kg体重/天，优选大约0.01mg至大约40mg/kg/天，为单一剂量或分剂量。例如，对于成年人(体重：50kg)，本发明化合物的日剂量通常可以为大约0.05mg至大约5000mg，并优选为大约0.5mg至大约2000mg。在某些情况下，低于上述范围下限的剂量水平可能是绰绰有余的，而在其他情况下，还可以使用更大剂量而不会引起任何有害副作用。通常可将所述较大剂量分为几个较小的剂量，用于全天给药。可将每日总剂量以单剂量或分剂量施用。根据医生的判断，每日总剂量可落在基于人类个体平均值例如具有大约50kg至大约70kg体重的个体的典型范围之外。对于体重超出所述范围的个体例如婴儿和老人，医生将能够很容易确定剂量。

实施例

[0773] 合成方法

[0774] 通过相似于和/或类似于下文通用操作的下述方法，制备下文列出的化合物。

[0775] 提供下述合成操作，用于解释说明所用的方法；对于给定的制备或步骤，所用的前体可不必得自根据给定描述中的步骤合成的个体批次。

[0776] 当将化合物描述为两种非对映异构体/差向异构体的混合物时，不具体指明立体中心的构型，并用直线表示。

[0777] 如本领域技术人员所理解的，利用所示策略合成的化合物可以作为溶剂合物例如水合物的形式存在和/或含有残留溶剂或少量杂质。作为盐形式分离的化合物可以是整数化学计量的即单盐或二盐或者是中间化学计量的。

[0778] 例如，取决于纯化方法中所用的酸，下文一些化合物作为盐分离。一些化合物作为游离碱分离。

[0779] 通常利用制备型手性HPLC(如通用方法中所述的)，将包含单一立体中心的化合物分离为单一异构体；在(或趋向)合成序列的最后阶段。在所述情况下，立体化学根据IUPAC，利用“虚的”或“实的”楔形线指定。除非另外说明，立体中心的直线表示化合物以两种异构体的混合物形式存在。

[0780] 通常通过制备型非手性和/或手性HPLC，将包含第二个立体中心的化合物拆分为单一异构体。

[0781] 可通过其旋光活性表征光学异构体(即作为+和-异构体或者作为d和l异构体)。根据Cahn、Ingold和Prelog制定的命名法，也可将立体中心指定为“R或S”，参见Jerry March著的Advanced Organic Chemistry，第4版，John Wiley&Sons，纽约，1992年，109-114页，并还参见Cahn、Ingold和Prelog，Angew.Chem.Int.Ed.Engl.，1966，5，385-415。

[0782] 可通过包括手性色谱(手性载体上的色谱)的多种技术拆分光学异构体，并且所述技术是本领域技术人员众所周知的。

[0783] 作为手性色谱的替代，可通过与手性酸例如(+)-酒石酸、(-)-焦谷氨酸、(-)-二-甲苯酰基-L-酒石酸、(+)-扁桃酸，(-)-苹果酸和(-)-樟脑磺酸形成非对映异构的盐，经优先结晶拆分非对映异构的盐，然后将盐解离，以得到游离碱的单一对映异构体，来分离碱性化合物的光学异构体。同样，可通过与手性胺例如马钱子碱、辛可尼丁、奎宁等形成非对映异构的盐，来分离酸性化合物的光学异构体。

[0784] 另外，可通过将对映体纯的手性助剂共价连接到化合物上，然后利用常规方法诸如色谱法完成非对映体拆分，来实现对映体的拆分。然后，将上述共价键裂解，以产生适当的对映体纯产物。示例可包括制备酸性化合物的薄荷醇酯。

[0785] 当式(I)化合物以两种或更多种光学异构体存在时，一对对映异构体中的一种对映异构体可以显示出优于另一对映异构体的优势，例如，就生物学活性而言。因此，在一些情况下，可能需要的是将一对对映异构体中的仅一种或多种非对映异构体的仅一种用作治疗剂。

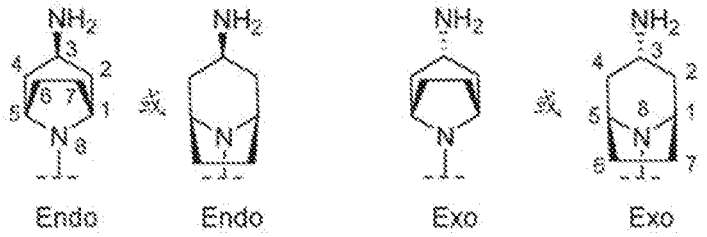
[0786] 因此，本发明提供包含具有一个或多个手性中心的式(I)化合物的组合物，其中至少55％(例如至少60％、65％、70％、75％、80％、85％、90％或95％)的式(I)化合物以单一光学异构体(例如对映异构体或非对映异构体)存在。在一通用实施方案中，式(I)化合物总量的99％或更多(例如基本全部)可作为单一光学异构体(例如对映异构体或非对映异构体)存在。

[0787] 包含双键的化合物在所述双键上可以具有E(反式)或Z(顺式)立体化学。二价环状或(部分)饱和基团上的取代基可以具有顺式(cis)-或反式(trans)-构型。当在文中使用时,术语顺式和反式是根据化学文摘(Chemical Abstracts)命名法(J.Org.Chem.1970,35(9),2849-2867),并且涉及环状基团上取代基的位置。

[0788] 特别关注的是立体化学纯的式(I)化合物。当将式(I)化合物例如指定为R时,这意指该化合物基本无S异构体。如果将式(I)化合物例如指定为E时,这意指该化合物基本无Z异构体。术语顺式、反式、R、S、E和Z是本领域技术人员众所周知的。

[0789] 术语exo和endo是指桥接的双环烷烃例如取代的莨菪烷(tropane)的立体化学,描述在PAC,1996,68,2193,立体化学的基本术语(IUPAC Recommendations 1996)中。如果取代基例如氨基基团朝向编号最高的桥,将其描述为exo;如果其朝向远离编号最高的桥,则将其描述为endo。当在相同碳原子上有两个取代基时,术语exo和endo涉及优先级更高的取代基。下图举例说明如何定义本专利中氨基莨菪烷的图形表示。

[0790] [化学式34]

[0791] 

[0792] 实施例

[0793] 将参考以下实施例中描述的具体实施方案说明但不是限制本发明。例如利用IUPAC规则,使用自动命名程序包例如AutoNom(MDL)或根据化学品供应商命名而将化合物进行命名。在实施例中,使用以下缩写。

[0794] [Math.1]

[0795] Ac 乙酰基

[0796] aq. 含水的

[0797] Boc 叔丁氧羰基

[0798] Boc_2O 二碳酸二叔丁酯

[0799] BuLi 丁基锂

[0800] t-BuOK 叔丁醇钾

[0801] t-BuONa 叔丁醇钠

[0802] Cbz 羧基苄基

[0803] DBU 1,8-二氮杂二环[5.4.0]十一-7-烯

[0804] DCM 二氯甲烷

[0805] DIAD 偶氮二甲酸二异丙酯

[0806] DIBAL-H 二异丁基氢化铝

[0807] DIPEA N,N-二异丙基乙胺

[0808] DMA N,N-二甲基乙酰胺

[0809] DME 1,2-二甲氧基乙烷

[0810] DMEAD 偶氮二甲酸二-2-甲氧基乙酯

[0811] DMF N,N-二甲基甲酰胺

[0812] DMSO 二甲基亚砜

[0813] Et_2O 乙醚

[0814] EtOAc 乙酸乙酯

[0815] EtOH 乙醇

[0816] h 小时

[0817] HATU O-(7-氮杂苯并三唑-1-基)-N,N,N′,N′-四甲基脲鎓六氟磷酸盐

[0818] HPLC 高效液相色谱

[0819] IPA 异丙醇

[0820] LDA 二异丙基氨基锂

[0821] i-PrMgCl 异丙基氯化镁

[0822] MeCN 乙腈

[0823] [Math.2]

[0824] MeOH 甲醇

[0825] min. 分钟

[0826] MS 质谱

[0827] MTBE 叔丁基甲基醚

[0828] NaOMe 甲醇钠

[0829] NBS N-溴代琥珀酰亚胺

[0830] NCS N-氯代琥珀酰亚胺

[0831] NMP N-甲基-2-吡咯烷酮

[0832] NMR 核磁共振波谱

[0833] PMB p-甲氧基苄基

[0834] PyBOP (苯并三唑-1-基氧基)三吡咯烷子基鏻六氟磷酸盐

[0835] RT 室温

[0836] Sat. 饱和的

[0837] SEM (2-(三甲基硅烷基)乙氧基)甲基

[0838] SEMCl 2-(三甲基硅烷基)乙氧基甲基氯

[0839] TBAF 氟化四丁铵

[0840] TBSCl 叔丁基二甲基氯硅烷

[0841] TEA 三乙胺

[0842] TBME 叔丁基甲基醚

[0843] TFA 三氟乙酸

[0844] THF 四氢呋喃

[0845] TLC 薄层色谱

[0846] TsCl p-甲苯磺酰氯

[0847] Z-chloride 氯甲酸苄酯

[0848] 合成方法

[0849] 所有起始原料和溶剂均可从商业渠道获得或根据文献引证进行制备。除非另外说

明，搅拌所有反应。将有机溶液常规地用无水硫酸镁干燥。在所述条件下或在氢气气球下，在Parr氢化器、Thales H-cube流动反应器中完成氢化。微波反应用Biotage(注册商标)Initiator、CEM Discover和Smithcreator微波反应器，利用可变功率微波辐射加热至恒定温度而完成。正相柱色谱常规地在自动快速色谱系统例如CombiFlash Companion或CombiFlash RF系统上使用预装硅胶(230-400目，40-63μm)柱完成。SCX购自Supelco，并在使用前用1M盐酸处理。除非另外说明，首先用MeOH稀释要纯化的反应混合物，并用几滴AcOH使其呈酸性。将该溶液直接进样到SCX上，并用MeOH洗涤。然后通过用溶剂例如含1％NH_3的MeOH洗涤而洗脱所需的物质。使用Strata NH_2(55μm，70 Å)柱，进行NH_2离子交换硅胶纯化，将所述柱直接加载到NH_2柱上，并用溶剂例如甲醇洗脱。Biotage(注册商标)SNAP Ultra硅胶柱和Biotage(注册商标)KP-NH SNAP硅胶柱购自Biotage(注册商标)。使用Biotage(注册商标)SNAP Ultra C18硅胶柱进行反相纯化，并从Biotage(注册商标)购买。

[0850] NMR数据

[0851] ^1H NMR谱在400MHz Bruker Avance III波谱仪、AL400(400MHz；JEOL生产的)、Mercury 400(400MHz；Agilent Technologies，Inc.生产的)、500MHz Bruker Avance III HD NMR波谱仪或Bruker Avance NEO NMR波谱仪(400MHz)上获得。可以将氯仿-d、二甲基亚砜-d_6的中心峰或内标四甲基硅烷作为参照。对于NMR数据，当归属的质子数小于分子中的理论质子数时，推测溶剂和/或水峰掩盖了明显缺失的信号。另外，当在质子NMR溶剂中获得波谱时，发生NH和/或OH质子与溶剂的交换，因此通常未观察到此类信号。

[0852] 分析型和制备型LC-MS系统

[0853] 分析型LC-MS系统和方法描述

[0854] 在下述实施例中，使用下文列出的系统和操作条件，通过质谱对化合物进行表征。当存在含有不同同位素的原子且报告单一质量时，该化合物报告的质量为单同位素质量(即^{35}Cl；^{79}Br等)。

[0855] [Math.3]

[0856] Shimadzu Nexera

[0857] HPLC系统：Shimadzu SIL-30AC自动进样器/2x Shimadzu LC-30AD泵

[0858] 质谱检测器 Shimadzu LCMS-2020单四极杆MS

[0859] 第二检测器： Shimadzu SPD-M20A二极管阵列检测器

[0860] MS运行条件

[0861]

Qarray DC 电压:	20V on ES Pos (-20V on ES Neg)
干燥气流:	20.0 L/min
DL 温度:	300 °C
Heat Block 温度:	350°
Nebulising 气流:	1.5 L/min
扫描范围:	100-750amu
离子化模式:	电喷雾正-负转换

[0862] [Math.4]

[0863] Agilent 1290Infinity II-6130LC-MS系统

[0864] HPLC系统： Agilent 1290Infinity II

[0865] 质谱检测器： Agilent 6130单四极杆

[0866] 第二检测器： Agilent 1290Infinity II二极管阵列检测器

[0867] MS运行条件：

毛细管电压:	3000V
Fragmentor/Gain:	70
Gain:	1

[0868]

干燥气流:	13.0 L/min
气体温度:	350°C
雾化器压力:	40 psig
扫描范围:	150-1000 amu
鞘(sheath)气温度:	360 °C
鞘气流:	10.0 L/min

[0869]

喷嘴电压:	300 (+ve 模式) /1750 (-ve 模式)
离子化模式:	Agilent Jet Stream 电喷雾正-负转换

[0870] 或者，用Waters Corporation生产的SQD在下述两个条件下测量LCMS谱，并显示$[M+H]^+$值。

[0871] [Math.5]

[0872] MS检测:ESI正

[0873] UV检测:254nm

[0874] 柱体流速:0.5mL/min

[0875] 流动相:水/乙腈(0.1%甲酸)

[0876] 进样体积:1μL

[0877] 方法

[0878] 柱子:Acguity BEH,2.1×50mm,1.7μm

[0879] 梯度：

[0880]

时间(min)	水/乙腈 (0.1%甲酸)
0	95/5
0.1	95/5
2.1	95/5
3.0	停止

[0881] 制备型LC-MS系统和方法描述

[0882] 制备型LC-MS是用于纯化有机小分子例如文中所述化合物的标准有效方法。可以改变液相色谱法(LC)和质谱法(MS)的方法,以提供粗物质更好的分离和通过MS的改进的样品检测。制备梯度LC方法的优化将涉及改变色谱柱、挥发性洗脱液和改性剂、以及梯度。用于优化制备型LC-MS方法,然后将其用于纯化化合物的方法是本领域众所周知的。所述方法描述于Rosentreter U,Huber U.;Optimal fraction collecting in preparative LC-MS;J Comb Chem.;2004;6(2),159-64和Leister W,Strauss K,Wisnoski D,Zhao Z,Lindsley C.,Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries,J Comb Chem.,2003,5(3),322-9中。

[0883] 下文描述了通过制备型LC-MS纯化化合物的几种系统,但是本领域技术人员会理解,能使用所述系统和方法的替代系统和方法。从本文提供的信息或采用替代色谱系统,本领域技术人员可以通过制备型LC-MS纯化本文所述的化合物。

[0884] 质量导向的LC-MS纯化系统

[0885] 制备型LC-MS是用于纯化有机小分子例如本文所述化合物的标准有效方法。可以改变液相色谱法(LC)和质谱法(MS)的方法,以提供粗物质的更好分离和通过MS改进对样品的检测。制备梯度LC方法的优化将涉及改变色谱柱、挥发性洗脱液和改性剂,以及梯度。用于优化制备型LC-MS方法,然后将其用于纯化化合物的方法是本领域众所周知的。所述方法描述于Rosentreter U,Huber U.;Optimal fraction collecting in preparative LC-MS;J Comb Chem.;2004;6(2),159-64和Leister W,Strauss K,Wisnoski D,Zhao Z,Lindsley C.,Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries,J Comb Chem.,2003,5(3),322-9中。

[0886] 下文描述一种用于通过制备型LC-MS纯化化合物的系统,但是本领域技术人员应该理解,可以使用所述的系统和方法的替代系统和方法。具体地讲,可以将基于正相制备型LC的方法用于代替此处所述的反相方法。大多数制备型LC-MS系统使用反相LC和挥发性酸性改性剂,因为该方法对于小分子的纯化非常有效,并且因为洗脱液与正离子电喷雾质谱是兼容的。可将利用其他色谱解决方案,例如上文所述分析方法中概述的正相LC、备选的缓冲流动相、碱性改性剂等替代地用于纯化化合物。

[0887] [Math.6]

[0888] Agilent 1260LC-MS制备系统

[0889] 硬件:

[0890] 自动进样器:G2260A Prep ALS

[0891] 泵:2x G1361A Prep Pumps,用于制备流梯度;G1311C Quat Pump VL,用于泵出制备流中的改性剂;和G1310B Iso Pump,用于补充泵流

[0892] UV检测器:G1365C 1260MWD

[0893] MS检测器:G6120B Quadrupole LC-MS

[0894] 级分收集器:2x G1364B 1260FC-PS

[0895] G1968D Active Splitter

[0896] 软件:

[0897] Agilent OpenLab C01.06

[0898] Agilent MS运行条件：

毛细管电压:	3000V
Fragmentor/Gain:	70/1
干燥气流:	12.0 L/min
[0899] 干燥气体温度:	275 °C
雾化器压力:	40 psig
汽化器温度:	200 °C
扫描范围:	125-800 amu
离子化模式	电喷雾正

[0900] [Math.7]

[0901] 柱子：

[0902] 1.Waters XBridge Prep C18 5m OBD 100x19mm

[0903] 通常用于基于碳酸氢铵的方法

[0904] 2.Waters SunFire Prep C18OBD 5m 100x19mm

[0905] 通常用于基于-TFA的方法

[0906] 3.Waters XBridge Prep Phenyl 5m OBD 100x19mm

[0907] 通常用于基于中性pH乙酸铵的方法

[0908] 4.Supelco Ascentis RP-Amide 5m 100x21.2mm

[0909] 通常用于基于甲酸的方法

[0910] 5.Phenomenex Synergi Fusion-RP 4m 100x21.2mm

[0911] 通常用于基于甲酸的方法

[0912] 洗脱剂：

[0913] 溶剂A:水

[0914] 溶剂B:乙腈

[0915] 溶剂C:可用的改性剂的选择：

[0916] 2.5%三氟乙酸水溶液；

[0917] 2.5%甲酸水溶液；

[0918] 250mM碳酸氢铵水溶液,pH 9.4；

[0919] 250mM乙酸铵

[0920] 补充(make up)溶剂：

[0921] 90:10甲醇:水+0.2%甲酸(用于所有色谱类型)

[0922] 方法：

[0923] 根据微量分析,选择最合适的制备色谱类型。典型的惯例是利用最适合化合物结构的色谱类型(低或高pH),运行分析型LC-MS。一旦微量分析显示出良好的色谱,就选择适当的相同类型的制备方法。低pH和高pH色谱方法的典型运行条件为：

[0924] 流速:25mL/min

[0925] 梯度:通常所有梯度具有用95%A+5%B(含有另外的改性剂C)的起始0.4分钟的步骤。然后,根据微量分析,选择6.6分钟的梯度,以实现良好的分离(例如对于早先的保留化合物,5%-50%的B;对于中间的保留化合物,35%-80%的B等)。

[0926] 清洗:在梯度结束时,完成1.6分钟的清洗步骤

[0927] 补充流速:0.8mL/min

[0928] 溶剂:

[0929] 通常将所有化合物溶于100%MeOH或100%DMSO中。

[0930] 根据提供的信息,本领域技术人员可以通过制备型LC-MS纯化本文所述的化合物。

[0931] [Math.8]

[0932] Waters Fractionlynx系统

[0933] 硬件:

[0934] 2767双定量环自动进样器/级分收集器

[0935] 2525制备型泵

[0936] CFO(column fluidic organiser),用于柱子选择;

[0937] RMA(Waters reagent manager),作为补充泵;

[0938] Waters ZQ质谱仪

[0939] Waters 2996Photo二极阵列检测器

[0940] Waters ZQ质谱仪

[0941] 软件:

[0942] Masslynx 4.1

[0943] Waters MS运行条件

[0944]

毛细管电压:	3.5 kV (3.2 kV on ES Negative)
锥电压:	25 V
源温度:	120℃
倍增器:	500 V
扫描范围:	125-800 amu
离子化模式:	电喷雾正或电喷雾负

[0945] 或者,在下述条件下完成反相制备型HPLC柱色谱。

[0946] [Math.9]

[0947]

柱子:	SHISEIDO 生产的 CAPCELL PAK C18 AQ, 30x50 mm, 5 μm
UV 检测:	254 nm
柱流速:	40 mL/min
流动相:	水/乙腈 (0.1%甲酸)
进样体积:	1.0 mL
基础梯度方法:	水/乙腈 0%-50% (8 分钟)

[0948] 非手性制备色谱

[0949] 利用根据Snyder L.R.,Dolan J.W.,High-Performance Gradient Elution The

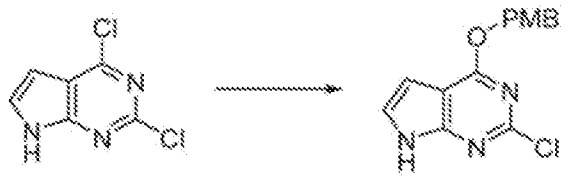
Practical Application of the Linear-Solvent-Strength Model,Wiley,Hoboken,2007年中所述的推荐建立的方法,将所述的化合物实例进行了HPLC纯化。

[0950] 手性制备色谱

[0951] 使用手性固定相(CSPs)的制备分离是用于拆分对映体混合物的天然技术。同样,它可以用于非对映异构体和非手性分子的分离。用于优化CSPs制备型手性分离,然后将其用于纯化化合物的方法是本领域众所周知的。所述方法描述于Beesley T.E.,Scott R.P.W.;Chiral Chromatography;Wiley,奇切斯特,1998年中。

[0952] 制备1:2-氯-4-((4-甲氧基苄基)氧基)-7H-吡咯并[2,3-d]嘧啶

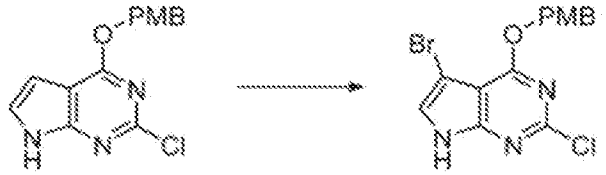
[0953] [化学式35]

[0954] 

[0955] 在RT下,向2,4-二氯-7H-吡咯并[2,3-d]嘧啶(2.5g,13.3mmol)和4-甲氧基苄醇(1.99mL,16.0mmol)的1,4-二氧六环(37.5mL)溶液中,加入叔丁醇钾(5.97g,53.2mmol)。将混合物在RT下搅拌1h。在RT下加入饱和NH_4Cl。收集沉淀物,用水和EtOAc清洗,并在50℃下减压干燥过夜,以得到标题化合物(3.14g)。MS:$[M+H]^+$=290,292.

[0956] 制备2:5-溴-2-氯-4-((4-甲氧基苄基)氧基)-7H-吡咯并[2,3-d]嘧啶

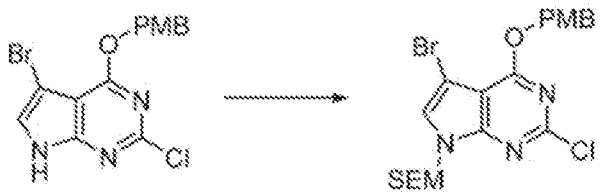
[0957] [化学式36]

[0958] 

[0959] 在-20℃下,向2-氯-4-((4-甲氧基苄基)氧基)-7H-吡咯并[2,3-d]嘧啶(3.14g,10.8mmol)的DMF(31.4mL)溶液中,加入NBS(2.12g,11.9mmol)。将混合物在-20℃下搅拌30min。加入饱和硫代硫酸钠(30mL)和EtOAc(15mL)。将混合物在RT下搅拌30min。收集沉淀,用水洗涤,并在50℃下减压干燥过夜,以得到标题化合物(3.78g)。MS:$[M+H]^+$=368,370.

[0960] 制备3:5-溴-2-氯-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶

[0961] [化学式37]

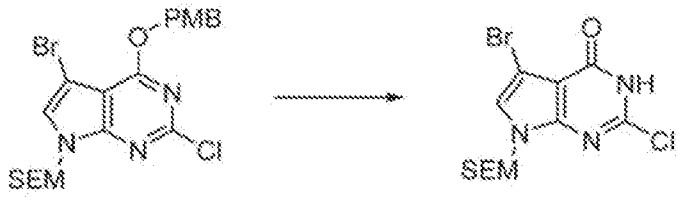
[0962] 

[0963] 在0℃下,向5-溴-2-氯-4-((4-甲氧基苄基)氧基)-7H-吡咯并[2,3-d]嘧啶(2.0g,5.43mmol)的DMF(40mL)溶液中,加入氢化钠(60%,在矿物油中,0.26g,6.51mmol)和SEMCl(1.14mL,6.51mmol)。将混合物在0℃下搅拌1h。加入饱和NH_4Cl,并将混合物用EtOAc萃取。有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残余物通过硅胶柱色谱纯

化(梯度洗脱,20-60%EtOAc/己烷),得到标题化合物(2.68g)。MS:$[M+H]^+$=498,500.

[0964] 制备4:5-溴-2-氯-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[0965] [化学式38]

[0966] 

[0967] 在RT下,向5-溴-2-氯-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶(1.6g,3.21mmol)的DCM(30.4mL)溶液中,加入2,3-二氯-5,6-二氰基-p-苯醌(2.18g,9.62mmol)和水(1.6mL)。将混合物在RT下搅拌3天。在RT下加入$CHCl_3$和sat.$NaHCO_3$。将混合物经硅藻土过滤,并用$CHCl_3$和水洗涤。滤液用$CHCl_3$萃取,无水Na_2SO_4干燥,过滤并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-60%EtOAc/己烷),得到标题化合物(0.746g)。MS:$[M+H]^+$=378,380.

[0968] 制备5:5-溴-2-氯-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

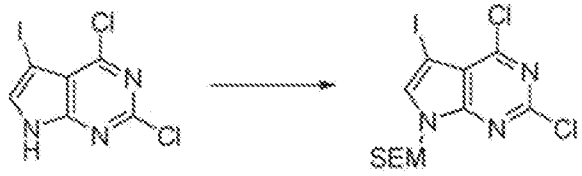
[0969] [化学式39]

[0970] 

[0971] 在RT下,向5-溴-2-氯-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(0.746g,1.97mmol)的DMF(7.46mL)溶液中,加入K_2CO_3(0.544g,3.94mmol)和碘甲烷(0.245mL,3.94mmol)。将混合物在RT下搅拌30min,倒入水中,并用EtOAc萃取。将有机层用水和盐水洗涤,无水Na_2SO_4干燥,过滤,并真空浓缩。残留物通过硅胶柱色谱纯化(梯度洗脱,0-60%EtOAc/己烷),得到标题化合物(0.7g)。MS:$[M+H]^+$=392,394.

[0972] 制备6:2,4-二氯-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶

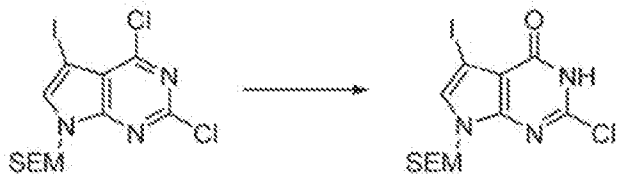
[0973] [化学式40]

[0974] 

[0975] 在RT下,向2,4-二氯-5-碘-7H-吡咯并[2,3-d]嘧啶(1g,3.18mmol)和DIPEA(1.66mL,9.55mmol)混合物的THF(10mL)溶液中,加入SEMCl(1.13mL,6.37mmol)。将混合物在RT下搅拌2h,并真空浓缩。将残余物经硅胶柱色谱纯化(梯度洗脱,0-30%EtOAc/己烷),得到标题化合物(1.5g)。MS:$[M+H]^+$=444,446.

[0976] 制备7:2-氯-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[0977] [化学式41]

[0978] 

[0979] 在RT下,向2,4-二氯-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶(0.3g,0.67mmol)混合物的1,4-二氧六环(4mL)溶液中,加入4M KOH(1mL,4mmol)。将混合物在60℃搅拌过夜,冷却至RT,用aq.HCl酸化,并用EtOAc萃取。将有机层用盐水洗涤,无水Na_2SO_4干燥,过滤,并真空浓缩。残留物通过硅胶柱色谱纯化(梯度洗脱,0-70%EtOAc/己烷),得到标题化合物(0.17g)。MS:$[M+H]^+$=426,428.

[0980] 制备8:2-氯-5-碘-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3d]嘧啶-4-酮

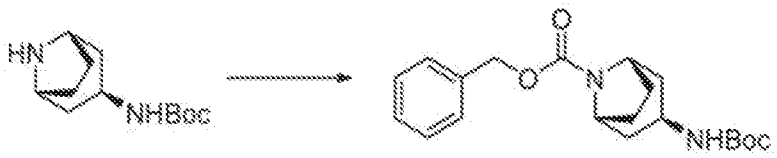
[0981] [化学式42]

[0982] 

[0983] 在RT下,向2-氯-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(0.17g,0.40mmol)和K_2CO_3(0.11g,0.79mmol)混合物的NMP(1mL)溶液中,加入碘甲烷(0.05mL,0.79mmol)。将混合物在RT下搅拌3h,用EtOAc稀释,用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残余物经硅胶柱色谱法纯化(梯度洗脱,0-50%EtOAc/己烷),得到标题化合物(0.15g)。MS:$[M+H]^+$=440,442.

[0984] 制备9:[endo-3-(叔丁氧羰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯

[0985] [化学式43]

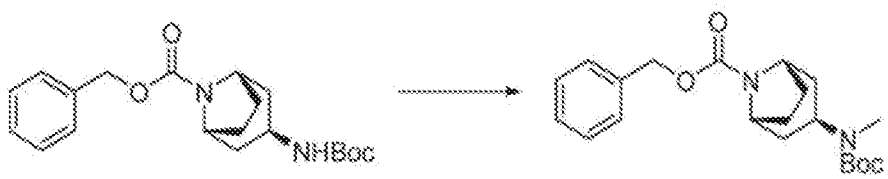
[0986] 

[0987] 在0℃下,于冰浴中,向(endo-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯(1.0g,4.4mmol)和TEA(1.2当量,5.3mmol)的THF(5.0mL)和DCM(3.0mL)混悬液中,加入Z-chloride(0.69mL,4.9mmol)。除去冰浴,并将混合物在RT下搅拌1h。在RT下,将Z-chloride(0.13mL,0.88mmol)加入到混合物中,并将混合物在RT下再搅拌3h。向混合物中加入稀HCl水溶液和EtOAc,并将混合物用EtOAc(X3)萃取。将有机萃取物用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残余物(浅黄色油状物,1.7g)经硅胶柱色谱纯化(梯度洗脱,0-8%MeOH/$CHCl_3$),得到标题化合物(1.4g,4.0mmol,91%产率),作为无色固体。MS:$[M+H]^+$=361.

[0988] 制备10:[endo-3-(叔丁氧羰基)(甲基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄

酯

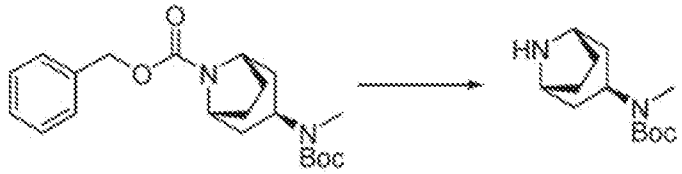
[0989] [化学式44]

[0990] 

[0991] 在0℃下,向[endo-3-(叔丁氧羰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(1.4g,4.0mmol)的DMF(5.0mL)溶液中,加入氢化钠(60%,在矿物油中,0.24g,5.99mmol),并将混合物在0℃下搅拌40min。在0℃下将碘甲烷(0.50mL,7.99mmol)加入到混合物中,并在5min内除去冰浴。在RT下搅拌30分钟后,将氢化钠(60%,在矿物油中,32mg,0.799mmol)和碘甲烷(0.12mL,2.00mmol)加入到混合物中,并将混合物在RT下再搅拌30min。向混合物中加入稀柠檬酸水溶液和EtOAc,并将混合物用EtOAc萃取。将有机萃取物用水和盐水洗涤,并经Na_2SO_4干燥。浓缩滤液,得到粗产物(黄色油状物,1.7g),将其经硅胶柱色谱法纯化(梯度洗脱,0-70%EtOAc/己烷),得到标题化合物(879mg,2.3mmol,产率58%),作为无色油状物。MS:$[M+H]^+$=375.

[0992] 制备11:(endo-8-氮杂二环[3.2.1]辛烷-3-基)(甲基)氨基甲酸叔丁酯

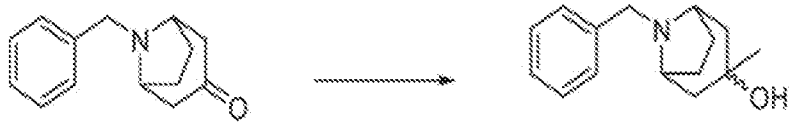
[0993] [化学式45]

[0994] 

[0995] 将[endo-3-(叔丁氧羰基)(甲基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(875mg,2.3mmol)和10%Pd-C(M)Wet(500mg)悬浮于MeOH(5.0mL)中,并将混合物用H_2取代。将混合物在RT下搅拌3h。将反应混合物施加到硅藻土垫上,并将滤液浓缩。将残余物溶解在MeOH中,并再次施加至硅藻土垫上,并将滤液浓缩,得到标题化合物(556mg,2.3mmol,产率99%),作为浅黄色油-固体。MS:$[M+H]^+$=241.

[0996] 制备12:8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-醇

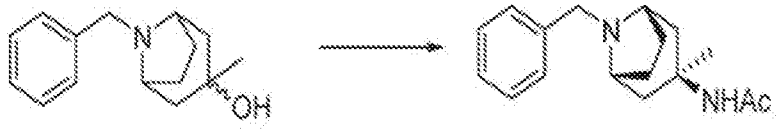
[0997] [化学式46]

[0998] 

[0999] 在MeCN-干冰浴中,向8-苄基-8-氮杂二环[3.2.1]辛烷-3-酮(4.28g,19.9mmol)的THF(47.0mL)溶液中,加入甲基氯化镁的THF溶液(29.4mL,88.4mmol),并将反应物在所述温度下搅拌30min,然后在RT下搅拌20h。在0℃下加入Sat.NH_4Cl溶液,并将混合物用EtOAc萃取。将合并的有机层用水和饱和氯化钠溶液洗涤,并用无水硫酸钠干燥。滤除干燥剂后,减压除去溶剂。残留物经硅胶柱色谱纯化(NH硅胶,梯度洗脱,20-50%$CHCl_3$/己烷),得到标题化合物(4.50g)。MS:$[M+H]^+$=232.

[1000] 制备13:N-(endo-8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)乙酰胺

[1001] [化学式47]

[1002] 

[1003] 在0℃下，向8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-醇(4.28g，18.48mmol)的乙腈(26mL)溶液中，历经15min滴加浓硫酸(18mL)，并在RT下搅拌18h。将反应混合物倒入冰(ca.200g)中，并用5mol/L氢氧化钠溶液(ca.100mL)碱化(ca pH 10)。将反应混合物用EtOAc萃取。将合并的有机层用水和饱和氯化钠溶液洗涤，并经无水硫酸钠干燥。滤除干燥剂后，减压除去溶剂。将残余物用乙醚和石油醚洗涤，得到标题化合物(2.45g)。MS：$[M+H]^+$=273.

[1004] 制备14：N-(endo-8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯

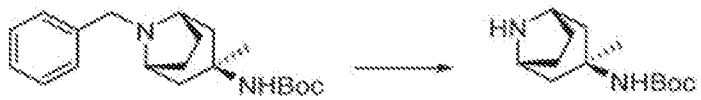
[1005] [化学式48]

[1006] 

[1007] 向N-(endo-8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)乙酰胺中，加入6mol/L盐酸(80mL)，并将混合物在140℃下搅拌11天。在0℃下，将反应混合物用4mol/L氢氧化钠溶液碱化，并加入1,4-二氧六环(20mL)和二碳酸二叔丁酯(3.93g，18.0mmol)。将反应物在0℃下搅拌1h，并在RT下搅拌18h。将反应混合物用EtOAc萃取。将合并的有机层用水和饱和氯化钠溶液洗涤，并经无水硫酸钠干燥。滤除干燥剂后，减压除去溶剂。将残余物经硅胶柱色谱法纯化(梯度洗脱，0-10％MeOH/DCM)，得到标题化合物(3.05g)。MS：$[M+H]^+$=331.

[1008] 制备15：N-(endo-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯

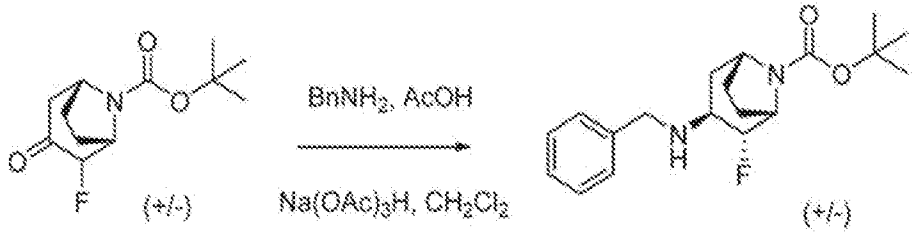
[1009] [化学式49]

[1010] 

[1011] 将$Pd(OH)_2/C$(10wt％Pd，637mg，0.454mmol)加入到N-(endo-8-苄基-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯(3.0g，9.08mmol)的MeOH(20mL)溶液中，并将反应物在环境压力和RT下氢化24h。将反应物经硅藻土过滤，并蒸发滤液。将残留物用乙醚研磨，得到标题化合物(1.86g)。MS：$[M+H]^+$=241.

[1012] 制备16：rac-(1S,2R,3S,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

[1013] [化学式50]

[1014] 

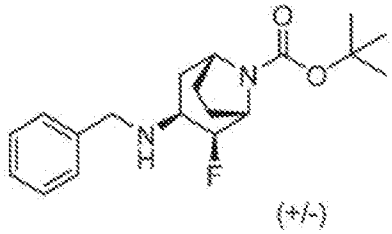
[1015] 将三乙酰氧基硼氢化钠(41g，193mmol)分批加入到(±)-2-氟-3-氧代-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(34.8g，129mmol)、乙酸(11.0ml，192mmol)和苄胺(20ml，

183mmol)的二氯甲烷(500mL)溶液中,然后在室温下搅拌过夜。将混合物用10%碳酸氢钠(500mL)稀释,然后用二氯甲烷(3x500mL)萃取。将合并的有机相干燥($MgSO_4$),过滤并减压浓缩。将粗物质从乙酸乙酯:异己烷(800mL,1:3)中重结晶,得到标题化合物(11.6g)。^1H NMR(500MHz,DMSO-d_6)δ:7.39-7.27(m,4H),7.27-7.19(m,1H),4.51(br d,1H),4.38-4.21(m,1H),4.13-4.04(m,1H),3.83-3.65(m,2H),2.80(dd,1H),2.48-2.33(m,1H),2.09(s,1H),2.03-1.88(m,2H),1.86-1.69(m,2H),1.56(d,1H),1.37(s,9H).

[1016] 将滤液减压浓缩,然后经硅胶柱色谱法纯化(梯度洗脱,0-50%EtOAc/异己烷),得到下述化合物:

[1017] 制备17:rac-(1S,2S,3S,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

[1018] [化学式51]

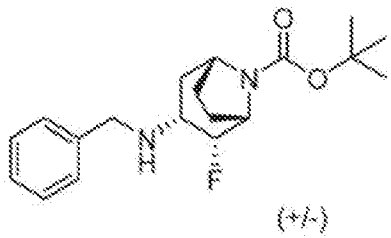
[1019] 

(+/-)

[1020] 得到标题化合物(3.8g)。^1H NMR(500MHz,DMSO-d_6)δ:7.42-7.28(m,4H),7.29-7.18(m,1H),4.68(dt,1H),4.16-4.04(m,1H),4.05-3.94(m,1H),3.82(dd,1H),3.63(dd,1H),3.29-3.20(m,1H),2.44-2.31(m,1H),2.21-2.04(m,2H),1.97-1.87(m,1H),1.89-1.61(m,3H),1.39(s,9H).

[1021] 制备18:rac-(1S,2R,3R,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

[1022] [化学式52]

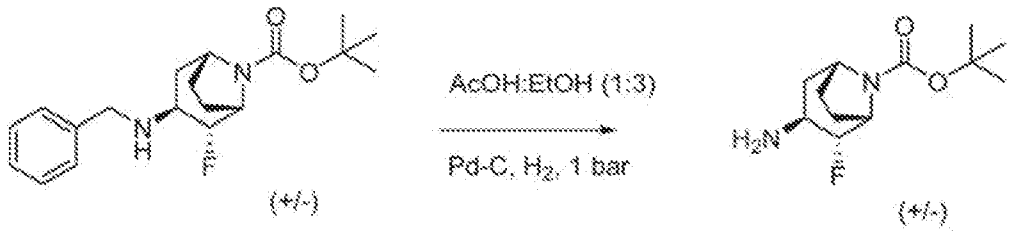
[1023] 

(+/-)

[1024] 得到14g无色油状物,将其经硅胶柱色谱纯化(梯度洗脱,0-50%EtOAc/异己烷),得到标题化合物(11.9g)。^1H NMR(500MHz,DMSO-d_6)δ:7.38-7.26(m,4H),7.26-7.15(m,1H),4.66(dt,1H),4.48-4.24(m,1H),4.19-4.06(m,1H),3.77(d,1H),3.72(d,1H),2.96-2.72(m,1H),1.95-1.64(m,4H),1.61-1.43(m,3H),1.38(s,9H).

[1025] 制备19:rac-(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

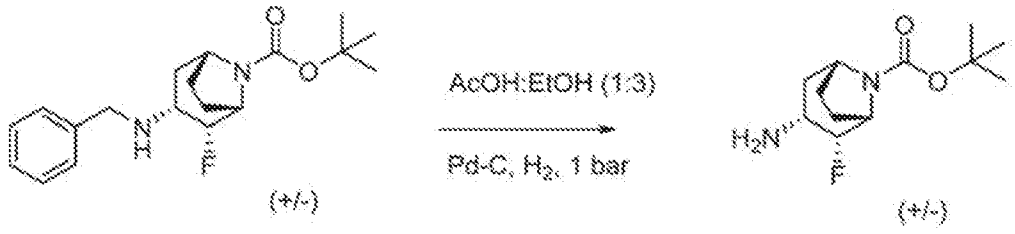
[1026] [化学式53]

[1027] 

[1028] 将rac-(1S,2R,3S,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(18.5g,55.3mmol)和10%钯碳(JM Type 39,57.3%湿度)(4.0g,1.605mmol)溶解于乙酸/乙醇(1:3,200mL)中,并在1bar氢气下搅拌2h。通过过滤除去催化剂,并将滤液减压浓缩。将残余物用碳酸氢钠浆液(10g,100mL)处理,然后用氯仿/IPA(9:1,3x100mL)萃取。将合并的有机相减压浓缩,得到标题化合物(13.5g)。^{1}H NMR(500MHz,DMSO-d_6)δ:4.39-4.15(m,2H),4.07(m,1H),3.11(dd,1H),2.12-1.88(m,4H),1.83-1.65(m,4H),1.37(s,9H).

[1029] 制备20:rac-(1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

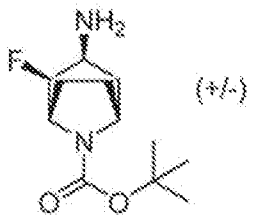
[1030] [化学式54]

[1031] 

[1032] 用与rac-(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯类似的方式,利用rac-(1S,2R,3R,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(11g,32.9mmol),制备标题化合物,得到标题化合物(8.25g)。^{1}H NMR(500MHz,DMSO-d_6)δ:4.37(dt,2H),4.38-4.33(m,1H),4.16-4.09(m,1H),2.95(dddd,1H),1.88-1.76(m,3H),1.66-1.46(m,4H),1.41(d,J=0.5Hz,9H).

[1033] 制备21:rac-(1S,2S,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

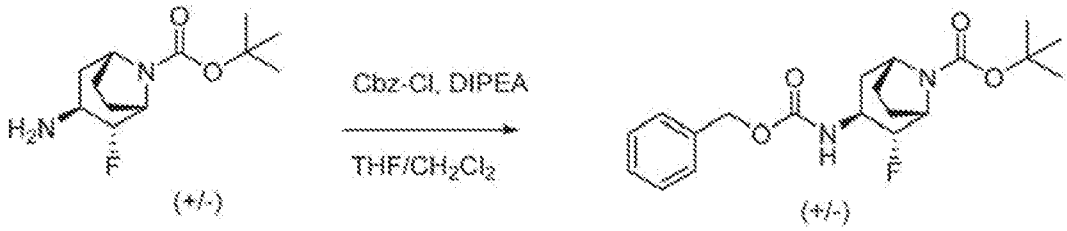
[1034] [化学式55]

[1035] 

[1036] 用与rac-(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯类似的方式,利用rac-(1S,2S,3S,5R)-3-(苄基氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(6.0g,17.0mmol),制备标题化合物,得到标题化合物(4.0g)。^{1}H NMR(500MHz,DMSO-d_6)δ:4.53(dt,1H),4.13-4.03(m,1H),4.03-3.91(m,1H),3.64-3.53(m,1H),2.50-2.40(m,1H),2.22-2.05(m,1H),1.97-1.49(m,6H),1.39(d,9H).

[1037] 制备22:rac-(1S,2R,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

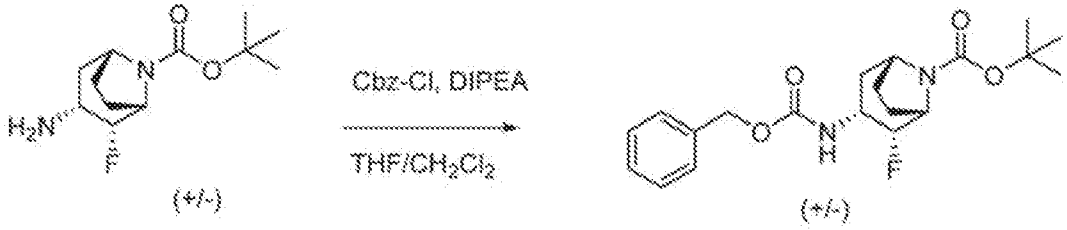
[1038] [化学式56]

[1039] 

[1040] 将氯甲酸苄酯(10mL,70.0mmol)加入到rac-(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(13.5g,52.5mmol)和DIPEA(27mL,155mmol)的THF/DCM(375mL:1:4)冷却(0℃)溶液中,然后在室温搅拌过夜。加入水(400mL),然后将混合物用二氯甲烷(3x400mL)萃取,并将合并的有机相减压浓缩。将粗产物经硅胶色谱(0-30%EtOAc/异己烷)纯化。将纯化的油再经硅胶柱色谱纯化(梯度洗脱,0-10%EtOAc/DCM),得到标题化合物(19.5g)。^{1}H NMR(500MHz,DMSO-d_6)δ:7.46-7.39(m,1H),7.39-7.34(m,4H),7.34-7.29(m,1H),5.07(d,1H),5.02(d,1H),4.51(br d,1H),4.38-4.20(m,1H),4.16-4.06(m,1H),3.64-3.49(m,1H),2.23-2.11(m,1H),1.94-1.79(m,2H),1.78-1.66(m,2H),1.49-1.43(m,1H),1.38(s,9H).

[1041] 制备23:rac-(1S,2R,3R,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

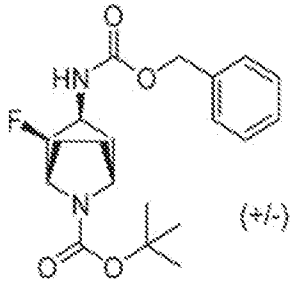
[1042] [化学式57]

[1043] 

[1044] 与rac-(1S,2R,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯类似的方式,利用rac-(1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(8.25g,32.1mmol),制备标题化合物,得到标题化合物(10.9g)。^{1}H NMR(500MHz,DMSO-d_6)δ:7.46-7.26(m,6H),5.11-4.94(m,2H),4.54(dt,1H),4.43-4.26(m,1H),4.20-4.06(m,1H),3.92-3.72(m,1H),1.99-1.69(m,3H),1.70-1.48(m,3H),1.38(s,9H).

[1045] 制备24:rac-(1S,2S,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯

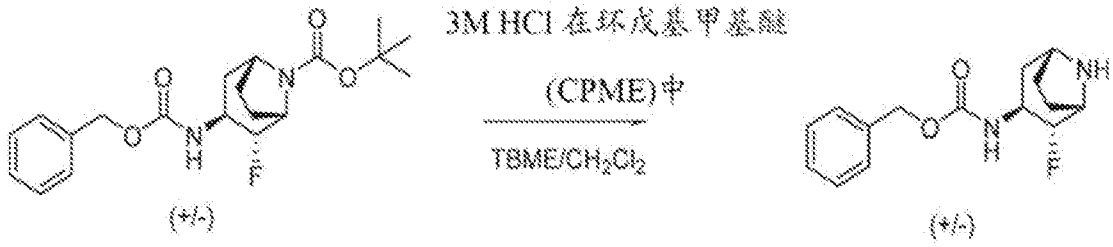
[1046] [化学式58]

[1047] 

[1048] 与rac-(1S,2R,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯类似的方式,利用rac-(1S,2S,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(4.0g,15.5mmol),制备标题化合物,得到标题化合物(5.45g)。^{1}H NMR(500MHz,DMSO-d_6)δ:7.41-7.35(m,4H),7.35-7.28(m,1H),7.14-6.93(m,1H),5.23-4.89(m,2H),4.85-4.65(m,1H),4.22-4.07(m,2H),4.07-3.97(m,1H),2.29-2.17(m,1H),2.08-2.02(m,1H),1.99-1.79(m,2H),1.80-1.64(m,2H),1.40(s,9H).

[1049] 制备25:rac-N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯

[1050] [化学式59]

[1051] 

[1052] 将3.0M氯化氢的环戊基甲基醚溶液(130mL,390mmol)加入到rac-(1S,2R,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(14.5g,36.4mmol)的叔丁基甲基醚(15mL)溶液中,然后在室温下搅拌18h。将混合物减压浓缩,然后在二氯甲烷(200mL)和饱和碳酸氢钠溶液(200mL)之间分配。将有机层减压浓缩,然后经硅胶柱色谱(梯度洗脱,0-10%(0.7M氨/MeOH)/DCM)纯化,得到标题化合物(6.0g)。^{1}H NMR(500MHz,DMSO-d_6)δ:7.41-7.28(m,5H),7.28-7.20(m,1H),5.10-4.97(m,2H),4.29(ddd,1H),3.69-3.51(m,1H),3.41(dd,1H),3.37-3.29(m,1H),2.30-2.09(m,1H),2.10-1.97(m,1H),1.77-1.63(m,2H),1.64-1.47(m,2H),1.30-1.14(m,1H).

[1053] 制备26:rac-N-[(1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐

[1054] [化学式60]

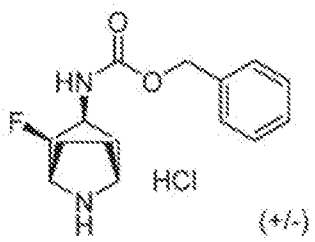
[1055] 

[1056] 将3.0M氯化氢的环戊基甲基醚溶液(100mL,300mmol)加入到(±)-(1S,2S,3R,5R)-3-(((苄基氧基)羰基)氨基)-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(10.9g,27.4mmol)的叔丁基甲基醚(15mL)和二氯甲烷(10mL)混悬液中,然后在室温下搅拌18h。经过滤收集产生的沉淀,得到标题化合物(8.8g)。^{1}H NMR(500MHz,DMSO-d_6)δ:10.28-9.22(m,1H),9.22-8.29(m,1H),7.74-7.59(m,1H),7.42-7.35(m,4H),7.35-7.29(m,1H),5.07(d,1H),5.04(d,1H),4.83(dt,1H),4.22-4.12(m,1H),3.99-3.92(m,1H),3.92-3.75(m,1H),2.08-1.86(m,4H),1.86-1.68(m,2H).

[1057] 制备27:rac-N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸

苄酯盐酸盐

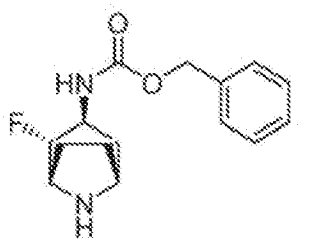
[1058] [化学式61]

[1059] 

[1060] 将rdc-(1S,2S,3S,5R)-3-{[(苄基氧基)羰基]氨基}-2-氟-8-氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯(5.45g,14.26mmol)溶解于二氯甲烷(5mL)中,然后与3.0M氯化氢的环戊基甲基醚溶液(50mL)一起在室温下搅拌4h。滴加TBME(c.a.10mL),同时仍然搅拌,直到浊度保持,然后将混合物搅拌过夜。将产生的沉淀经过滤收集,然后用TBME(10mL)和异己烷(10mL)冲洗,得到标题化合物(3.9g)。^{1}H NMR(500MHz,DMSO-d_6)δ:10.08-9.28(m,2H),7.46-7.14(m,6H),5.21-5.00(m,3H),4.27-4.15(m,1H),4.13-4.04(m,1H),3.96-3.88(m,1H),2.42(ddd,1H),2.36-2.26(m,1H),2.16(ddd,1H),2.04-1.90(m,2H),1.89-1.78(m,1H).

[1061] 制备28:N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(快速洗脱的异构体)

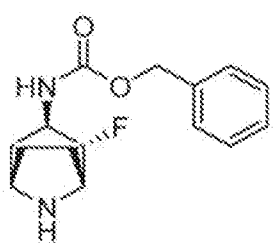
[1062] [化学式62]

[1063] 

[1064] 将rac-N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(5.82g)溶解于甲醇中(150mL),然后经手性制备型超临界流体色谱纯化(Lux A1柱,(21.2mm x250mm,5um);40℃,流速50mL/min,BPR 100BarG,在210nm检测,进样体积200μL(30mg),35:65MeOH:CO_2(0.2%v/v NH_3))。将纯的级分合并,然后蒸发,得到标题化合物(2.58g),作为较快速洗脱对映体。^{1}H NMR(500MHz,DMSO-d_6)δ:7.41-7.28(m,5H),7.28-7.20(m,1H),5.10-4.97(m,2H),4.29(ddd,1H),3.69-3.51(m,1H),3.41(dd,1H),3.37-3.29(m,1H),2.30-2.09(m,1H),2.10-1.97(m,1H),1.77-1.63(m,2H),1.64-1.47(m,2H),1.30-1.14(m,1H).

[1065] 制备29:N-[(1R,2R,3R,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(慢洗脱异构体)

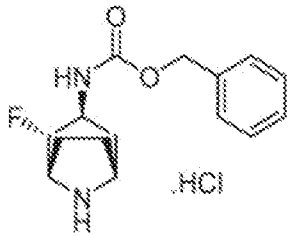
[1066] [化学式63]

[1067] 

[1068] 将rac-N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(5.82g)溶解于甲醇(150mL)中,然后经手性制备型超临界流体色谱纯化(Lux A1柱,(21.2mm x250mm,5μm);40℃;流速50mL/min,BPR 100BarG,在210nm检测,进样体积200μL(30mg),35:65MeOH:CO_2(0.2%v/v NH_3))。将纯的级分合并,然后蒸发,得到标题化合物(2.99g)。^{1}H NMR(500MHz,DMSO-d_6)δ:7.41-7.28(m,5H),7.28-7.20(m,1H),5.10-4.97(m,2H),4.29(ddd,1H),3.69-3.51(m,1H),3.41(dd,1H),3.37-3.29(m,1H),2.30-2.09(m,1H),2.10-1.97(m,1H),1.77-1.63(m,2H),1.64-1.47(m,2H),1.30-1.14(m,1H).

[1069] 制备30:N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐

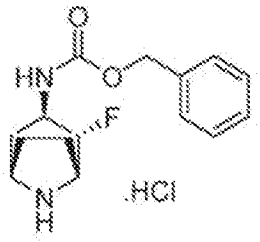
[1070] [化学式64]

[1071] 

[1072] 将快速洗脱的异构体N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(3.8g)溶解于二氯甲烷(10mL)中,然后用3.0M氯化氢的环戊基甲基醚溶液(10ml,30.0mmol)处理,得到白色固体物,将其在乙腈(50mL)中重结晶,得到标题化合物(2.2g)。^{1}H NMR(500MHz,DMSO-d_6)δ:9.34(br s,2H),7.76-7.56(m,1H),7.45-7.27(m,5H),5.09(d,1H),5.04(d,1H),4.95-4.77(m,1H),4.17-4.06(m,1H),3.98-3.87(m,1H),3.77-3.60(m,1H),2.33(ddd,1H),2.18(q,1H),2.03-1.89(m,3H),1.79(d,1H).

[1073] 制备31:N-[(1R,2R,3R,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐

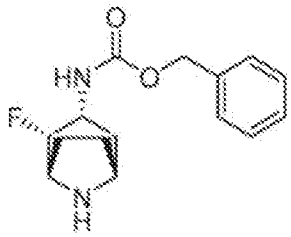
[1074] [化学式65]

[1075] 

[1076] 将慢洗脱异构体N-[(1R,2R,3R,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(3.8g)溶解于二氯甲烷(10mL)中,然后用3.0M氯化氢的环戊基甲基醚溶液(10ml,30.0mmol)处理,得到白色固体物,将其在乙腈(50mL)中重结晶,得到标题化合物(3.2g)。^{1}H NMR(500MHz,DMSO-d_6)δ:9.34(br s,2H),7.76-7.56(m,1H),7.45-7.27(m,5H),5.09(d,1H),5.04(d,1H),4.95-4.77(m,1H),4.17-4.06(m,1H),3.98-3.87(m,1H),3.77-3.60(m,1H),2.33(ddd,1H),2.18(q,1H),2.03-1.89(m,3H),1.79(d,1H).

[1077] 制备32:N-[(1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(快速洗脱的异构体)

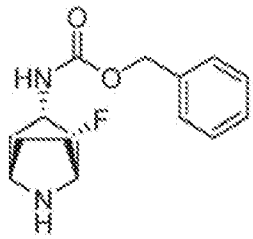
[1078] [化学式66]

[1079] 

[1080] 将rac-N-[(1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(8.8g)溶解于甲醇(50mg mL^{-1})中,然后经手性制备型超临界流体色谱纯化(Lux C2(4.6mm x250mm,5um);40℃,流速50mL/min,BPR 100BarG,在210nm检测,进样体积500μL(25mg),35:65EtOH:CO_2(0.2%v/vNH3))。将纯的级分合并,然后蒸发,得到标题化合物(4.04g),作为较快洗脱对映体。^{1}H NMR(500MHz,DMSO-d_6)δ:8.08-7.57(m,2),7.53(d,1H),7.41-7.28(m,5H),5.04(d,1H),5.02(d,1H),4.67(dt,1H),3.99-3.89(m,1H),3.85-3.67(m,2H),1.97-1.59(m,6H).(化合物作为部分盐酸盐分离)

[1081] 制备33:N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(慢洗脱对映体)

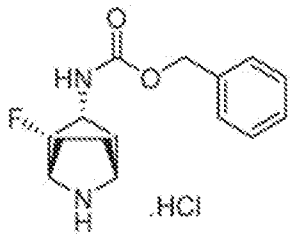
[1082] [化学式67]

[1083] 

[1084] 将rac-N-[(1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(8.8g)溶解于甲醇(50mg mL^{-1})中,然后经手性制备型超临界流体色谱纯化(Lux C2(4.6mm x250mm,5μm);40℃,流速50mL/min,BPR 100BarG,在210nm检测,进样体积500μL(25mg),35:65EtOH:CO_2(0.2%v/v NH3))。将纯的级分合并,然后蒸发,得到标题化合物(4.01g),作为较慢洗脱的对映体。^{1}H NMR(500MHz,DMSO-d_6)δ:7.47-7.28(m,6H),5.97-4.75(m,2H),5.08-4.99(m,2H),4.52(dt,1H),3.82-3.72(m,1H),3.73-3.65(m,2H),3.59-3.51(m,1H),1.85-1.72(m,2H),1.72-1.50(m,3H).(化合物作为部分盐酸盐分离)

[1085] 制备34:N-[(1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐

[1086] [化学式68]

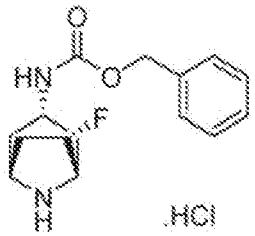
[1087] 

[1088] 将((1S,2S,3R,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(较快洗脱的对映体)(4.0g,13.65mmol)的部分HCl盐在最少量的二氯甲烷(10mL)和叔丁基甲基醚(50mL)中浆化,然后用3M氯化氢的环戊基甲基醚溶液(7ml,21.00mmol)处理。将混合物浆化

过夜，然后经过滤收集，得到标题化合物(4.19g)。^{1}H NMR(500MHz,DMSO-d_6)δ:10.3-8.10(br m,2H),7.65(d,1H),7.46-7.24(m,5H),5.18-4.94(m,2H),4.82(d,J=47.7Hz,1H),4.25-4.09(m,1H),3.99-3.90(m,1H),3.90-3.75(m,1H),2.08-1.73(m,6H).[α]$^{20}_D$=15.47°(c 1.00,MeOH).

[1089] 制备35:N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐

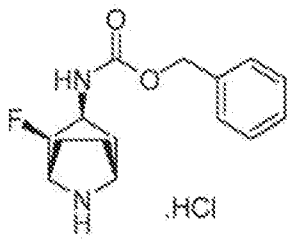
[1090] [化学式69]

[1091] 

[1092] 将((1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(慢洗脱的异构体)(4.0g,13.65mmol)在最少量的二氯甲烷(10mL)和叔丁基甲基醚(50mL)中浆化，然后用3M氯化氢的环戊基甲基醚溶液(7ml,21.00mmol)处理。将混合物浆化过夜，然后经过滤收集，得到标题化合物(4.23g)。^{1}H NMR(500MHz,DMSO-d_6)δ:10.3-8.10(br m,2H),7.65(d,1H),7.46-7.24(m,5H),5.18-4.94(m,2H),4.82(d,J=47.7Hz,1H),4.25-4.09(m,1H),3.99-3.90(m,1H),3.90-3.75(m,1H),2.08-1.73(m,6H).[α]$^{20}_D$=-11.88°(c 1.05,MeOH).

[1093] 制备36:N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐(快速洗脱的异构体)

[1094] [化学式70]

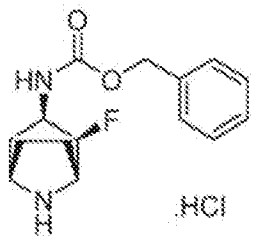
[1095] 

[1096] 将rac-N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(3.83g)溶解于甲醇(50mg mL-1)中，然后经手性制备型超临界流体色谱纯化(Lux A1(4.6mm x250mm,5μm)；40℃，流速50mL/min,BPR 125 BarG,在210nm检测，进样体积1000μL(50mg)，50:50MeOH:CO_2(0.7%v/v DEA))。将N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯作为较快洗脱的对映体分离)。将纯的级分合并，然后蒸发。然后，将残留物溶解于二氯甲烷(5mL)中，然后滴加至搅拌的叔丁基甲基醚(20mL)和异己烷(20mL)和3.0M氯化氢的环戊基甲基醚溶液(2mL,6.00mmol)混合物中，得到固体物，将其在乙腈(15mL)中重结晶，得到标题化合物(1.15g)。^{1}H NMR(500MHz,DMSO-d_6)δ:9.82-9.29(m,2H),7.62-6.86(m,6H),5.25-4.87(m,3H),4.29-4.13(m,1H),4.13-4.00(m,1H),3.98-3.85(m,1H),2.42(ddd,J=14.1,9.7,4.7Hz,1H),2.33-2.23(m,1H),2.22-2.11(m,1H),2.03-1.86(m,2H),1.87-1.73(m,1H).

[1097] 制备37:N-[(1R,2S,3R,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯

盐酸盐(慢洗脱异构体)

[1098] [化学式71]

[1099] 

[1100] 将rac-N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯进行手性制备型超临界流体色谱(如上所述),并作为慢洗脱的对映体分离。将纯的组分合并,然后蒸发。然后,将残留物溶解于二氯甲烷(5mL)中,然后用叔丁基甲基醚(20mL)稀释,并用3.0M氯化氢的环戊基甲基醚溶液(2ml,6.00mmol)处理,得到粘稠的混悬液。将混悬液用异己烷(30mL)稀释,然后搅拌18h,并经过滤收集,得到标题化合物(1.5g)。^{1}H NMR(500MHz,DMSO-d_6)δ:9.82-9.29(m,2H),7.62-6.86(m,6H),5.25-4.87(m,3H),4.29-4.13(m,1H),4.13-4.00(m,1H),3.98-3.85(m,1H),2.42(ddd,J=14.1,9.7,4.7Hz,1H),2.33-2.23(m,1H),2.22-2.11(m,1H),2.03-1.86(m,2H),1.87-1.73(m,1H).

[1101] 制备38:((1R,2R,4S)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

[1102] [化学式72]

[1103] 

[1104] 步骤1

[1105] 将rac-((1S,2S,4R)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯盐酸盐(36mg)溶解于DCM(2.89mL)中。在RT下,向其中加入TEA(0.040mL)和氯甲酸苄酯(0.025mL),随后在RT下搅拌1h。将溶剂蒸发除去,并向其中加入氯仿和水。将混合物用氯仿萃取两次,并用水和饱和盐水洗涤。蒸发除去溶剂,并将残余物经硅胶柱色谱法纯化(梯度洗脱:己烷/EtOAc),得到rac-(1S,2S,4R)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯。

[1106] 将rac-(1S,2S,4R)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯作为10mg/mL乙醇溶液得到,并在下述条件下完成分离。

[1107] 柱子:Daicel CHIRALPAK IC 2.0x25cm

[1108] 流动相:己烷/2-丙醇=85/15

[1109] 流速:12.5mL/min

[1110] 各异构体的保留时间:

[1111] (1R,2R,4S)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯:16.93分钟

[1112] (1S,2S,4R)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯:23.82分钟。

[1113] 手性分析条件:

[1114] 柱子:CHIRALPAK IC 4.6x150mm

[1115] 流动相:己烷/2-丙醇=85/15

[1116] 流速:1.0mL/min

[1117] 各异构体的保留时间:

[1118] (1R,2R,4S)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯:6.972分钟

[1119] (1S,2S,4R)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯:9.895分钟。

[1120] 步骤2

[1121] 将(1R,2R,4S)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯(93g)和10%Pd/C(10g)悬浮于甲醇(1.0L)中。在氢气气氛(50psi)下,将混合物于RT下搅拌5h。过滤反应溶液,并将滤液浓缩,得到标题化合物。MS:$[M+H]^+$=213.^{1}H-NMR(DMSO-d_6)δ:6.96-6.92(1H,m),3.63-3.56(1H,m),3.41-3.38(1H,m),3.35-3.32(1H,m),1.79-1.72(1H,m),1.67-1.61(1H,m),1.42-1.30(11H,m),1.27-1.19(1H,m),0.98-0.93(1H,m).

[1122] 制备39:((1S,2S,4R)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

[1123] [化学式73]

[1124] 

[1125] 除了将制备38的步骤1中得到的(1S,2S,4R)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯用于代替(1R,2R,4S)-2-((叔丁氧羰基)氨基)-7-氮杂二环[2.2.1]庚烷-7-甲酸苄酯外,根据制备38的步骤2,得到标题化合物。MS:$[M+H]^+$=213.^{1}H-NMR(DMSO-d_6)δ:6.97-6.93(1H,m),3.63-3.57(1H,m),3.42-3.38(1H,m),3.36-3.32(1H,m),1.79-1.72(1H,m),1.67-1.61(1H,m),1.43-1.30(11H,m),1.28-1.20(1H,m),0.99-0.92(1H,m).

[1126] 制备40:1-氧杂-6-氮杂螺[2.5]辛烷-6-甲酸苄酯

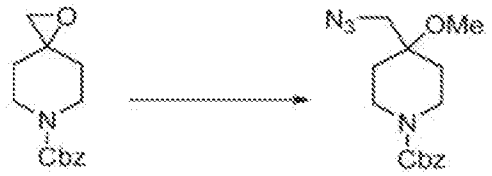
[1127] [化学式74]

[1128] 

[1129] 向4-氧代哌啶-1-甲酸苄酯(11.7g,50mmol)和三甲基碘化亚砜(trimethylsulfoxonium iodide)(12.1g,55mmol)在DME(200mL)的混合物中,加入叔丁醇钾(6.17g,55mmol),并在100℃下搅拌5h。在RT下加入水,并将混合物用EtOAc萃取。将有机层用水和盐水洗涤,并用无水Na_2SO_4干燥,过滤,并真空浓缩,将残留物经硅胶柱色谱纯化(梯度洗脱,EtOAc:己烷=1:5至1:2),得到标题化合物(7.58g)。MS:$[M+H]^+$=248.

[1130] 制备41:4-(叠氮基甲基)-4-甲氧基哌啶-1-甲酸苄酯

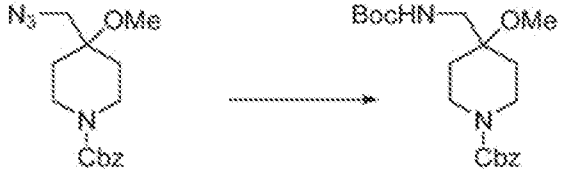
[1131] [化学式75]

[1132] 

[1133] 向1-氧杂-6-氮杂螺[2.5]辛烷-6-甲酸苄酯(1.24g,5.0mmol)的MeOH(30mL)和水(6ml)溶液中,加入叠氮化钠(1.63g,25mmol)和NH_4Cl(535mg,10mmol),并在90℃下搅拌14h。减压除去溶剂,并将混合物用EtOAc萃取。将有机层用水和盐水洗涤,并经无水Na_2SO_4干燥,过滤,并真空浓缩。在0℃下,将残留物的THF溶液(15mL)加入氢化钠(55%,在矿物油中,262mg,6.0mmol)中,并搅拌15min,然后加入碘甲烷(0.40mL,6.5mmol),并在RT下搅拌15h。在0℃下加入Sat.NH_4Cl,将混合物用EtOAc萃取。将有机层用水和盐水洗涤,并经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,EtOAc:己烷=1:5至1:2),得到标题化合物(1.16g)。MS:$[M+H]^+$=305.

[1134] 制备42:4-(((叔丁氧羰基)氨基)甲基)-4-甲氧基哌啶-1-甲酸苄酯

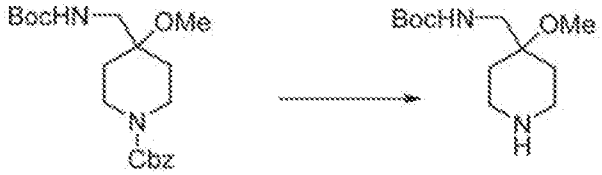
[1135] [化学式76]

[1136] 

[1137] 在RT下,向4-(叠氮基甲基)-4-甲氧基哌啶-1-甲酸苄酯(1.07g,3.5mmol)的THF(15mL)和水(0.63mL,35mmol)溶液中,加入三苯基膦(1.84g,7.0mmol),并在45℃下搅拌15h。在0℃下,将混合物加入2M NaOH(3.5mL,7.0mmol)和二碳酸二叔丁酯(918mg,4.2mmol)中,并在RT搅拌2h。将混合物用EtOAc萃取。将有机层用水和盐水洗涤,并经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,EtOAc:己烷=1:3至2:3),得到标题化合物(1.32g)。MS:$[M+H]^+$=379.

[1138] 制备43:((4-甲氧基哌啶-4-基)甲基)氨基甲酸叔丁酯

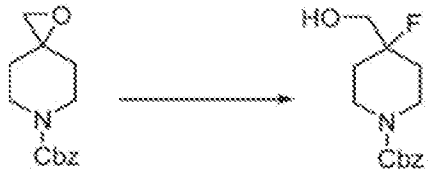
[1139] [化学式77]

[1140] 

[1141] 向4-(((叔丁氧羰基)氨基)甲基)-4-甲氧基哌啶-1-甲酸苄酯(1.14g,3.0mmol)的THF(15mL)溶液中,加入10%钯碳(46.7%湿的,280mg,0.12mmol),并在氢气气氛下搅拌6h。将反应混合物用硅藻土过滤后,减压除去溶剂,得到标题化合物(742mg)。MS:$[M+H]^+$=245.

[1142] 制备44:4-氟-4-(羟基甲基)哌啶-1-甲酸苄酯

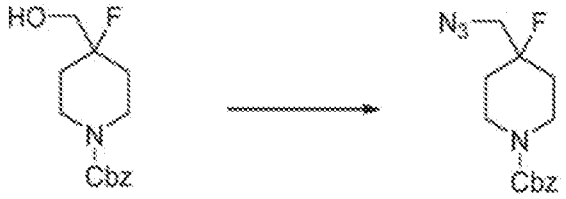
[1143] [化学式782]

[1144] 

[1145] 在-10℃，向1-氧杂-6-氮杂螺[2.5]辛烷-6-甲酸苄酯(2.47g，10.0mmol)的DCM(15mL)溶液中，在加入氟化氢吡啶(2.0mL，14mmol)的DCM(5mL)溶液，并在RT下搅拌2h。在0℃下加入Sat.$NaHCO_3$，将混合物用EtOAc萃取。将有机层用水和盐水洗涤，并经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，EtOAc:$CHCl_3$=1:10至1:3)，得到标题化合物(1.71g).MS:$[M+H]^+$=268.

[1146] 制备45:4-(叠氮基甲基)-4-氟哌啶-1-甲酸苄酯

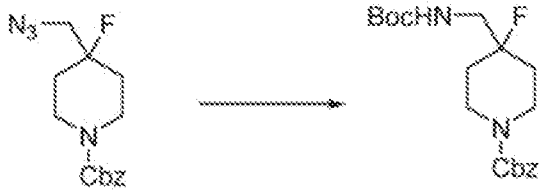
[1147] [化学式79]

[1148] 

[1149] 在RT下，向4-氟-4-(羟基甲基)哌啶-1-甲酸苄酯(1.60g，6.0mmol)的DCM(20mL)溶液中，加入Et_3N(1.68mL，12mmol)和甲磺酰氯(0.56mL，7.2mmol)，并搅拌1h。在0℃下加入水，并将混合物用EtOAc萃取。将有机层用水和盐水洗涤，并经无水Na_2SO_4干燥，过滤，并真空浓缩。向残余物的DMF溶液(15mL)加入叠氮化钠(1.94g，30mmol)，并在110℃下搅拌48h。在RT下加入水，并将混合物用EtOAc萃取。将有机层用水和盐水洗涤，并经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，EtOAc:己烷=1:5至1:2)，得到标题化合物(1.20g)。MS:$[M+H]^+$=293.

[1150] 制备46:4-(((叔丁氧羰基)氨基)甲基)-4-氟哌啶-1-甲酸苄酯

[1151] [化学式80]

[1152] 

[1153] 在RT下，向4-(叠氮基甲基)-4-氟哌啶-1-甲酸苄酯(1.02g，3.5mmol)的THF(15mL)和水(0.63mL，35mmol)溶液中，加入三苯基膦(1.84g，7.0mmol)，并在45℃下搅拌15h。在0℃下，向所述混合物中，加入2M NaOH(3.5mL，7.0mmol)和二碳酸二叔丁酯(918mg，4.2mmol)，并在RT搅拌6h。将混合物用EtOAc萃取。将有机层用水和盐水洗涤，并经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，EtOAc:己烷=1:3至2:3)，得到标题化合物(1.24g)。MS:$[M+H]^+$=367.

[1154] 制备47:((4-氟哌啶-4-基)甲基)氨基甲酸叔丁酯

[1155] [化学式81]

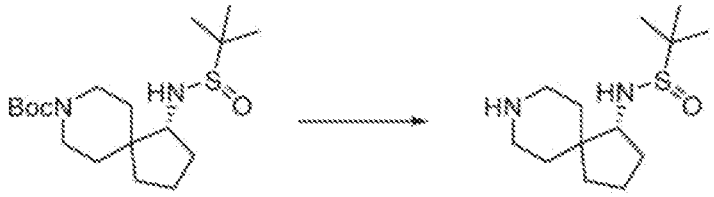
[1156] 

[1157] 向4-(((叔丁氧羰基)氨基)甲基)-4-氟哌啶-1-甲酸苄酯(1.10g，3.0mmol)的THF(15mL)和MeOH(15mL)溶液中，加入10％钯碳(46.7％湿的，345mg，0.15mmol)，并在氢气气氛

下搅拌8h。将反应混合物用硅藻土过滤后，减压除去溶剂，得到标题化合物(718mg)。MS：[M+H]$^+$=233.

[1158] 制备48：2-甲基-N-((R)-8-氮杂螺[4.5]癸烷-1-基)丙烷-2-亚磺酰胺

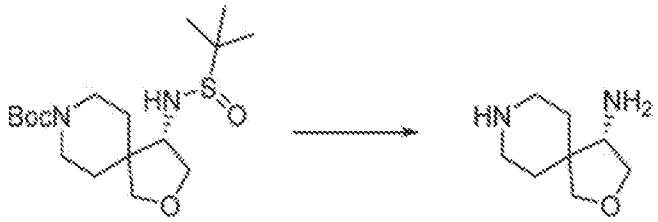
[1159] [化学式82]

[1160] 

[1161] 在RT下，向根据WO2016203405中所述的方法制备的(1R)-1-((叔丁基亚磺酰基)氨基)-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(0.10g，0.28mmol)的$CHCl_3$(1mL)溶液中，加入TFA(0.20mL，2.6mmol)。将混合物在RT下搅拌2h。减压除去挥发物，并且不需进一步纯化而使用得到的粗2-甲基-N-((R)-8-氮杂螺[4.5]癸烷-1-基)丙烷-2-亚磺酰胺盐。MS：[M+H]$^+$=259.

[1162] 制备49：(S)-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺

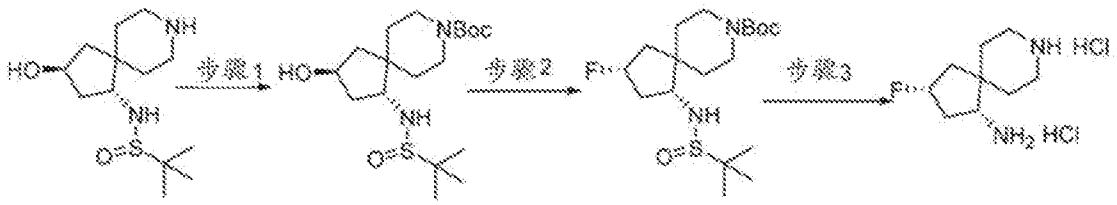
[1163] [化学式83]

[1164] 

[1165] 在RT下，向根据WO2016203405中所述的方法制备的(4S)-4-((叔丁基亚磺酰基)氨基)-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(0.10g，0.28mmol)的MeOH(1mL)溶液中，加入4M HCl的1，4-二氧六环(0.70mL，2.8mmol)溶液。将混合物在50℃下搅拌30min，并冷却至RT。减压除去挥发物，经残留物与甲苯共沸，并且不需进一步纯化而使用得到的粗(S)-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺盐。MS：[M+H]$^+$=157.

[1166] 制备50：(1R，3R)-3-氟-8-氮杂螺[4.5]癸烷-1-胺二盐酸盐

[1167] [化学式84]

[1168] 

[1169] 步骤1：(1R，3S)-1-(1，1-二甲基乙基亚磺酰氨基)-3-羟基-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1170] 将N-((1R，3S)-3-羟基-8-氮杂螺[4.5]癸烷-1-基)-2-甲基丙烷-2-亚磺酰胺(950mg，3.46mmol)溶解于THF(5mL)中，并加入Boc_2O(754mg，3.46mmol)。将溶液在50℃搅拌4小时，然后浓缩。将粗物质经硅胶色谱纯化(12g柱，0-10％MeOH/DCM)，得到(1R，3S)-1-(1，1-二甲基乙基亚磺酰氨基)-3-羟基-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(210mg，0.53mmol，产率15％)，作为无色固体。MS：[M+Na]$^+$=397.

[1171] 步骤2:(1R,3R)-1-(1,1-二甲基乙基亚磺酰氨基)-3-氟-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

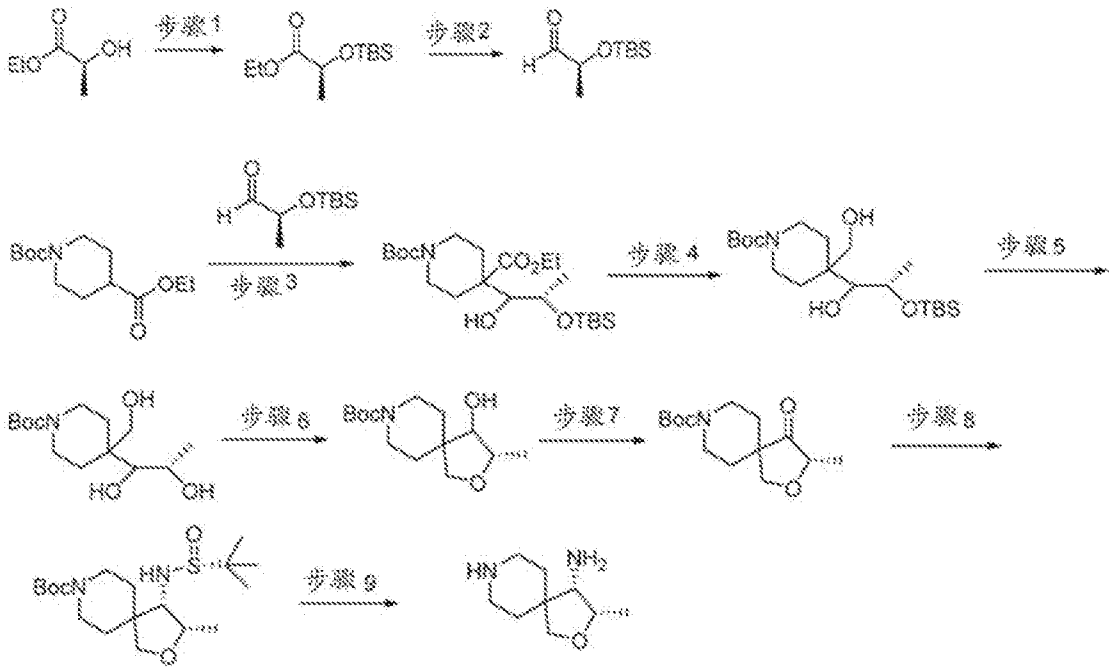
[1172] 将(1R,3S)-1-(1,1-二甲基乙基亚磺酰氨基)-3-羟基-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(200mg,0.53mmol)溶解于DCM(2.5mL)中,并将溶液冷却至0℃。滴加Deoxofluor(50wt%的甲苯溶液)(0.35mL,0.934mmol),并将混合物在室温搅拌3小时。加入另一份Deoxofluor(50wt%的甲苯溶液)(0.35mL,0.934mmol),并将反应物在0℃下搅拌3小时,然后在环境温度下搅拌30分钟。用饱和$NaHCO_3$水溶液(5mL)淬灭反应,并将混合物搅拌15分钟。分离有机相,并将水相进一步用DCM(2x10mL)萃取。将合并的有机相干燥($MgSO_4$),过滤,并浓缩,得到粗品,作为橙色油状物。将粗产物经硅胶色谱(4g柱,0-10%MeOH/DCM)纯化,得到(1R,3R)-1-(1,1-二甲基乙基亚磺酰氨基)-3-氟-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(135mg,0.32mmol,产率60%),作为浅黄色胶状物。MS:$[M+Na]^+$=399.

[1173] 步骤3:(1R,3R)-3-氟-8-氮杂螺[4.5]癸烷-1-胺二盐酸盐

[1174] 将HCl(4M的二氧六环溶液)(1.0mL)加入到(1R,3R)-1-(1,1-二甲基乙基亚磺酰氨基)-3-氟-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(130mg,0.345mmol)中,并将混合物在室温下搅拌。加入另一份HCl(4M的二氧六环溶液)(1.0mL),并将反应物在室温下搅拌1小时30分钟。将混合物浓缩,得到橙色固体物。将粗品直接用于下面步骤。

[1175] 制备51:(3S,4S)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺盐酸盐

[1176] [化学式85]

[1177] 

[1178] 步骤1:(2S)-2-[(叔丁基二甲基硅烷基)氧基]丙酸乙酯

[1179] 将反应混合物DCM(1L)中的(2S)-2-羟基丙酸乙酯(95.0g,0.8mol)冷却至0℃,然后加入咪唑(81.6g,1.2mol)和TBSCl(133.3g,0.88mol),在环境温度下搅拌1.5h。将反应混合物倒入水(1.0L)中,用DCM(2x500mL)萃取,然后用盐水清洗,经Na_2SO_4干燥,真空浓缩,硅胶柱纯化(石油醚/EtOAc=50/1-20/1),得到产物(180.0g,97%),作为无色油状物。^1H NMR(500MHz,$CDCl_3$)δ:4.33(s,1H),4.22(s,2H),1.44(d,3H),1.32(t,3H),0.97(s,9H),0.15(s,6H).

[1180] 步骤2:(2S)-2-[(叔丁基二甲基硅烷基)氧基]丙醛

[1181] 将(2S)-2-[(叔丁基二甲基硅烷基)氧基]丙酸乙酯(131.0g,0.56mol)的甲苯溶液(800mL)冷却至-60℃,滴加DIBAL-H(1.5M,560mL,0.85mol),然后在-60℃搅拌2h。将反应混合物倒入水(800mL)中,用EtOAc(2x500mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物。不需纯化,将其用于下一步骤。

[1182] 步骤3:4-[(2S)-2-[(叔丁基二甲基硅烷基)氧基]-1-羟基丙基]哌啶-1,4-二甲酸1-叔丁酯4-乙酯

[1183] 将二异丙基胺(65.0g,0.64mol)的THF(400mL)溶液冷却至-20℃。滴加n-BuLi(2.5M,224mL,0.56mol),然后在-10℃搅拌1h。在-10℃,滴加哌啶-1,4-二甲酸1-叔丁酯4-乙酯(110.0g,0.43mol)的THF(200mL)溶液,然后在N_2气氛下,从-10℃至环境温度搅拌1h。在-10℃,滴加(2S)-2-[(叔丁基二甲基硅烷基)氧基]丙醛(120.0g,0.64mol)的THF(200mL)溶液,然后在-10℃至0℃搅拌2h。将反应混合物倒入sat.NH_4Cl(1L)中,用EtOAc(2x500mL)萃取,将合并的EtOAc相用盐水冲洗,经Na_2SO_4干燥,真空浓缩,通过硅胶柱纯化(石油醚/EtOAc=50/1至30/1至20/1),得到产物(70.0g,37%),作为黄色油状物。^1H NMR(400MHz,$CDCl_3$)δ:4.29-4.09(m,2H),4.06-3.88(m,2H),3.79(d,1H),3.60-3.48(m,1H),2.78(s,2H),2.66-2.25(m,1H),2.24-1.94(m,2H),1.74(m,2H),1.50-1.37(m,9H),1.34-1.18(m,5H),1.12(d,3H),0.91(s,10H),0.04(s,6H).

[1184] 步骤4:4-[(2S)-2-[(叔丁基二甲基硅烷基)氧基]-1-羟基丙基]-4-(羟基甲基)哌啶-1-甲酸叔丁酯

[1185] 在0℃,向4-[(2S)-2-[(叔丁基二甲基硅烷基)氧基]-1-羟基丙基]哌啶-1,4-二甲酸1-叔丁酯4-乙酯(70.0g,0.157mol)的THF(700mL)溶液中,加入$LiBH_4$(2M,118mL,0.236mol),然后在环境温度下搅拌过夜。将混合物倒入水中(500mL),在环境温度下搅拌20min,用EtOAc(2x300mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物(60.0g)。不需纯化,将其用于下一步骤。

[1186] 步骤5:4-[(2S)-1,2-二羟基丙基]-4-(羟基甲基)哌啶-1-甲酸叔丁酯

[1187] 向冷却(0℃)的4-[(2S)-2-[(叔丁基二甲基硅烷基)氧基]-1-羟基丙基]-4-(羟基甲基)哌啶-1-甲酸叔丁酯(60.0g,0.149mol)的THF(600mL)溶液中,加入TBAF(1M,223mL,0.223mol),并在环境温度下搅拌2h。加入$NaHCO_3$(aq.600mL),在环境温度下搅拌10min,用EtOAc(2x300mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,经硅胶柱纯化(DCM/MeOH=100/1至50/1至30/1),得到产物(37.0g,86%),作为黄色油状物。^1H NMR(400MHz,$CDCl_3$)δ:4.02-3.87(m,1H),3.74(m,4H),3.36(d,4H),3.10(s,2H),1.66(s,3H),1.40(s,10H),1.31(s,3H).

[1188] 步骤6:(3S)-4-羟基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1189] 向冰冷的4-[(2S)-1,2-二羟基丙基]-4-(羟基甲基)哌啶-1-甲酸叔丁酯(37.0g,0.127mol)的THF(400mL)溶液中,分批加入NaH(17.8g,0.44mol),然后加入TsCl(25.5g,0.134mol)的THF(200mL)溶液,将反应混合物在0℃搅拌2h。将反应混合物倒入冰和NH_4Cl(aq.600mL)中,用EtOAc(3x400mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,经硅胶柱纯化(DCM/MeOH=100/1至50/1至30/1),得到产物(20.0g,58%),作为黄色油状物。^1H NMR(400MHz,$CDCl_3$)δ:3.94-3.57(m,4H),3.45(d,1H),2.96(s,2H),1.70(s,3H),1.42(s,10H),

1.29(m,4H).

[1190] 步骤7:(3S)-3-甲基-4-氧代-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1191] 向冰冷的(3S)-4-羟基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(20.0g,0.074mol)的DCM(200mL)溶液中,分批加入DMP(37.5g,0.088mol)。将反应混合物在环境温度下搅拌1h,倒入$NaHCO_3$(aq.)中,用DCM萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到产物(19.0g,95%),作为黄色油状物。将其直接用于下一步骤。

[1192] 步骤8:(3S,4S)-3-甲基-4-[(2-甲基丙烷-2-亚磺酰基)氨基]-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

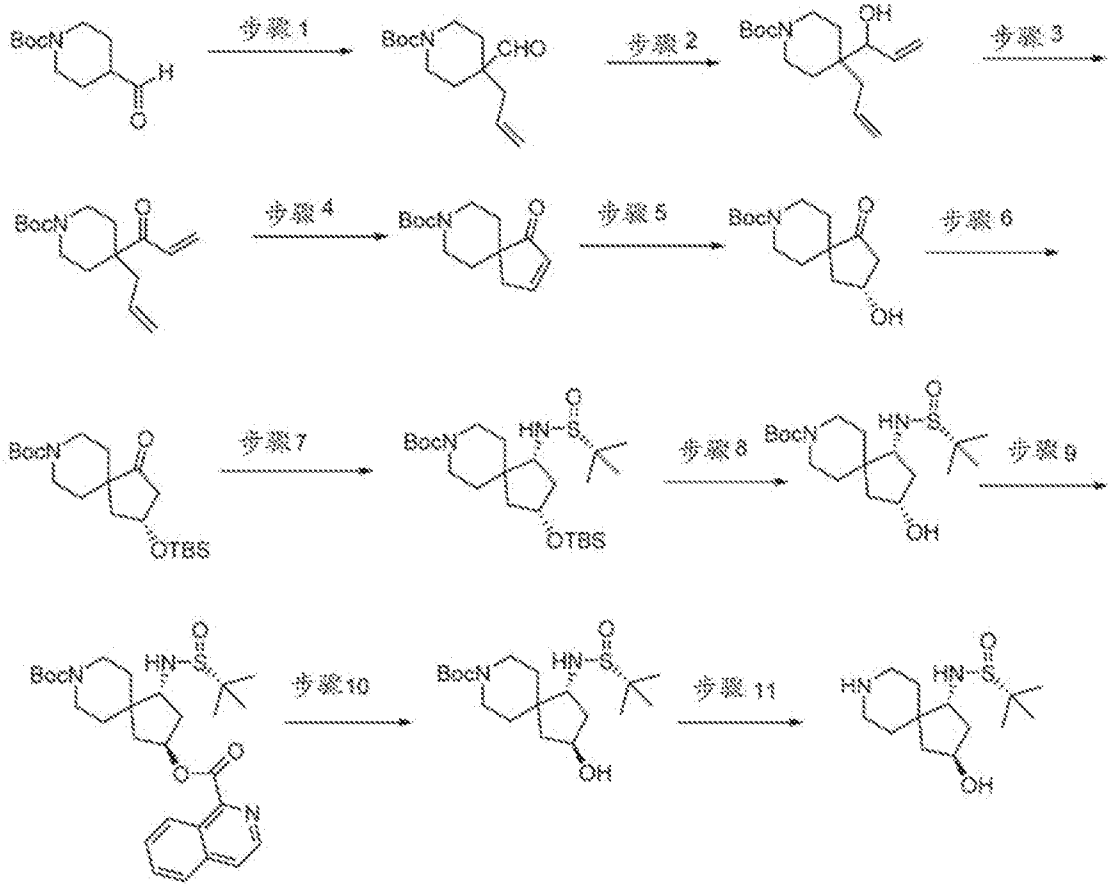
[1193] 向(3S)-3-甲基-4-氧代-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(11.0g,0.04mol)的THF(250mL)溶液中,加入(R)-2-甲基丙烷-2-亚磺酰胺(9.9g,0.08mol)、$Ti(OEt)_4$(36.5g,0.16mol),并将反应混合物在75℃下搅拌过夜。将反应混合物冷却至-10℃,滴加$LiBH_4$(2M,30mL,0.06mol),然后在-10℃下搅拌1h。将反应混合物倒入冰和NH_4Cl(aq.300mL)和EtOAc(300mL)中,在环境温度下搅拌20min,然后经硅藻土过滤。将反应混合物用EtOAc(2x300mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,经硅胶柱纯化(石油醚/EtOAc=10/1至5/1至3/1至2/1),得到产物(7.0g,47%)。^1H NMR(400MHz,DMSO-d_6)δ:5.07(d,J=11.0Hz,1H),4.06(s,1H),3.74(m,3H),3.37(d,3H),2.84(s,2H),1.69-1.50(m,2H),1.39(s,11H),1.15(s,9H),1.06(m,3H).

[1194] 步骤9:(3S,4S)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺盐酸盐

[1195] 向(3S,4S)-3-甲基-4-[(2-甲基丙烷-2-亚磺酰基)氨基]-2-氧杂-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(5.8g,15.5mmol)的MeOH(20mL)溶液中,加入HCl/二氧六环(4M,39mL,155mmol),然后在50℃搅拌2h。将反应混合物冷却至环境温度,并真空浓缩。将粗产物溶于水(50mL)中,用EtOAc(3x40mL)萃取。将水相冻干,得到产物的HCl盐(4.0g),作为黄色固体物。MS:$[M+H]^+$=171.^1H NMR(400MHz,DMSO-d_6)δ:4.44(m,1H),4.05-3.88(m,2H),3.67(s,1H),3.58-3.39(m,2H),3.22-3.01(m,2H),1.98(m,4H),1.34(s,3H).

[1196] 制备52:N-((1R,3S)-3-羟基-8-氮杂螺[4.5]癸烷-1-基)-2-甲基丙烷-2-亚磺酰胺

[1197] [化学式86]

[1198] 

[1199] 步骤1:4-甲酰基-4-(丙-2-烯-1-基)哌啶-1-甲酸叔丁酯

[1200] 将4-甲酰基哌啶-1-甲酸叔丁酯(300.0g,1.40mol)的THF(3L)溶液冷却至-25℃,加入烯丙基溴(187.7g,1.55mol),然后分批加入t-BuOK(173.0g,1.55mol),然后在-25℃～-15℃搅拌45min。将反应混合物倒入冰和NH_4Cl(aq.3L)中,用EtOAc(2x2L)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,经硅胶柱纯化(石油醚/EtOAc=50/1至20/1至10/1),得到产物(210.0g,60%),作为无色油状物。^1H NMR(400MHz,$CDCl_3$)δ:9.48(s,1H),5.58(s,1H),5.03(s,2H),3.76(s,2H),2.90(s,2H),2.21(s,2H),1.89(s,2H),1.43(s,9H).

[1201] 步骤2:4-(1-羟基丙-2-烯-1-基)-4-(丙-2-烯-1-基)哌啶-1-甲酸叔丁酯

[1202] 将4-甲酰基-4-(丙-2-烯-1-基)哌啶-1-甲酸叔丁酯(250.0g,0.99mol)的THF溶液(2.5L)冷却至-60℃,加入乙烯基溴化镁(1.18L,1.18mol),然后在环境温度下搅拌1h。将混合物倒入NH_4Cl(aq.3L)中,用EtOAc(2x2L)萃取,用盐水冲洗,经Na_2SO_4干燥,得到产物(270.0g,97%),作为棕色油状物。^1H NMR(400MHz,$CDCl_3$)δ:6.00-5.78(m,2H),5.28-5.15(m,2H),5.11-4.99(m,2H),3.98(d,1H),3.79-3.56(m,2H),3.09(s,2H),2.24(ddd,7.5Hz,2H),1.86(d,1H),1.65-1.49(m,2H),1.45-1.38(m,11H).

[1203] 步骤3:4-(丙-2-烯-1-基)-4-(丙-2-烯酰基)哌啶-1-甲酸叔丁酯

[1204] 将4-(1-羟基丙-2-烯-1-基)-4-(丙-2-烯-1-基)哌啶-1-甲酸叔丁酯(286.0g,1.01mol)的DCM(1.5L)溶液冷却至0℃,加入DMP(471.0g,1.1mol),并在环境温度下搅拌2h。将反应混合物倒入$NaHCO_3/Na_2SO_3$(1:1,2L)中,用DCM(1L)萃取,将合并的DCM相用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物(840.0g),作为黄色油状物。^1H NMR(400MHz,CDC13)δ:6.88-6.70(m,1H),6.37(d,1H),5.68(d,1H),5.55(d,1H),5.02(t,2H),3.74(s,2H),2.93

(s,2H),2.28(s,2H),2.06(s,2H),1.43(s,11H).

[1205] 步骤4:1-氧代-8-氮杂螺[4.5]癸-2-烯-8-甲酸叔丁酯

[1206] 向4-(丙-2-烯-1-基)-4-(丙-2-烯酰基)哌啶-1-甲酸叔丁酯(256.0g,0.91mol)的甲苯(3L)溶液中,加入二氯[1,3-双(2,4,6-三甲基苯基)-2-咪唑烷亚基](苄叉)(三环己基膦)钌(II)(31.1g,0.037mol),并在85℃搅拌3h。将反应混合物真空浓缩,经硅胶柱纯化(石油醚/EtOAc=50/1至30/1至15/1),得到产物(370.0g),作为棕色固体。^{1}H NMR(400MHz,$CDCl_3$)δ:7.64(s,1H),6.16(s,1H),4.08(s,2H),2.90(s,2H),2.60(s,2H),1.72(m,2H),1.46(s,9H),1.25(s,2H).

[1207] 步骤5:(3R)-3-羟基-1-氧代-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1208] 将THF(900mL)中的CuCl(1.55g,0.0156mol)、(S)-TolBINAP(10.6g,0.0156mol)、t-BuONa(1.5g,0.0156mol)的混合物在环境温度搅拌30min。加入双(频哪醇合)二硼(145.3g,0.572mol)的THF(400mL)溶液,并在环境温度搅拌15min。加入1-氧代-8-氮杂螺[4.5]癸-2-烯-8-甲酸叔丁酯(130.0g,0.52mol)的(THF 200mL)和MeOH(33.3g,1.04mol)溶液,并将反应混合物在环境温度搅拌过夜。加入水(1.6L)和$NaBO_3$(400.0g,2.6mol),并将反应混合物在环境温度搅拌1h。将混合物过滤,用EtOAc萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,并经硅胶柱纯化(石油醚/EtOAc=20/1至10/1至3/1),得到产物(100.0g,71%),作为棕色固体物。^{1}H NMR(400MHz,$CDCl_3$)δ:4.61(s,1H),3.88(s,2H),3.03(m,2H),2.65(s,1H),2.38(s,1H),2.19(s,3H),1.73(m,4H),1.44(s,9H).

[1209] 步骤6:(3R)-3-[(叔丁基二甲基硅烷基)氧基]-1-氧代-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1210] 向(3R)-3-羟基-1-氧代-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(110.0g,0.4mol)的DMF(1.0L)溶液中,加入咪唑(41.0g,0.6mol)、TBSCl(73.3g,0.48mol),并将反应混合物在环境温度搅拌过夜。将反应混合物倒入水(5L)中,用EtOAc(2x2L)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,并经硅胶柱纯化(石油醚/EtOAc=20/1至10/1至3/1),得到产物(120.0g,78%),作为黄色油状物。^{1}H NMR(400MHz,$CDCl_3$)δ:4.49(s,1H),3.88(s,2H),2.97(s,2H),2.52(s,1H),2.21(s,2H),2.06(s,2H),1.66(s,4H),1.43(s,9H),0.87(s,9H),0.03(s,6H).

[1211] 步骤7:(1R,3R)-3-[(叔丁基二甲基硅烷基)氧基]-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1212] 向(3R)-3-[(叔丁基二甲基硅烷基)氧基]-1-氧代-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(80.0g,0.2mol)的THF(1.3L)溶液中,加入(R)-2-甲基丙烷-2-亚磺酰胺(50.6g,0.4mol)、$Ti(OEt)_4$(182.5g,0.8mol),然后在65℃搅拌过夜。将反应混合物冷却至-60℃,滴加$LiBH_4$(2M,300mL,0.6mol),在-60℃搅拌过夜。将反应混合物倒入NH_4Cl(aq.2L)中,用EtOAc(2x1L)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,并经硅胶柱纯化(石油醚/EtOAc=10/1至3/1),得到产物(120.0g),作为黄色油状物。1H NMR(400MHz,$CDCl_3$)δ:4.30(s,1H),3.94(s,2H),3.58(s,1H),3.28(s,1H),2.82(s,2H),2.30(s,1H),1.76(m,7H),1.38(s,9H),1.19(s,9H),0.85(s,9H),0.01(s,6H).

[1213] 步骤8:(1R,3R)-3-羟基-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1214] 向(1R,3R)-3-[(叔丁基二甲基硅烷基)氧基]-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(135.0g,0.276mol)的THF(800mL)溶液中,加入TBAF(553mL,0.553mol),并在环境温度搅拌4h。将反应混合物倒入水(1L)中,用EtOAc(2x500mL)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物(100.0g,97%),作为黄色油状物。不需纯化,将其用于下一步骤。^{1}H NMR(400MHz,DMSO-d_6)δ:5.05(s,1H),4.67(s,1H),4.04(s,1H),3.82(s,2H),3.05(s,1H),2.74(br,s,2H),2.10(m,1H),1.67(m,4H),1.42(m,11H),1.24(s,2H),1.09(m,9H)。

[1215] 步骤9:(1R,3S)-3-(异喹啉-1-羰基氧基)-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[1216] 向(1R,3R)-3-羟基-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(120.0g,0.32mol)的THF(1L)溶液中,加入异喹啉-1-甲酸(166.6g,0.96mol)、DIAD(97.1g,0.48mol)、TPP(125.9g,0.48mol),并将反应混合物在环境温度搅拌2h。将反应混合物倒入$NaHCO_3$(aq.2L)中,用EtOAc(2x1L)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物,将其经硅胶柱纯化(DCM/EtOAc=50/1至20/1至DCM/MeOH=20/1),得到产物(120.0g,71%),作为黄色固体。MS:$[M+H]^+$=530.^{1}H NMR(400MHz,DMSO-d_6)δ:8.59(s,1H),8.40(s,1H),8.04(s,2H),7.83(d,2H),5.48(s,1H),5.23(s,1H),3.85(s,2H),3.50(s,1H),2.77(s,2H),2.49-2.38(m,1H),2.14(d,2H),1.73(s,2H),1.47(s,1H),1.38(s,9H),1.25(s,3H),1.15-1.11(m,9H)。

[1217] 步骤10:(1R,3S)-3-羟基-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯

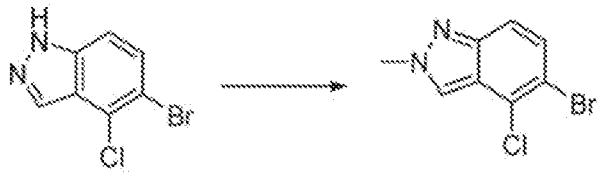
[1218] 向(1R,3S)-3-(异喹啉-1-羰基氧基)-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(120.0g,0.227mol)的THF/H_2O(1/1,1L)溶液中,加入LiOH·H_2O(92.9g,2.27mol),并在环境温度下搅拌2h。将反应混合物倒入NH_4Cl(aq.2L)中,用EtOAc(2x1L)萃取,用盐水冲洗,经Na_2SO_4干燥,真空浓缩,得到粗产物,将其从EtOAc/己烷中结晶,得到产物(64.0g,75%),作为白色固体物。MS:$[M+H-Boc]^+$=275.^{1}H NMR(400MHz,DMSO-d_6)δ:4.97(s,1H),4.51(s,1H),4.06(s,1H),3.82(s,2H),3.39(s,1H),2.74(s,2H),1.99(s,1H),1.81(s,3H),1.39(s,11H),1.28-1.16(m,1H),1.11(s,9H)。

[1219] 步骤11:N-[(1R,3S)-3-羟基-8-氮杂螺[4.5]癸烷-1-基]-2-甲基丙烷-2-亚磺酰胺

[1220] 向(1R,3S)-3-羟基-1-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂螺[4.5]癸烷-8-甲酸叔丁酯(64.0g,0.171mol)的DCM(600mL)溶液中,加入TFA(195.3g,1.71mol),并在环境温度搅拌2h。将反应混合物倒入水(2L)中,用Et_2O(5x300mL)萃取,以除去杂质,然后用$NaHCO_3$(aq.)将pH调至pH=8,将水冷冻干燥,得到产物(50.0g),作为无色油状物。MS:$[M+H]^+$=275.^{1}H NMR(400MHz,DMSO-d_6)δ:5.13(d,1H),4.83(br,s,3H),4.08(s,1H),3.44(m,1H),3.15(m,2H),2.78(m,2H),2.01-1.64(m,4H),1.40(m,2H),1.25(m,1H),1.15(s,9H)。

[1221] 制备53:5-溴-4-氯-2-甲基-2H-吲唑

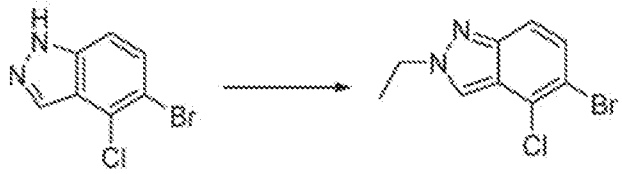
[1222] [化学式87]

[1223] 

[1224] 在RT下，向5-溴-4-氯-1H-吲唑(10.0g，43.2mmol)的EtOAc混悬液(200mL)中，加入三甲基氧鎓四氟硼酸盐(9.58g，64.8mmol)。将混合物在RT搅拌20h，用sat.$NaHCO_3$淬灭，并用EtOAc萃取。将有机层用盐水冲洗，经Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-50％EtOAc/己烷)，得到标题化合物(9.16g)。MS：$[M+H]^+$＝245，247.

[1225] 制备54：5-溴-4-氯-2-乙基-2H-吲唑

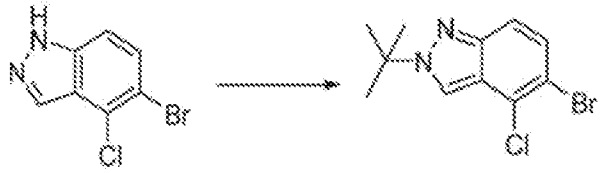
[1226] [化学式88]

[1227] 

[1228] 在RT下，向5-溴-4-氯-1H-吲唑(5.0g，21.6mmol)的EtOAc(100mL)混悬液中，加入三乙基氧鎓六氟磷酸盐(8.04g，32.4mmol)。将混合物在RT搅拌过夜，用sat.$NaHCO_3$淬灭，并用EtOAc萃取。将有机层用盐水冲洗，经Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-50％EtOAc/己烷)，得到标题化合物(5.05g)。MS：$[M+H]^+$＝259，261.

[1229] 制备55：5-溴-2-(叔丁基)-4-氯-2H-吲唑

[1230] [化学式89]

[1231] 

[1232] 在RT下，向5-溴-4-氯-1H-吲唑(0.93g，4.0mmol)的甲苯混悬液(8.0mL)中，加入乙酸叔丁酯(4.7g，40mmol)和甲磺酸(0.38g，4.0mmol)。

[1233] 将混合物在95℃搅拌1d。向混合物中，加入乙酸叔丁酯(4.7g，40mmol)和甲磺酸(0.38g，4.0mmol)，并再搅拌1d。将混合物用EtOAc稀释，并用水和盐水冲洗。真空浓缩有机层。将残留物经硅胶柱色谱纯化(梯度洗脱，0-20％EtOAc/己烷)，得到标题化合物(1.1g)。MS：$[M+H]^+$＝287，289.

[1234] 制备56：5-溴-2-甲基-2H-吲唑

[1235] [化学式90]

[1236] 

[1237] 利用5-溴-4-氯-2-甲基-2H-吲唑的类似制备方法，由5-溴-1H-吲唑制备，得到标题化合物。MS：$[M+H]^+$＝211，213.

[1238] 制备57：5-溴-4-氟-2-甲基-2H-吲唑

[1239] [化学式91]

[1240] 

[1241] 利用5-溴-4-氯-2-甲基-2H-吲唑的类似制备方法，由5-溴-4-氟-1H-吲唑制备，得到标题化合物。MS:$[M+H]^+$=229,231.

[1242] 制备58:5-溴-6-氟-2-甲基-2H-吲唑

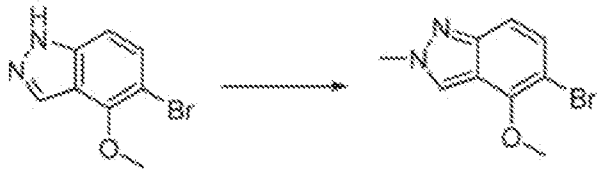
[1243] [化学式92]

[1244] 

[1245] 利用5-溴-4-氯-2-甲基-2H-吲唑的类似制备方法，由5-溴-6-氟-1H-吲唑制备，得到标题化合物。MS:$[M+H]^+$=229,231.

[1246] 制备59:5-溴-4-甲氧基-2-甲基-2H-吲唑

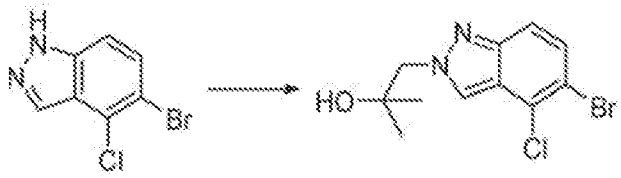
[1247] [化学式93]

[1248] 

[1249] 利用5-溴-4-氯-2-甲基-2H-吲唑的类似制备方法，由5-溴-4-甲氧基-1H-吲唑制备，得到标题化合物。MS:$[M+H]^+$=241,243.

[1250] 制备60:1-(5-溴-4-氯-2H-吲唑-2-基)-2-甲基丙烷-2-醇

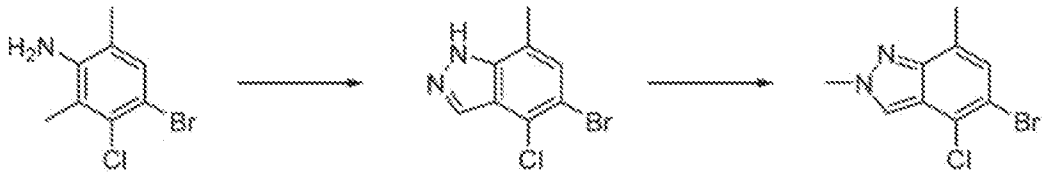
[1251] [化学式94]

[1252] 

[1253] 在RT下，向5-溴-4-氯-1H-吲唑(1.0g,4.32mmol)的DMF溶液(10mL)中，加入K_2CO_3(1.19g,8.64mmol)和氧化异丁烯(0.58mL,6.48mmol)。将混合物在100℃搅拌2h，用水稀释，并用EtOAc萃取。将有机层用盐水冲洗，经Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，10-20%EtOAc/己烷)，得到标题化合物(0.55g)。MS:$[M+H]^+$=303,305.

[1254] 制备61:5-溴-4-氯-2,7-二甲基-2H-吲唑

[1255] [化学式95]

[1256] 

[1257] 在RT下，向4-溴-3-氯-2,6-二甲基苯胺(4.8g,20mmol)、乙酸钾(3.1g,31mmol)、乙酸(1.8g,29mmol)和甲苯(61mL)的混合物中，加入亚硝酸叔丁基酯(2.5g,25mmol)。将混合物在45℃搅拌过夜。向混合物中，加入EtOAc(40mL)和1M NaOH aq.(40mL)。将分离的有机层用盐水冲洗，并真空浓缩。将残留物悬浮于甲苯和庚烷中。收集沉淀，并将其在50℃减压干燥，得到5-溴-4-氯-7-甲基-1H-吲唑和5-溴-6-氯-7-甲基-1H-吲唑(3.4g)的混合物。MS:[M+H]$^+$=245,247.

[1258] 利用5-溴-4-氯-2-甲基-2H-吲唑的类似制备方法，由5-溴-4-氯-7-甲基-1H-吲唑和5-溴-6-氯-7-甲基-1H-吲唑的混合物制备，得到标题化合物。MS:[M+H]$^+$=259,261

[1259] 制备62:5-溴-3,4-二氯-2-甲基-2H-吲唑

[1260] [化学式96]

[1261] 

[1262] 在0℃下，向5-溴-4-氯-2-甲基-2H-吲唑(5g,20.3mmol)的DMF溶液(50mL)中，加入NCS(2.99g,22.4mmol)。将混合物在RT搅拌过夜。在RT下加入水(150mL)。将混合物在RT搅拌1h。收集沉淀，并将其用水冲洗，并在60℃减压干燥3h，得到标题化合物(5.63g)。MS:[M+H]$^+$=279,281.

[1263] 制备63:5-溴-4-氯-2,3-二甲基-2H-吲唑

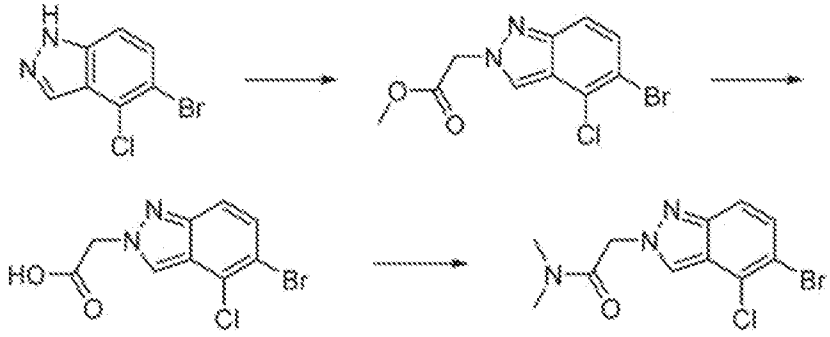
[1264] [化学式97]

[1265] 

[1266] 在-78℃，向5-溴-4-氯-2-甲基-2H-吲唑(500mg,2.03mmol)的THF溶液(10mL)中，加入LDA(1.08M的THF溶液，2.26mL,2.44mmol)。将混合物在0℃搅拌30min，并冷却至-78℃。在-78℃加入碘甲烷(0.190mL,3.05mmol)。将混合物在-78℃搅拌2h，用sat.NH_4Cl淬灭，并用EtOAc萃取。将有机层用盐水冲洗，经Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-60%EtOAc/己烷)，得到标题化合物(442mg)。MS:[M+H]$^+$=259,261.

[1267] 制备64:2-(5-溴-4-氯-2H-吲唑-2-基)-M,N-二甲基乙酰胺

[1268] [化学式98]

[1269] 

[1270] 步骤1

[1271] 在RT下，向5-溴-4-氯-1H-吲唑(500mg,2.16mmol)和羟乙酸甲酯(0.25mL,

3.24mmol)的THF(10mL)溶液中，加入DMEAD(759mg，3.24mmol)和三苯基膦(850mg，3.24mmol)。将混合物在RT搅拌2h。将反应液真空浓缩，并将残留物经硅胶柱色谱纯化(梯度洗脱，20-40％EtOAc/己烷)，得到2-(5-溴-4-氯-2H-吲唑-2-基)乙酸甲酯(190mg)。MS：$[M+H]^+$＝303，305.

[1272] 步骤2

[1273] 在RT下，向2-(5-溴-4-氯-2H-吲唑-2-基)乙酸甲酯(190mg，0.63mmol)的THF溶液(1.9mL)中，加入LiOH(90mg，3.76mmol)的水溶液(0.95mL)。并将混合物在RT搅拌20min，用MTBE稀释，并加入2MNaOH。将水层加入6M HCl，并用$CHCl_3$萃取三次。将有机层用盐水冲洗，经Na_2SO_4干燥，过滤，并真空浓缩，得到2-(5-溴-4-氯-2H-吲唑-2-基)乙酸(140mg)。MS：$[M+H]^+$＝289，291.

[1274] 步骤3

[1275] 在RT下，向2-(5-溴-4-氯-2H-吲唑-2-基)乙酸(140mg，0.48mmol)的THF(1.4mL)溶液中，加入TEA(0.27mL，1.93mmol)、HATU(276mg，0.73mmol)和二甲胺盐酸盐(59mg，0.73mmol)。将混合物在50℃搅拌1h。将反应液真空浓缩，并将残留物经硅胶柱色谱纯化(梯度洗脱，40-100％EtOAc/己烷)，得到标题化合物(125mg)。MS：$[M+H]^+$＝316，318.

[1276] 制备65：6-溴-7-氯-2，3-二氢-1，3-苯并噻唑-2-硫酮

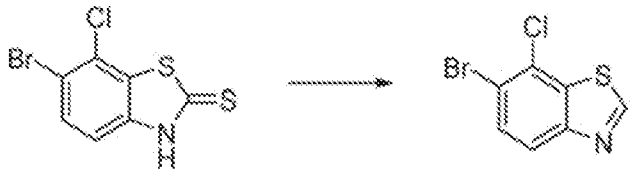
[1277] [化学式99]

[1278] 

[1279] 将4-溴-2，3-二氯苯胺(10.0g，41.5mmol)和乙基黄原酸钾(15.0g，93.4mmol)混合物的DMF溶液(100mL)在120℃搅拌18h。将混合物用2M aq.HCl(80ml)和水(400mL)淬灭。将混合物过滤，并用水清洗，得到标题化合物(1.13g)。^{1}H-NMR(400MHz，DMSO-d_6)δ：14.10(1H，s)，7.78(1H，d)，7.19(1H，d).

[1280] 制备66：6-溴-7-氯-1，3-苯并噻唑

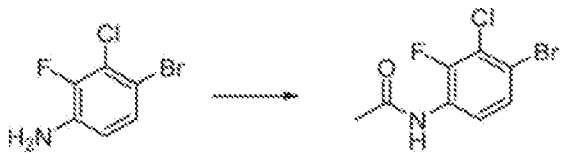
[1281] [化学式100]

[1282] 

[1283] 将在RT填充6-溴-7-氯-2，3-二氢-1，3-苯并噻唑-2-硫酮(1.13g，40.3mmol)、铁粉(12.4g，221.5mmol)和乙酸(200mL)的圆底烧瓶在120℃搅拌(用机械搅拌器)2h。此外，加入铁粉(24.8g，443.0mmol)，并将混合物在120℃搅拌2h。加入另外的铁粉(12.4g，221.5mmol)，并将反应在120℃搅拌15h。将混合物过滤，并将滤液减压浓缩。将残留物通过从EtOAc中重结晶，然后经硅胶柱色谱(10％EtOAc/Petrol)纯化，得到标题化合物(0.27g)。MS：$[M+H]^+$＝248.

[1284] 制备67：N-(4-溴-3-氯-2-氟苯基)乙酰胺

[1285] [化学式101]

[1286] 

[1287] 历经1.5h，向在冰浴中冷却的4-溴-3-氯-2-氟苯胺(25g，111mmol)和DIPEA(48.5ml，278mmol)的DCM(250mL)中，加入乙酸酐(11.05ml，117mmol)。将反应物升温至RT，并搅拌24h。将反应物用HCl(1M，250mL)、$NaHCO_3$(150mL)和水(100mL)洗涤。将有机相干燥($MgSO_4$)，并减压浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-40％EtOAc/Petrol)，得到标题化合物(23.8g)。^{1}H-NMR(500MHz，DMSO-d_6)δ:9.97(s，1H)，7.95-7.77(m，1H)，7.56(dd，1H)，2.10(s，3H)。

[1288] 制备68:6-溴-7-氯-2-甲基-1,3-苯并噻唑

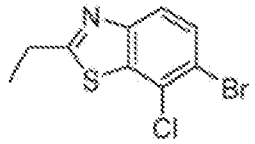
[1289] [化学式102]

[1290] 

[1291] 向N-(4-溴-3-氯-2-氟苯基)乙酰胺(1.0g，3.77mmol)的二甲苯(9.86mL)溶液中，加入劳森试剂(Lawesson′s Reagent)(1.53g，2.26mmol)。将反应物加热至110℃，保持18h。加入碳酸铯(4.11g，7.55mmol)，并将混合物在110℃搅拌18h。将反应物冷却至RT，并将反应物用水(500mL)和乙酸乙酯稀释。分离有机层，并将其用饱和盐水清洗，然后经无水Na_2SO_4干燥，过滤并减压浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-20％EtOAc/Petrol)纯化，得到标题化合物(0.97g)。^{1}H-NMR(400MHz，DMSO-d_6)δ:7.85(2H，d)，2.83(3H，s)。

[1292] 制备69:6-溴-7-氯-2-乙基苯并[d]噻唑

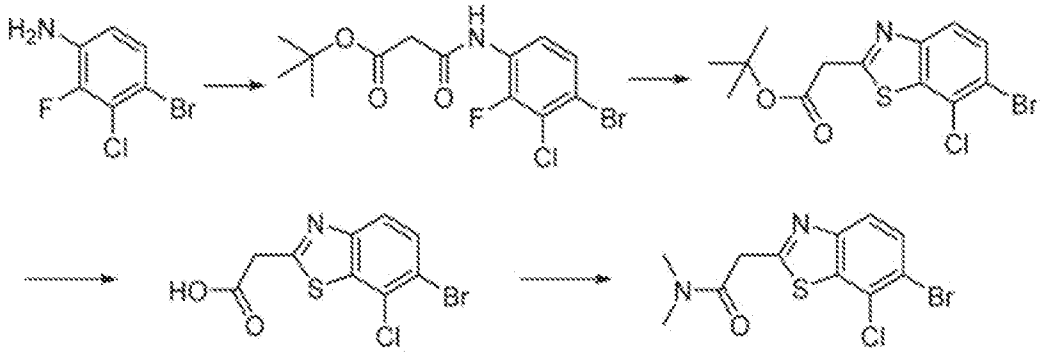
[1293] [化学式103]

[1294] 

[1295] 利用6-溴-7-氯-2-甲基-1,3-苯并噻唑的类似制备方法，由丙酰氯制备，得到标题化合物。MS:$[M+H]^+$=211，213。

[1296] 制备70:2-(6-溴-7-氯苯并[d]噻唑-2-基)-N,N-二甲基乙酰胺

[1297] [化学式104]

[1298] 

[1299] 步骤1

[1300] 在RT下，向4-溴-3-氯-2-氟-苯胺(3g，13.4mmol)和HATU(10.2g，26.7mmol)的DMA(30mL)溶液中，加入TEA(5.58mL，40.1mmol)和3-叔丁氧基-3-氧代丙酸(3.09mL，20.0mmol)。将混合物在50℃搅拌1h，用水稀释，并用EtOAc萃取。将有机层用盐水清洗，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，30-70％EtOAc/己烷)，得到3-(4-溴-3-氯-2-氟-苯氨基)-3-氧代-丙酸叔丁酯(3.35g)。

[1301] 步骤2

[1302] 在RT下，向3-(4-溴-3-氯-2-氟-苯氨基)-3-氧代-丙酸叔丁酯(2g，5.47mmol)的甲苯混悬液(20mL)中，加入劳森试剂(1.32g，3.27mmol)。将混合物在110℃搅拌3h。加入Cs_2CO_3(3.56g，10.9mmol)。将混合物在110℃搅拌19h，冷却至RT，并过滤。真空浓缩滤液。将残留物经硅胶柱色谱纯化(梯度洗脱，0-20％EtOAc/$CHCl_3$)，得到2-(6-溴-7-氯苯并[d]噻唑-2-基)乙酸叔丁酯(983mg)。

[1303] 步骤3

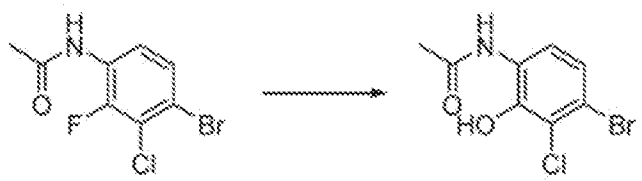
[1304] 在RT下，向2-(6-溴-7-氯苯并[d]噻唑-2-基)乙酸叔丁酯(500mg，1.38mmol)的$CHCl_3$(5mL)溶液中，加入TFA(2.5mL，32mmol)。将混合物在60℃搅拌1h。将反应液真空浓缩，并将残留物悬浮于己烷中。收集沉淀物，用己烷洗涤，并在60℃减压干燥3h，得到2-(6-溴-7-氯苯并[d]噻唑-2-基)乙酸(200mg)。MS：$[M+H]^+$＝306，308.

[1305] 步骤4

[1306] 在RT下，向2-(6-溴-7-氯苯并[d]噻唑-2-基)乙酸(200mg，0.65mmol)的THF(4mL)溶液中，加入TEA(0.45mL，3.26mmol)、丙基膦酸酐(1.6M的THF溶液，0.82mL，1.30mmol)和二甲胺(2.0M的THF溶液，0.65mL，1.30mmol)。将混合物在RT搅拌10min。将反应液真空浓缩，并将残留物经硅胶柱色谱纯化(梯度洗脱，80-100％EtOAc/己烷)，得到标题化合物(168mg)。MS：$[M+H]^+$＝333，335.

[1307] 制备71：N-(4-溴-3-氯-2-羟基苯基)乙酰胺

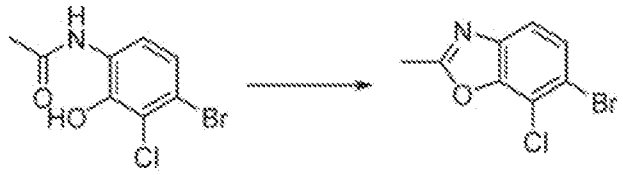
[1308] [化学式105]

[1309] 

[1310] 将N-(4-溴-3-氯-2-氟-苯基)乙酰胺(1.0g，3.8mmol)、碳酸铯(2.0当量，7.5mmol)的NMP(6.0mL)混悬液在150℃微波(Initiator，Biotage)照射5h。向混合物中，加入NMP(15mL)，并将混合物再在150℃下微波照射5h。将反应混合物用EtOAc和水稀释，并用5N HCl水溶液酸化，以将其pH调至1-2。将混合物用EtOAc(X3)萃取，并将有机萃取物用盐水洗涤，并经Na_2SO_4干燥。浓缩得到粗混合物(1.20g，棕色油状物)，将其进行柱色谱(梯度洗脱，5-70％EtOAc/己烷)纯化，得到标题化合物(425mg，1.61mmol，产率43％)，作为黄色固体物。MS：$[M+H]^+$＝264，266.

[1311] 制备72：6-溴-7-氯-2-甲基苯并[d]噁唑

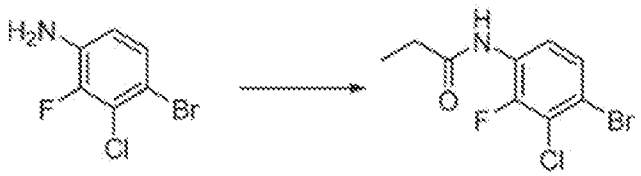
[1312] [化学式106]

[1313] 

[1314] 向N-(4-溴-3-氯-2-羟基苯基)乙酰胺(1.09g,4.12mmol)、三苯基膦(1.62g,6.18mmol)的THF溶液(30mL)中,加入偶氮二甲酸二异丙酯(1.21mL,6.18mmol),并将混合物在50℃的油浴中加热2h 45min。浓缩反应混合物,得到粗油状物(4.30g,棕色油状物),将其进行柱色谱(梯度洗脱,5-70%EtOAc/己烷)纯化,随后悬浮于己烷中,并经过滤收集,得到标题化合物(908mg,3.68mmol,产率89%),作为无色固体。MS:$[M+H]^+$=246,248.

[1315] 制备73:N-(4-溴-3-氯-2-氟苯基)丙酰胺

[1316] [化学式107]

[1317] 

[1318] 在0℃,向4-溴-3-氯-2-氟苯胺(5.00g,22.3mmol)的DCM(40mL)溶液中,加入TEA(2.0当量,44.6mmol)和丙酰氯(2.34mL,26.7mmol)。除去冰水浴,并将混合物在RT搅拌17h。在RT下,向混合物中加入丙酰氯(0.779mL,8.92mmol)。在RT搅拌45min后,向混合物中加入水。用EtOAc(X2)萃取混合物,并将有机萃取物用水、稀NH_4Cl水溶液、$NaHCO_3$aq.和盐水清洗,并经Na_2SO_4干燥。将浓缩的粗混合物悬浮于己烷-EtOAc(4/1)中,并经Kiriyama-roshi(No.4)收集,得到标题化合物(4.22g,15.0mmol,产率67%),作为无色针状物。将滤液(橙色固体,2.23g)进行柱色谱(梯度洗脱,5-40%EtOAc/己烷)纯化,得到标题化合物(1.33g,4.74mmol,产率21%),作为无色针状物。MS:$[M+H]^+$=280,282.

[1319] 制备74:N-(4-溴-3-氯-2-羟基苯基)丙酰胺

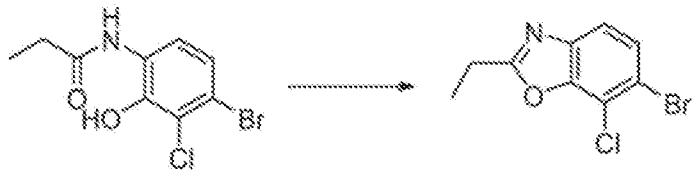
[1320] [化学式108]

[1321] 

[1322] 将N-(4-溴-3-氯-2-氟-苯基)丙酰胺(2.50g,8.91mmol)、碳酸铯(5.80g,17.8mmol)的NMP(15mL)混悬液在150℃微波(Initiator,Biotage)照射5h。向混合物中,加入NMP(15mL),并将混合物再在150℃下微波照射5h。将反应混合物用EtOAc和水稀释,并用5N HCl水溶液酸化,以将其pH调至1-2。将混合物用EtOAc(X3)萃取,并将有机萃取物用盐水洗涤,并经Na_2SO_4干燥。浓缩得到粗混合物(5.90g,棕色油状物),将其进行柱色谱(梯度洗脱,5-100%EtOAc/己烷)纯化,得到标题化合物(1.27g,4.56mmol,产率51%)。MS:$[M+H]^+$=278,280.

[1323] 制备75:6-溴-7-氯-2-乙基苯并[d]噁唑

[1324] [化学式109]

[1325] 

[1326] 向N-(4-溴-3-氯-2-羟基苯基)丙酰胺(607mg,2.18mmol)、三苯基膦(857mg,3.27mmo)的THF(10mL)溶液中,加入偶氮二甲酸二异丙酯(0.642mL,3.27mmol),并将混合物在50℃的油浴中加热1h 45min。浓缩反应混合物,得到粗油状物(2.38g,棕色油状物),将其进行柱色谱(梯度洗脱,5-50%EtOAc/己烷)纯化,得到标题化合物(525mg,2.02mmol,产率92%),作为浅黄色固体。MS:$[M+H]^+$=260,262.

[1327] 制备76:6-溴-7-氯-1-甲基-1H-苯并[d][1,2,3]三唑

[1328] [化学式110]

[1329] 

[1330] 在RT下,向6-溴-7-氯-1H-苯并[d][1,2,3]三唑(400mg,1.72mmol)的THF(8mL)溶液中,加入三苯基膦(542mg,2.06mmol)、MeOH(0.084mL,2.06mmol)和DMEAD(484mg,2.06mmol)。将混合物在RT搅拌2h。然后,将反应液真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,10-40%EtOAc/己烷)。收集含有目标产物的级分,并真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱,0-20%EtOAc/己烷)纯化,得到标题化合物(152mg)。^{1}H-NMR($CDCl_3$)δ:7.82(1H,d,J=8.8Hz),7.58(1H,d,J=8.8Hz),4.57(3H,s).MS:$[M+H]^+$=246,248.

[1331] 制备77:5-溴-4-氯-2-甲基-2H-苯并[d][1,2,3]三唑

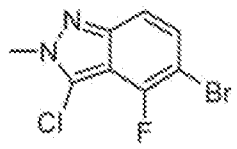
[1332] [化学式111]

[1333] 

[1334] 在RT下,向6-溴-7-氯-1H-苯并[d][1,2,3]三唑(400mg,1.72mmol)的THF溶液(8mL)中,加入三苯基膦(542mg,2.06mmol)、MeOH(0.084mL,2.06mmol)和DMEAD(484mg,2.06mmol)。将混合物在RT搅拌2h。然后,将反应液真空浓缩,并将残留物经硅胶柱色谱(梯度洗脱,10-40%EtOAc/己烷)纯化。收集含有目标产物的级分,并真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱,0-20%EtOAc/己烷)纯化,得到标题化合物(160mg)。^{1}H-NMR($CDCl_3$)δ:7.66(1H,d,J=9.0Hz),7.57(1H,d,J=9.0Hz),4.54(3H,s).MS:$[M+H]^+$=246,248.

[1335] 制备78:5-溴-3-氯-4-氟-2-甲基-2H-吲唑

[1336] [化学式112]

[1337] 

[1338] 利用5-溴-3,4-二氯-2-甲基-2H-吲唑的类似制备方法,由5-溴-4-氟-2-甲基-2H-

吲唑制备，得到标题化合物。MS：$[M+H]^+$＝263，265.

[1339] 制备79：5-溴-4-氯-2-乙基-2H-吲唑-3-甲醛

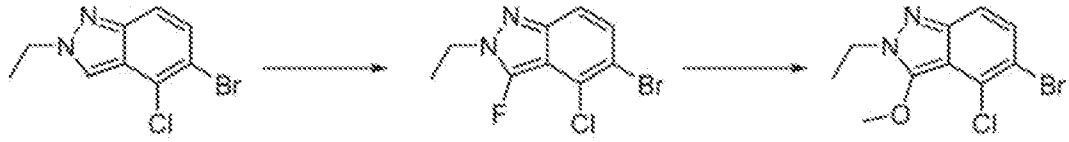
[1340] [化学式113]

[1341] 

[1342] 在-78℃下，向5-溴-4-氯-2-乙基-2H-吲唑(1.1g，4.1mmol)的THF(8.3mL)溶液中，加入LDA(1.08M的己烷-THF溶液，5.8mL，6.3mmol)。将混合物在0℃搅拌30min。在0℃加入N，N-二甲基甲酰胺(0.61g，8.3mmol)。将混合物在RT搅拌过夜，用sat.NH_4Cl aq.淬灭，并用EtOAc萃取。将有机层用盐水清洗，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-40％EtOAc/己烷)纯化，得到标题化合物(772mg)。MS：$[M+H]^+$＝287，289.

[1343] 制备80：5-溴-4-氯-2-乙基-3-甲氧基-2H-吲唑

[1344] [化学式114]

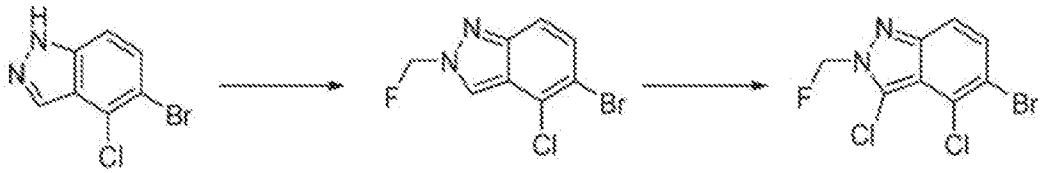
[1345] 

[1346] 在-78℃下，向5-溴-4-氯-2-乙基-2H-吲唑(500mg，1.92mmol)的THF(10mL)溶液中，加入LDA(1.08M的THF溶液，2.14mL，2.31mmol)。将混合物在0℃搅拌30min。在0℃加入N-氟苯磺酰亚胺(850mg，2.69mmol)。将混合物在0℃搅拌1h，用水淬灭，并用EtOAc萃取。将有机层用盐水清洗，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-60％EtOAc/己烷)纯化，得到5-溴-4-氯-2-乙基-3-氟-2H-吲唑(185mg)。MS：$[M+H]^+$＝277，279.

[1347] 在RT下，向5-溴-4-氯-2-乙基-3-氟-2H-吲唑(183mg，0.659mmol)的THF(3mL)溶液中，加入NaOMe(28％的MeOH溶液，0.472mL，1.97mmol)。将混合物在60℃搅拌4h，冷却至RT，倒入水中，并用EtOAc萃取。将有机层用盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-60％EtOAc/己烷)纯化，得到标题化合物(166mg)。MS：$[M+H]^+$＝289，291.

[1348] 制备81：5-溴-3，4-二氯-2-(氟甲基)-2H-吲唑

[1349] [化学式115]

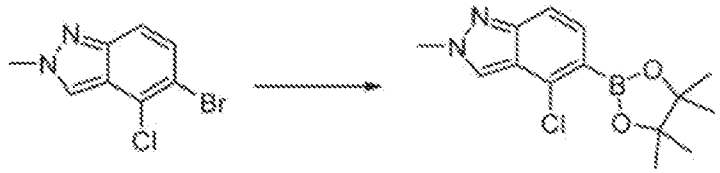
[1350] 

[1351] 将5-溴-4-氯-1H-吲唑(1.00g，4.32mmol)、p-甲苯磺酸氟甲酯(0.970g，4.75mmol)、Cs_2CO_3(1.68g，5.18mmol)和NMP(10mL)的混合物在60℃搅拌11h，冷却至RT，倒入水中，并用EtOAc萃取。将有机层用水和盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-60％EtOAc/己烷)纯化，得到5-溴-4-氯-2-(氟甲基)-2H-吲唑(346mg)。MS：$[M+H]^+$＝263，265.

[1352] 在0℃，向5-溴-4-氯-2-(氟甲基)-2H-吲唑(378mg，1.43mmol)的DMF(4mL)溶液中，加入NCS(210mg，1.57mmol)。将混合物在RT搅拌44h。在RT加入NCS(40mg，0.299mmol)。将混合物在RT搅拌24h，倒入水中，并用EtOAc萃取。将有机层用水和盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，10-35％EtOAc/己烷)纯化，得到标题化合物(401mg).MS:$[M+H]^+$＝297，299.

[1353] 制备82:4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

[1354] [化学式116]

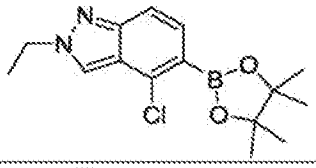
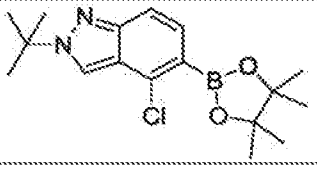
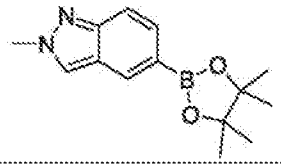
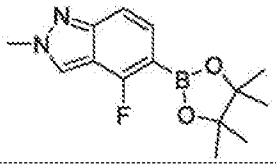
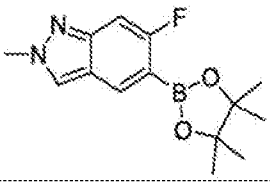
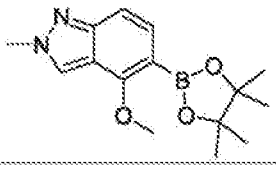
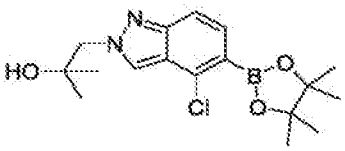
[1355] 

[1356] 将5-溴-4-氯-2-甲基-2H-吲唑(12.14g，49.45mmol)、双(频哪醇合)二硼(18.83g，74.18mmol)、[1，1′-二(二苯基膦基)二茂铁]二氯钯(II)与二氯甲烷的络合物(4.038g，4.945mmol)和乙酸钾(9.706g，98.90mmol)的1，4-二氧六环溶液(120mL)脱气，填充氮气，并在120℃搅拌5h。将反应物冷却至RT，经硅藻土垫过滤，并用EtOAc洗涤。将滤液真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱，0-70％EtOAc/己烷)纯化，得到标题化合物(14.36g)。MS:$[M+H]^+$＝293，295.

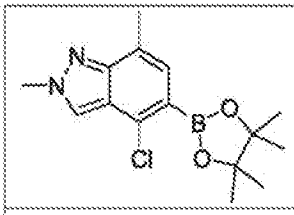
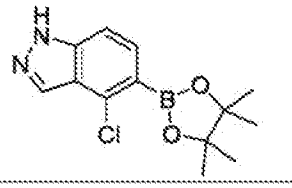
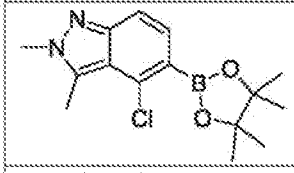
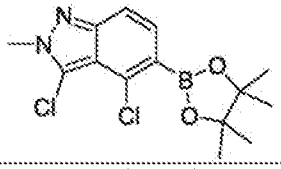
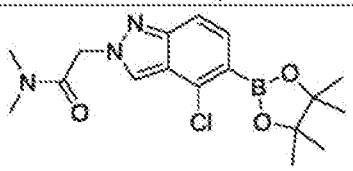
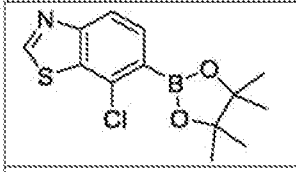
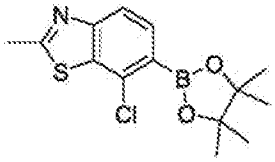
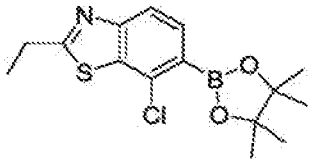
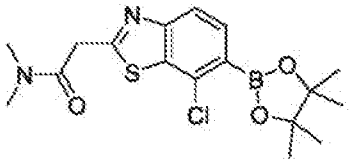
[1357] 利用与制备82中所述类似的方法，从适当的取代芳基卤化物(如上所述合成，具有下文所示的任何显著变异)开始，制备下表1的化合物。

[1358] 表1

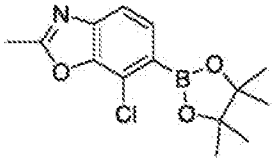
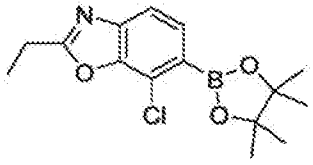
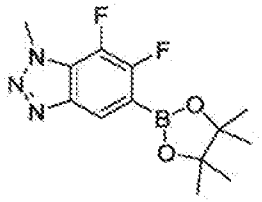
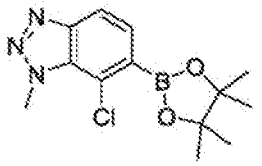
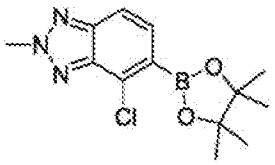
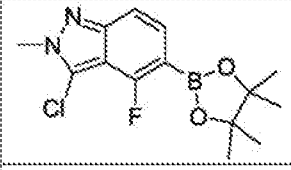
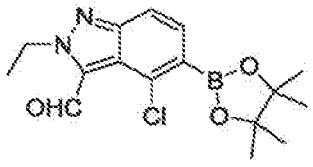
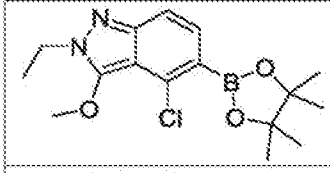
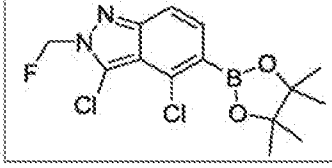
[1359]

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	307, 309	根据上述制备 82，利用 5-溴-4-氯-2-乙基-2*H*-吲唑制备
	2-(叔丁基)-4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	335, 337	根据上述制备 82，利用 5-溴-2-(叔丁基)-4-氯-2*H*-吲唑制备
	2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	259	根据上述制备 82，利用 5-溴-2-甲基-2*H*-吲唑制备
	4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	277	根据上述制备 82，利用 5-溴-4-氯-2-甲基-2*H*-吲唑制备
	6-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	277	根据上述制备 82，利用 5-溴-6-氟-2-甲基-2*H*-吲唑制备
	4-甲氧基-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	289	根据上述制备 82，利用 5-溴-4-甲氧基-2-甲基-2*H*-吲唑制备
	1-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-2-甲基丙烷-2-醇	351, 353	根据上述制备 82，利用 1-(5-溴-4-氯-2*H*-吲唑-2-基)-2-甲基丙烷-2-醇制备

[1360]

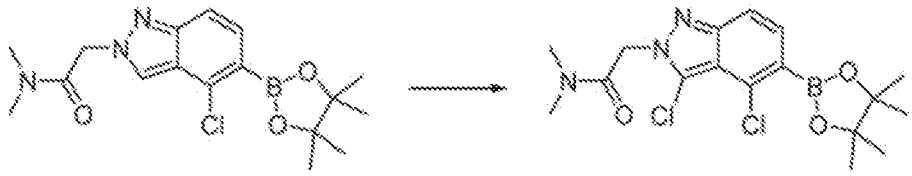
	4-氯-2,7-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	307, 309	根据上述制备 82，利用 5-溴-4-氯-2,7-二甲基-2*H*-吲唑制备
	4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-吲唑	279, 281	根据上述制备 82，利用 5-溴-4-氯-1*H*-吲唑制备
	4-氯-2,3-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	307, 309	根据上述制备 82，利用 5-溴-4-氯-2,3-二甲基-2*H*-吲唑制备
	3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	327, 329	根据上述制备 82，利用 5-溴-3,4-二氯-2-甲基-2*H*-吲唑制备
	2-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基乙酰胺	364, 366	根据上述制备 82，利用 2-(5-溴-4-氯-2*H*-吲唑-2-基)-*N*,*N*-二甲基乙酰胺制备
	7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑	296, 298	根据上述制备 82，利用 6-溴-7-氯苯并[*d*]噻唑制备
	7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑	310, 312	根据上述制备 82，利用 6-溴-7-氯-2-甲基苯并[*d*]噻唑制备
	7-氯-2-乙基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑	324, 326	根据上述制备 82，利用 6-溴-7-氯-2-乙基苯并[*d*]噻唑制备
	2-(7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑-2-基)-*N*,*N*-二甲基乙酰胺	381, 383	根据上述制备 82，利用 2-(6-溴-7-氯苯并[*d*]噻唑-2-基)-*N*,*N*-二甲基乙酰胺制备

[1361]

	7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噁唑	294, 296	根据上述制备82，利用6-溴-7-氯-2-甲基苯并[*d*]噁唑制备
	7-氯-2-乙基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噁唑	308, 310	根据上述制备82，利用6-溴-7-氯-2-乙基苯并[*d*]噁唑制备
	6,7-二氟-1-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-苯并[*d*][1,2,3]三唑	296	根据上述制备82，利用5-溴-6,7-二氟-1-甲基-1*H*-苯并[*d*][1,2,3]三唑制备
	7-氯-1-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-苯并[*d*][1,2,3]三唑	294, 296	根据上述制备82，利用6-溴-7-氯-1-甲基-1*H*-苯并[*d*][1,2,3]三唑制备
	4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-苯并[*d*][1,2,3]三唑	294, 296	根据上述制备82，利用5-溴-4-氯-2-甲基-2*H*-苯并[*d*][1,2,3]三唑制备
	3-氯-4-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	311, 313	根据上述制备82，利用5-溴-3-氯-4-氟-2-甲基-2*H*-吲唑制备
	4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-3-甲醛	335, 337	根据上述制备82，利用5-溴-4-氯-2-乙基-2*H*-吲唑-3-甲醛制备
	4-氯-2-乙基-3-甲氧基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	337, 339	根据上述制备82，利用5-溴-4-氯-2-乙基-3-甲氧基-2*H*-吲唑制备
	3,4-二氯-2-(氟甲基)-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑	345, 347	根据上述制备82，利用5-溴-3,4-二氯-2-(氟甲基)-2*H*-吲唑制备

[1362] 制备83:2-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)-N,N-二甲基乙酰胺

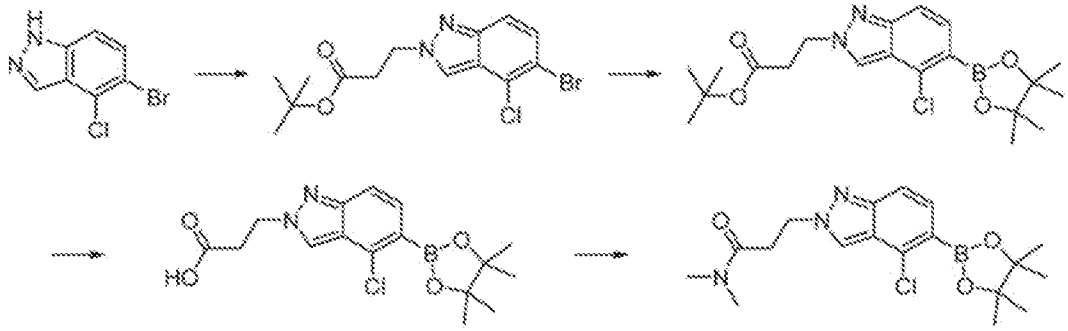
[1363] [化学式117]

[1364] 

[1365] 在RT下，向2-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)-N,N-二甲基乙酰胺(109mg,0.30mmol)的MeCN(2.18mL)溶液中，加入NCS(48mg,0.36mmol)。将混合物在50℃搅拌18h。然后将反应液真空浓缩，并将残留物经硅胶柱色谱纯化(梯度洗脱,0-20%MeOH/$CHCl_3$)，得到标题化合物(71mg)。MS:$[M+H]^+$=398,400.

[1366] 制备84:3-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)-N,N-二甲基丙酰胺

[1367] [化学式118]

[1368] 

[1369] 步骤1

[1370] 在RT下，向5-溴-4-氯-1H-吲唑(1g,4.32mmol)的DMF(10mL)溶液中，加入K_2CO_3(1.19g,8.64mmol)和3-溴丙酸叔丁酯(1.44mL,8.64mmol)。将混合物在100℃搅拌2h，用水稀释，并用EtOAc萃取。将有机层用盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,5-30%EtOAc/己烷)，得到3-(5-溴-4-氯-2H-吲唑-2-基)丙酸叔丁酯(599mg)。MS:$[M+H]^+$=361,363.

[1371] 步骤2

[1372] 将3-(5-溴-4-氯-2H-吲唑-2-基)丙酸叔丁酯(599mg,1.67mmol)、双(频哪醇合)二硼(634mg,2.50mmol)、[1,1′-二(二苯基膦基)二茂铁]合二氯钯(II)与二氯甲烷的络合物(109mg,0.133mmol)和乙酸钾(327g,3.33mmol)混合物的1,4-二氧六环溶液(6mL)脱气，氮气冲洗，并在120℃搅拌5h。将反应物冷却至RT，经硅藻土垫过滤，并用EtOAc洗涤。将滤液真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱,10-30%EtOAc/己烷)纯化，得到3-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)丙酸叔丁酯(553g)。MS:$[M+H]^+$=406,408.

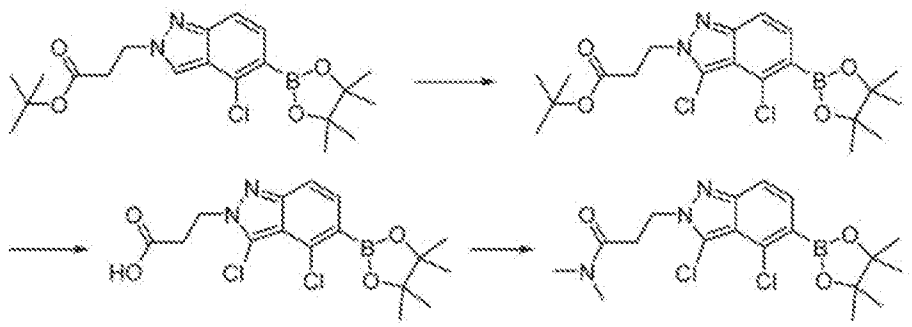
[1373] 步骤3

[1374] 在RT下，向3-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)丙酸叔丁酯(200mg,0.492mmol)的$CHCl_3$(2mL)溶液中，加入TFA(1mL,13.0mmol)。将混合物在60℃搅拌1h，用水稀释，并用$CHCl_3$萃取。将有机层用盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物用THF(4mL)稀释。在RT下，向混合物中加入TEA(0.685mL,4.92mmol)、丙基膦酸酐(1.6M的THF溶液,0.92mL,1.48mmol)和二甲胺(2.0M的THF溶液，

0.98mL,1.97mmol)。将混合物在RT下搅拌30min。然后,将反应液真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/$CHCl_3$),得到标题化合物(116mg)。MS:$[M+H]^+$=378,380.

[1375] 制备85:3,4-二氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

[1376] [化学式119]

[1377] 

[1378] 步骤1

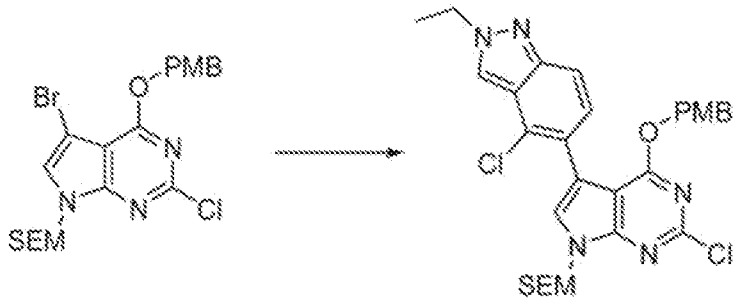
[1379] 在RT下,向3-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)丙酸叔丁酯(250mg,0.615mmol)的MeCN(5mL)溶液中,加入NCS(99mg,0.738mmol)。将混合物在60℃搅拌12h。然后,将反应液真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,10-20%EtOAc/己烷),得到3-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)丙酸叔丁酯(164mg)。MS:$[M+H]^+$=441,443.

[1380] 步骤2

[1381] 在RT下,向3-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑-2-基)丙酸叔丁酯(164mg,0.372mmol)的$CHCl_3$(1mL)溶液中,加入TFA(1mL,13.0mmol)。将混合物在70℃搅拌10min,用水稀释,并用$CHCl_3$萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物用THF(2.58mL)稀释。在RT下,向混合物中加入TEA(0.233mL,1.68mmol)、丙基膦酸酐(1.6M的THF溶液,0.420mL,0.670mmol)和二甲胺(2.0M的THF溶液,0.34mL,0.670mmol)。将混合物在RT下搅拌30min。然后,将反应液真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/$CHCl_3$),得到标题化合物(128mg)。MS:$[M+H]^+$=412,414.

[1382] 制备86:2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶

[1383] [化学式120]

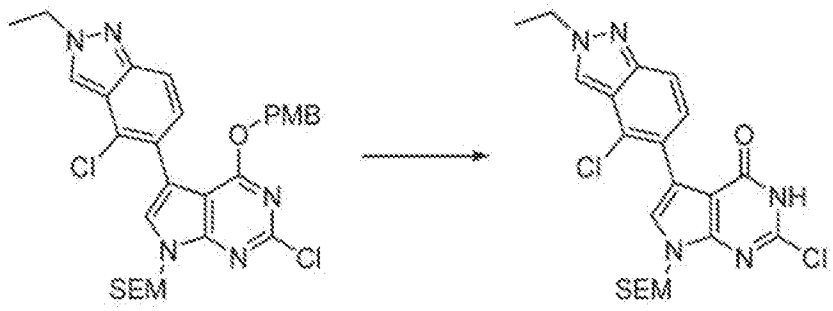
[1384] 

[1385] 将5-溴-2-氯-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-

7H-吡咯并[2,3-d]嘧啶(2.68g,5.37mmol)、4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(2.47g,6.45mmol)、K_3PO_4(2.28g,10.7mmol)、[1,1′-二(二苯基膦基)二茂铁]合二氯钯(II)与二氯甲烷的络合物(0.439g,0.537mmol)、1,4-二氧六环(53.6mL)和水(5.36mL)的混合物在120℃搅拌1h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(1.7g).MS:$[M+H]^+$=598,600.

[1386] 制备87:2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

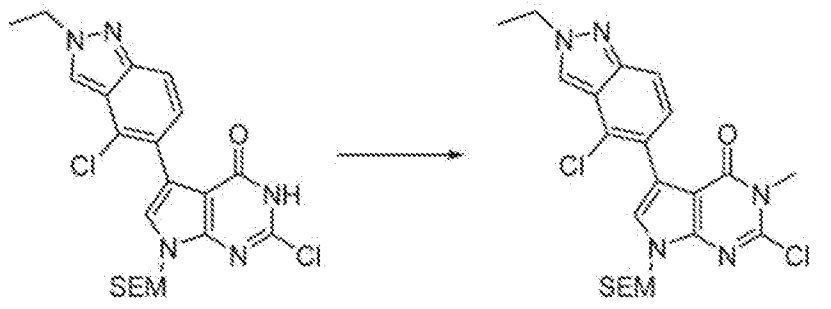
[1387] [化学式121]

[1388] 

[1389] 在RT下,向2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶(1.7g,2.84mmol)的DCM(32.3mL)溶液中,加入2,3-二氯-5,6-二氰基-p-苯醌(1.93g,8.52mmol)和水(1.7mL)。将混合物在RT搅拌过夜。在RT下,加入$CHCl_3$和sat.$NaHCO_3$。将混合物经硅藻土垫过滤,并用$CHCl_3$和水冲洗。将滤液用$CHCl_3$萃取,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(0.713g)。MS:$[M+H]^+$=478,480.

[1390] 制备88:2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[1391] [化学式122]

[1392] 

[1393] 在RT下,向2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(0.713g,1.49mmol)的DMF(7.13mL)溶液中,加入K_2CO_3(0.412g,2.98mmol)和碘甲烷(0.186mL,2.98mmol)。将混合物在RT搅拌30min,倒入水中,并用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(0.717g)。MS:$[M+H]^+$=492,494.

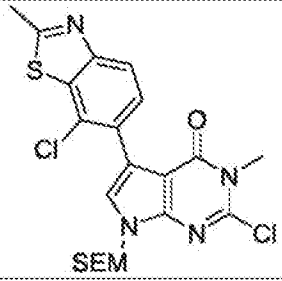
[1394] 利用与制备86-88中所述类似的方法,从适当的取代硼酸芳基酯(采用下文所示的

任何显著变化，如上所述合成)开始，制备下表2的化合物。

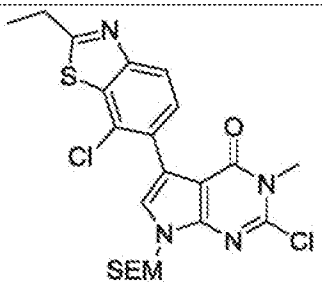
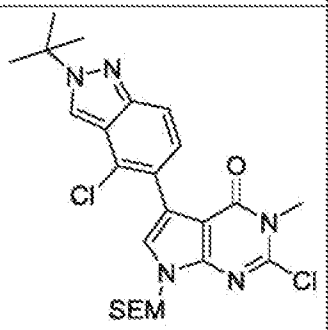
[1395] [表2]

[1396] 表2

[1397]

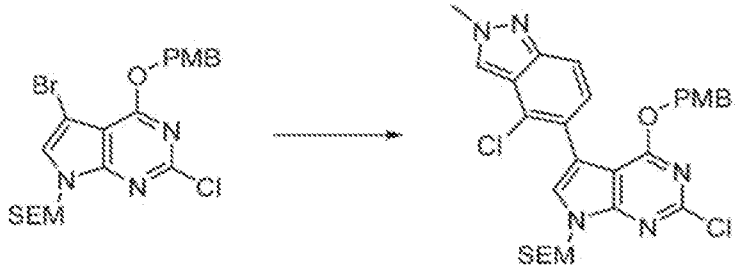
化合物	化合物名称	MS: [M+H]+ m/z	方法
	2-氯-5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	495, 497	根据上述制备86，利用 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

[1398]

	2-氯-5-(7-氯-2-乙基苯并[*d*]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	509, 511	根据上述制备86，利用 7-氯-2-乙基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	5-(2-(叔丁基)-4-氯-2*H*-吲唑-5-基)-2-氯-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	520, 522	根据上述制备86，利用 2-(叔丁基)-4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

[1399] 制备89：2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶

[1400] [化学式123]

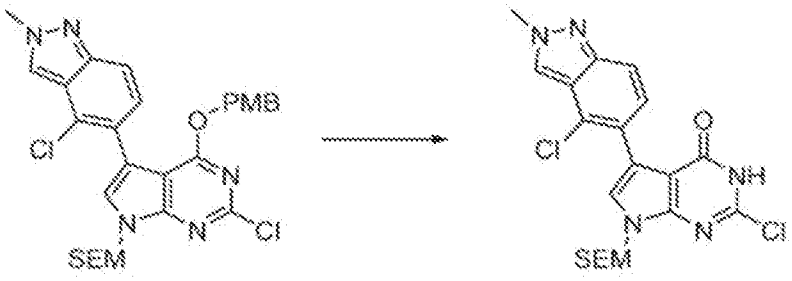
[1401] 

[1402] 利用2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶的类似制备方法，由4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑制备，得到标题化合物。MS：[M+

H]$^+$=584,586.

[1403] 制备90:2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

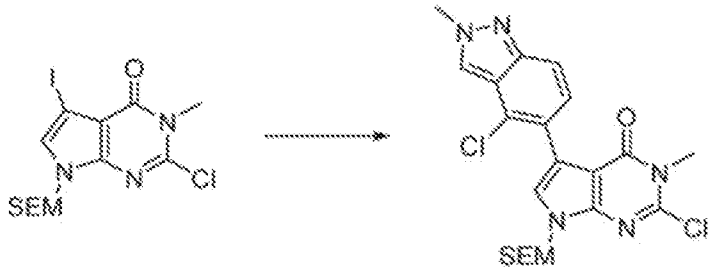
[1404] [化学式124]

[1405] 

[1406] 利用2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮的类似制备方法,由2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-4-((4-甲氧基苄基)氧基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶制备,得到标题化合物。MS:[M+H]$^+$=464,466.

[1407] 制备91:2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

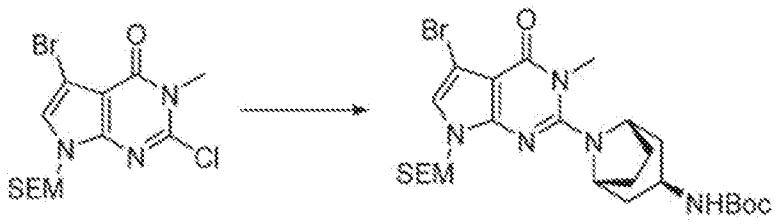
[1408] [化学式125]

[1409] 

[1410] 将2-氯-5-碘-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(150mg,0.341mmol)、4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(171mg,0.409mmol)、K_2CO_3(110mg,0.798mmol)、[1,1′-二(二苯基膦基)二茂铁]合二氯钯(II)与二氯甲烷的络合物(27.8mg,0.0341mmol)、1,4-二氧六环(2.5mL)和水(0.5mL)的混合物在70℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(90mg)。MS:[M+H]$^+$=478,480.

[1411] 制备92:(endo-8-(5-溴-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯

[1412] [化学式126]

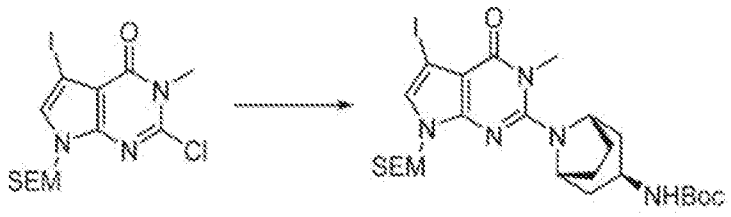
[1413] 

[1414] 将5-溴-2-氯-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯

并[2,3-d]嘧啶-4-酮(0.700g,1,.78mmol)、endo-(8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯(1.21g,5.34mmol)、DIPEA(3.10mL,17.8mmol)和NMP(1mL)的混合物在120℃搅拌30min,并冷却至RT。加入水,并将混合物用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物。MS:$[M+H]^+$=581,583.

[1415] 制备93:(endo-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯

[1416] [化学式127]

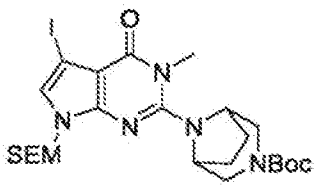
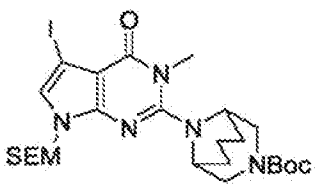
[1417] 

[1418] 将5-碘-2-氯-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(2.00g,4.55mmol)、endo-(8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯(1.24g,5.46mmol)、DIPEA(1.58mL,9.10mmol)和NMP(10mL)的混合物在120℃搅拌8h,并冷却至RT。加入水,将混合物用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-80%EtOAc/己烷),得到标题化合物(2.41g)。MS:$[M+H]^+$=630.

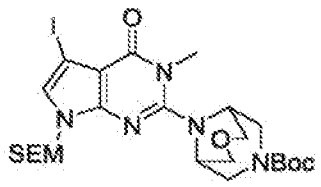
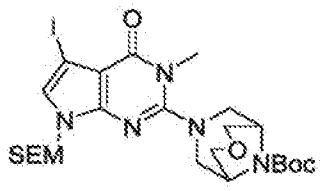
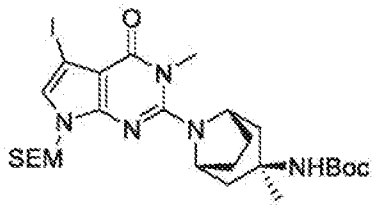
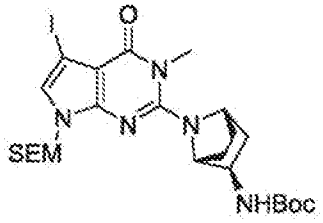
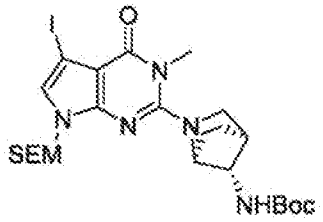
[1419] 利用与制备93中所述类似的方法,从适当的取代胺开始,制备下表3的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1420] 表3

[1421]

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	616	根据上述制备93,利用3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯制备
	9-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	630	根据上述制备93,利用3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯制备

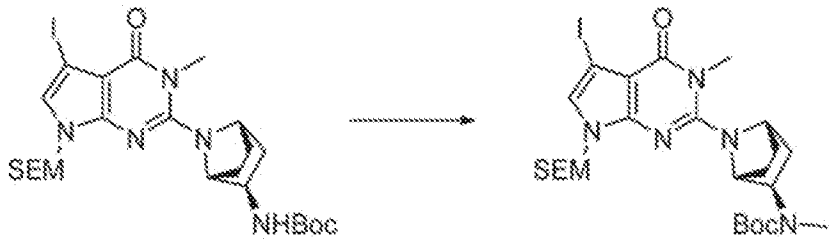
[1422]

	9-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-甲酸叔丁酯	632	根据上述制备93，利用3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-甲酸叔丁酯制备
	7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	632	根据上述制备93，利用3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯制备
	(*endo*-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	644	根据上述制备93，利用(*endo*-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	616	根据上述制备93，利用((1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	*rac*-((1*S*,4*S*,7*S*)-2-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	616	根据上述制备93，利用*rac*-((1*S*,4*S*,7*S*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备

[1423] 制备94：((1R,2R,4S)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基

甲酸叔丁酯

[1424] [化学式128]

[1425] 

[1426] 在0℃,向((1R,2R,4S)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(500mg,0.812mmol)的THF(15mL)溶液中,加入NaH(60%,在矿物油中,64.9mg,1.62mmol)。将混合物在0℃搅拌15min。在0℃加入碘甲烷(0.101mL,1.62mmol)。将混合物在RT搅拌过夜,倒入sat.NH_4Cl中,并用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,30-50%EtOAc/己烷),得到标题化合物(493mg)。MS:$[M+H]^+$=630.

[1427] 制备95:3-溴-4,6-二氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶

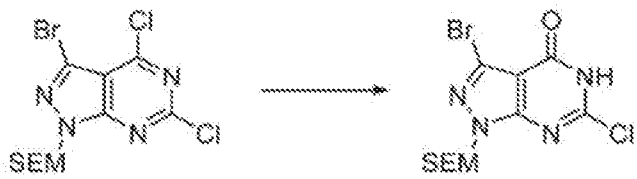
[1428] [化学式129]

[1429] 

[1430] 在RT下,向3-溴-4,6-二氯-1H-吡唑并[3,4-d]嘧啶(1.00g,3.73mmol)和DIPEA(1.95mL,11.2mmol)的DCM(10mL)混合物中,加入SEMCl(0.794mL,4.47mmol)。将混合物在RT搅拌1h,并经硅胶柱色谱(梯度洗脱,0-15%EtOAc/己烷)纯化,得到标题化合物(1.12g)。MS:$[M+H]^+$=397,399.

[1431] 制备96:3-溴-6-氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

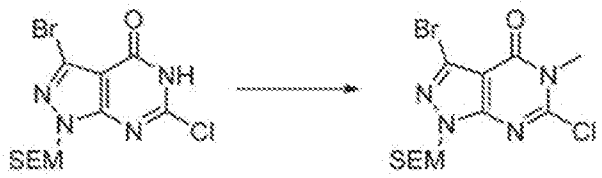
[1432] [化学式130]

[1433] 

[1434] 在RT下,向3-溴-4,6-二氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶(1.12g,2.81mmol)的THF(10mL)溶液中,加入5M NaOH(5.06mL,25.3mmol)。将混合物在RT搅拌7h,用2-甲基四氢呋喃稀释,用6M HCl酸化,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩,得到标题化合物(1.05g)。MS:$[M+H]^+$=379,381.

[1435] 制备97:3-溴-6-氯-5-甲基-1-((2-(三甲基硅烷基)乙氧基)甲基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

[1436] [化学式131]

[1437] 

[1438] 在RT下，向3-溴-6-氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(1.05g,2.77mmol)和K_2CO_3(0.764g,5.53mmol)混合物的DMF(10mL)溶液中，加入碘甲烷(0.344mL,5.53mmol)。将混合物在RT搅拌30min，用EtOAc稀释，用水和盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-50%EtOAc/己烷)，得到标题化合物(0.780g)。MS:$[M+H]^+$=393,395.

[1439] 制备98:3-溴-4,6-二氯-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[3,4-d]嘧啶

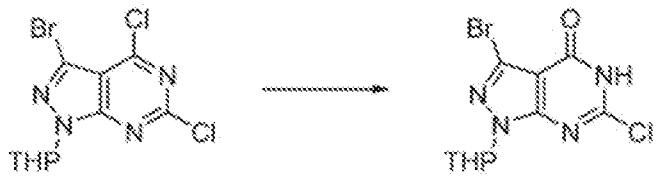
[1440] [化学式132]

[1441] 

[1442] 将3-溴-4,6-二氯-1H-吡唑并[3,4-d]嘧啶(4.55g,17.0mmol)、3,4-二氢-2H-吡喃(4.62mL,51.0mmol)和p-甲苯磺酸一水合物(0.646g,3.40mmol)溶解于THF(74mL)中，并在70℃加热2h。真空除去溶剂，并将固体残留物在40℃于Et_2O(30mL)中研磨2h。将得到的混悬液缓慢冷却至室温。经过滤收集固体物，并用Et_2O洗涤。将所述湿固体在真空干燥箱中于50℃干燥，得到标题化合物(4.8g)。MS:$[M+H]^+$=353,355.

[1443] 制备99:3-溴-6-氯-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

[1444] [化学式133]

[1445] 

[1446] 在0℃，向3-溴-4,6-二氯-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[3,4-d]嘧啶(5.42g,15.4mmol)的THF(54mL)溶液中，加入5M NaOH(27mL)。将混合物在RT搅拌过夜。将混合物用2-甲基四氢呋喃稀释，用6M HCl酸化，并用2-甲基四氢呋喃萃取。将有机层用盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩，得到标题化合物(5.14g)。MS:$[M+H]^+$=333,335.

[1447] 制备100:3-溴-6-氯-5-甲基-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

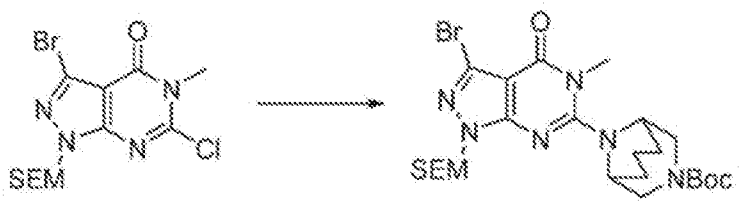
[1448] [化学式134]

[1449] 

[1450] 在RT下，向3-溴-6-氯-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(12.8g,38.4mmol)和K_2CO_3(10.6g,76.7mmol)混合物的NMP(256mL)溶液中，加入碘甲烷(4.78mL,76.7mmol)。将混合物在RT搅拌1h，用EtOAc稀释，用水(x2)和盐水洗涤，经Na_2SO_4干燥，过滤，然后真空浓缩，得到标题化合物(9.08g)。MS:$[M+H]^+$=347,349.

[1451] 制备101:9-(3-溴-5-甲基-4-氧代-1-((2-(三甲基硅烷基)乙氧基)甲基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯

[1452] [化学式135]

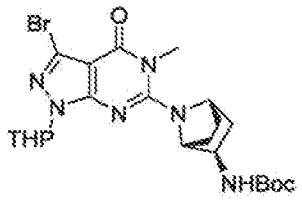
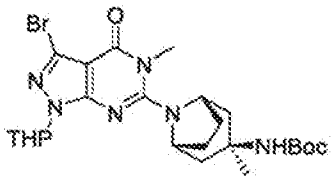
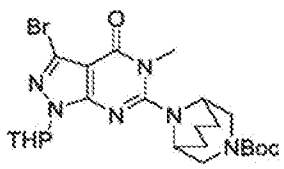
[1453] 

[1454] 将3-溴-6-氯-5-甲基-1-((2-(三甲基硅烷基)乙氧基)甲基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(780mg,1.981mmol)、3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯(0.89g,3.9620mmol)、DIPEA(1.72mL,9.90mmol)和NMP(8mL)的混合物在120℃搅拌5h，冷却至RT，倒入水中，并用EtOAc萃取。将有机层用水和盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-100%EtOAc/己烷)纯化，得到标题化合物(1.10g)。MS:$[M+H]^+$=583,585.

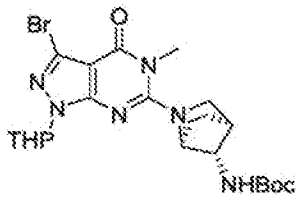
[1455] 利用与制备101中所述类似的方法，从适当的取代胺开始，制备下表4的化合物(如上所述合成，具有下文所示的任何显著变化)。

[1456] 表4

[1457]

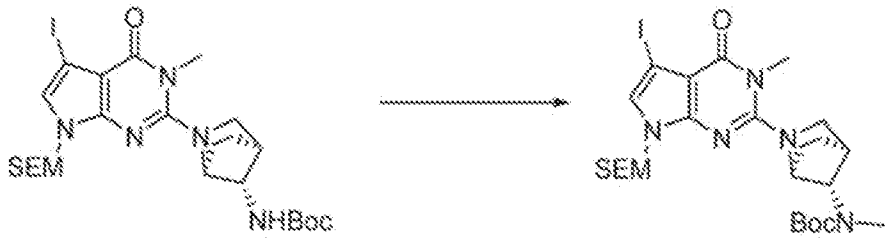
化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	523, 525	根据上述制备101，利用3-溴-6-氯-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和((1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	(*endo*-8-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	551, 553	根据上述制备101，利用3-溴-6-氯-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(*endo*-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	9-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	537, 539	根据上述制备101，利用3-溴-6-氯-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯制备

[1458]

	*rac*-((1*S*,4*S*,7*S*)-2-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	523, 525	根据上述制备101，利用3-溴-6-氯-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 *rac*-((1*S*,4*S*,7*S*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备

[1459] 制备102：rac-((1S,4S,7S)-2-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)(甲基)氨基甲酸叔丁酯

[1460] [化学式136]

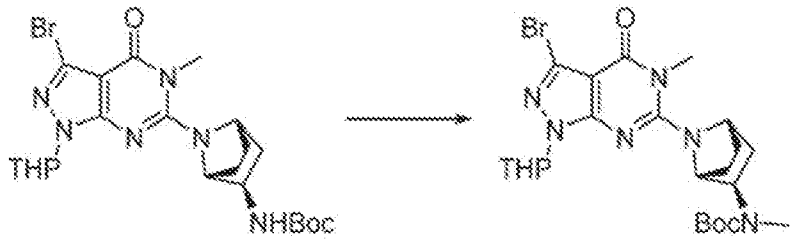
[1461] 

[1462] 利用制备94中所述的类似方法，由rac-((1S,4S,7S)-2-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备rac-((1S,4S,7S)-2-(5-碘-3-甲基-4-氧代-7-

((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)(甲基)氨基甲酸叔丁酯。MS:$[M+H]^+$=630.

[1463] 制备103:((1R,2R,4S)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯

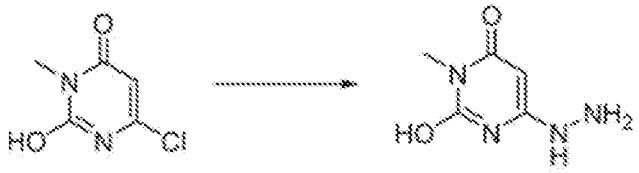
[1464] [化学式137]

[1465] 

[1466] 在0℃,向((1R,2R,4S)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(1.5g,2.90mmol)的THF(30mL)溶液中,加入氢化钠(60%,在矿物油中,230mg,5.70mmol)。将混合物在0℃搅拌15min。在0℃加入碘甲烷(0.360mL,5.70mmol)。将混合物在RT下搅拌过夜,倒入Sat.NH_4Cl中,并用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,20-50%EtOAc/己烷),得到标题化合物(1.37g)。MS:$[M+H]^+$=537,539.

[1467] 制备104:6-肼基-2-羟基-3-甲基-3,4-二氢嘧啶-4-酮

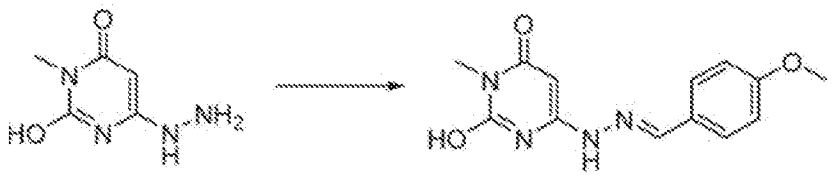
[1468] [化学式138]

[1469] 

[1470] 在室温下,向6-氯-2-羟基-3-甲基嘧啶-4(3H)-酮(27.15g,169mmol)的EtOH(250mL)混悬液中,加入肼-H_2O(49.7mL,507mmol)。将得到的混悬液在80℃搅拌18h。将反应物冷却至室温,然后在0℃于冰浴中保持1h。收集灰白色沉淀,并用冷EtOH(2x100mL)冲洗。MS:$[M+H]^+$=157.

[1471] 制备105:2-羟基-6-[(E)-2-[(4-甲氧基苯基)亚甲基]肼-1-基]-3-甲基-3,4-二氢嘧啶-4-酮

[1472] [化学式139]

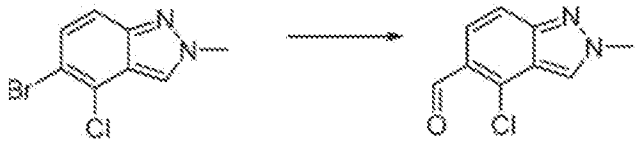
[1473] 

[1474] 将4-甲氧基苯甲醛(11.68mL,96mmol)缓慢加入6-肼基-2-羟基-3-甲基-3,4-二氢嘧啶-4-酮(10g,64.0mmol)的甲醇(250mL)混悬液中,并将混合物搅拌3小时,然后过滤。将沉淀用MeOH(3x100mL)洗涤后,转移至烧瓶中,并与3:1DCM/EtOAc(400mL)一起搅拌过夜。将

沉淀过滤，并将其在烧结物(sinter)上干燥，得到标题化合物(9.56g，31.7mmol，产率49.5%)，作为无色固体物。MS：$[M+H]^+$＝275.

[1475] 制备106：4-氯-2-甲基-2H-吲唑-5-甲醛

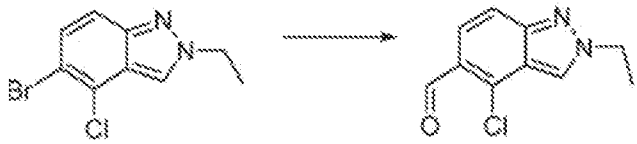
[1476] [化学式140]

[1477] 

[1478] 在氮气气氛下，将5-溴-4-氯-2-甲基-2H-吲唑(8.78g，35.8mmol)的THF(60mL)溶液历经10分钟缓慢加入含i-PrMgCl·LiCl(55mL，71.5mmol)的三颈瓶中。将反应物在30℃搅拌4小时后，缓慢加入DMF(13.84mL，179mmol)。将反应物在30℃搅拌1小时后，历经10分钟加入MeOH(40mL)。将混合物在室温静置过夜。将混合物真空浓缩，并将残留物溶于EtOAc(150mL)、DCM(10mL)和MeOH(10mL)的混合物中。将所述溶液用水(100mL)和盐水(100mL)洗涤。分离有机相，并将水相再用EtOAc(100mL)萃取。然后，将合并的有机相用水(2x100mL)洗涤，然后干燥($MgSO_4$)，过滤，并浓缩，得到粗品。将其与4:1异己烷/EtOAc(4x25mL)一起研磨，并过滤固体物。然后，将其再与4:1异己烷/EtOAc(2x25mL)一起研磨，得到4-氯-2-甲基-2H-吲唑-5-甲醛(1.17g，5.89mmol，产率16.48%)，作为浅棕色固体物。MS：$[M+H]^+$＝195.

[1479] 制备107：4-氯-2-乙基-2H-吲唑-5-甲醛

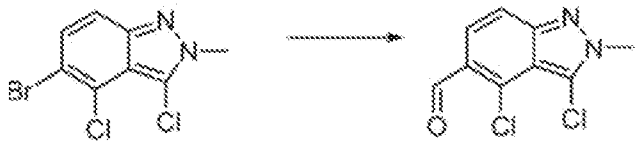
[1480] [化学式141]

[1481] 

[1482] 利用与制备106中所述类似的方法，由5-溴-4-氯-2-乙基-2H-吲唑制备4-氯-2-乙基-2H-吲唑-5-甲醛。MS：$[M+H]^+$＝209.

[1483] 制备108：3,4-二氯-2-甲基-2H-吲唑-5-甲醛

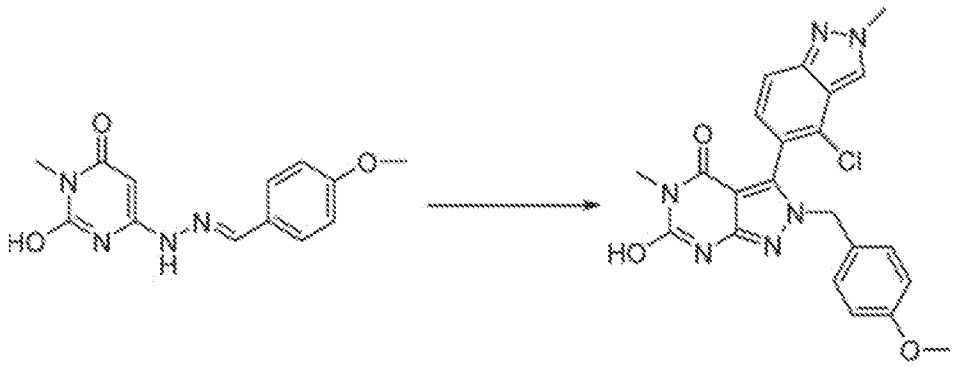
[1484] [化学式142]

[1485] 

[1486] 利用与制备106中所述类似的方法，由5-溴-3,4-二氯-2-甲基-2H-吲唑制备3,4-二氯-2-甲基-2H-吲唑-5-甲醛。MS：$[M+H]^+$＝229.

[1487] 制备109：3-(4-氯-2-甲基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

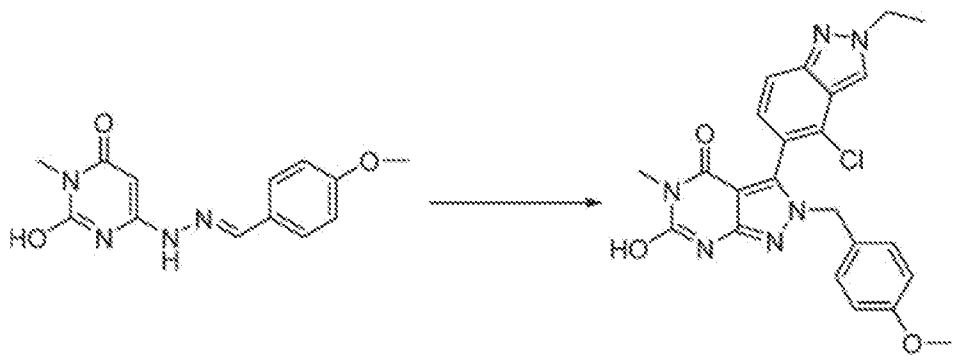
[1488] [化学式143]

[1489] 

[1490] 将2-羟基-6-[(E)-2-[(4-甲氧基苯基)亚甲基]肼-1-基]-3-甲基-3,4-二氢嘧啶-4-酮(2.013g,7.34mmol)和4-氯-2-甲基-2H-吲唑-5-甲醛(1.5g,7.71mmol)在DMF/IPA(2:1,55mL)中的混悬液于室温搅拌。一次性加入哌啶(0.763mL,7.71mmol),并将反应物在35℃搅拌过夜。将反应混合物倒入水(200mL)中,并用EtOAc(2x100mL)和10%MeOH的DCM溶液(2x100mL)萃取。将合并的有机相干燥($MgSO_4$)、过滤,并浓缩,得到粗品。将粗产物经硅胶色谱(80g柱,0-3%MeOH/DCM)纯化,得到标题化合物(932mg,2.0mmol,产率27.3%),作为淡橙色固体。MS:$[M+H]^+$=451.^{1}H NMR(500MHz,DMSO-d_6)δ:11.74(s,1H),8.65(s,1H),7.70(dd,J=8.8,1.0Hz,1H),7.23(d,J=8.8Hz,1H),6.94(d,J=8.7Hz,2H),6.80(d,J=8.7Hz,2H),5.08(d,J=15.1Hz,1H),4.99(d,J=15.1Hz,1H),4.25(s,3H),3.69(s,3H),3.10(s,3H).

[1491] 制备110:3-(4-氯-2-乙基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

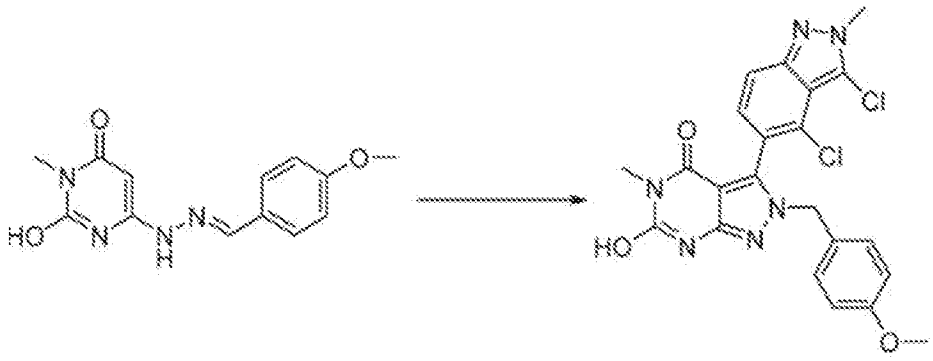
[1492] [化学式144]

[1493] 

[1494] 利用制备109所述的类似方法,由2-羟基-6-[(E)-2-[(4-甲氧基苯基)亚甲基]肼-1-基]-3-甲基-3,4-二氢嘧啶-4-酮和4-氯-2-乙基-2H-吲唑-5-甲醛开始,制备3-(4-氯-2-乙基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮。MS:$[M+H]^+$=465.^{1}H NMR(500MHz,DMSO-d_6)δ:11.73(s,1H),8.70(s,1H),7.71(dd,J=8.8,0.7Hz,1H),7.23(d,J=8.8Hz,1H),6.96(d,J=8.7Hz,2H),6.81(d,J=8.7Hz,2H),5.09(d,J=15.1Hz,1H),5.00(d,J=15.1Hz,1H),4.54(q,J=7.3Hz,2H),3.69(s,3H),3.10(s,3H),1.55(t,J=7.3Hz,3H).

[1495] 制备111:3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

[1496] [化学式145]

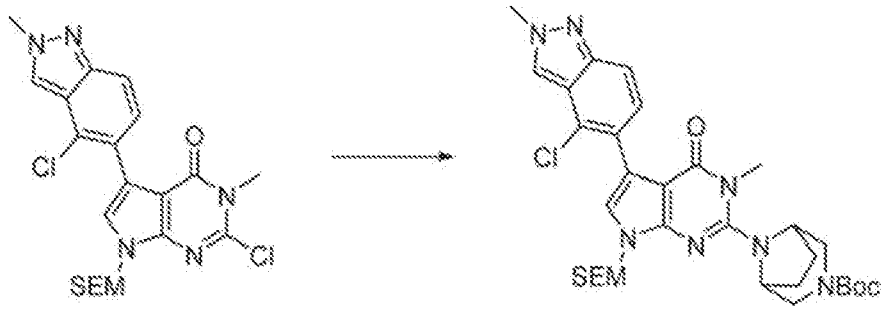
[1497] 

[1498] 利用制备109所述的类似方法，由2-羟基-6-[(E)-2-[(4-甲氧基苯基)亚甲基]肼-1-基]-3-甲基-3,4-二氢嘧啶-4-酮和3,4-二氯-2-甲基-2H-吲唑-5-甲醛开始，制备3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮。MS:$[M+H]^+$=485.

[1499] ^1H NMR(500MHz,DMSO-d_6)δ:11.76(s,1H),7.72(d,J=8.8Hz,1H),7.26(d,J=8.8Hz,1H),6.96(d,J=8.7Hz,2H),6.81(d,J=8.7Hz,2H),5.08(d,J=15.1Hz,1H),5.01(d,J=15.1Hz,1H),4.19(s,3H),3.69(s,3H),3.10(s,3H).

[1500] 通用方法1:8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯

[1501] [化学式146]

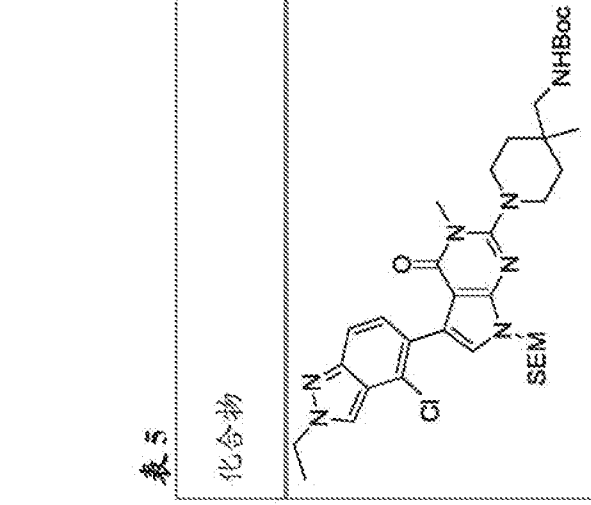
[1502] 

[1503] 将2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(100mg,0.209mmol)、3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯(88.7mg,0.418mmol)、DIPEA(0.109mL,0.627mmol)和NMP(2mL)的混合物在120℃搅拌8h，冷却至RT，用EtOAc稀释，用水和盐水洗涤，经无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-100%EtOAc/己烷)纯化，得到标题化合物(140mg)。MS:$[M+H]^+$=654,656.

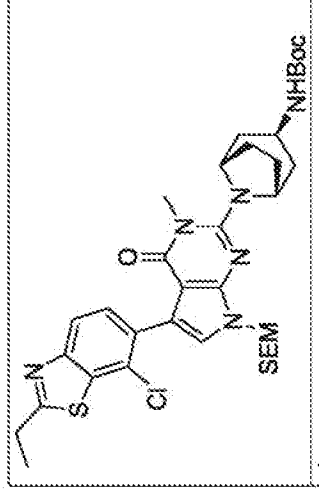
[1504] 利用与通用方法1中所述的类似方法，从适当取代保护的吡咯并嘧啶酮，和不同胺开始，制备下表5的化合物(如上所述合成，具有下文所示的任何显著变化)。

[1505]

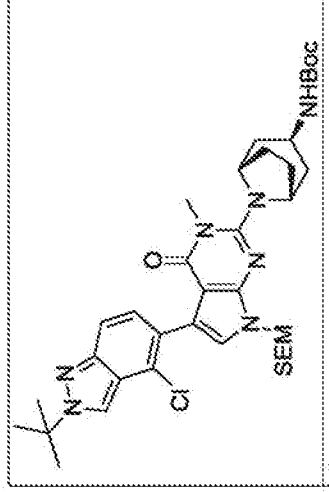
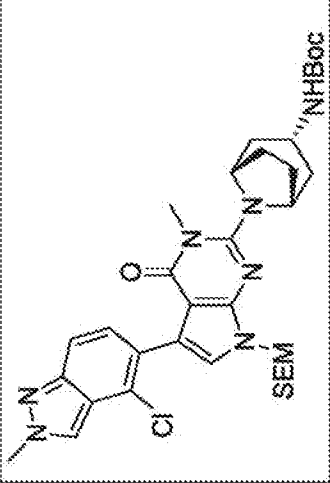
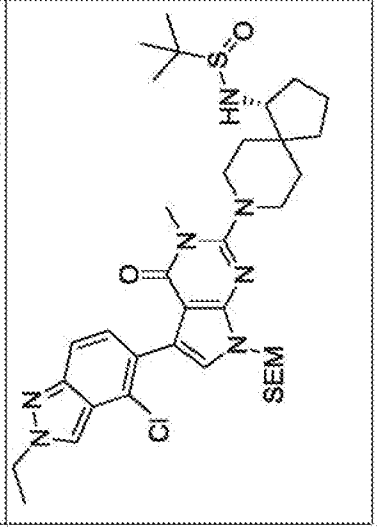
表5

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	((1-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-甲基哌啶-4-基)甲基)氨基甲酸叔丁酯	684, 686	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((4-甲基哌啶-4-基)甲基)氨基甲酸叔丁酯制备
	(1-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-甲基哌啶-4-基)氨基甲酸叔丁酯	670, 672	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(4-甲基哌啶-4-基)氨基甲酸叔丁酯制备
	(*endo*-8-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	682, 684	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备

[1506]

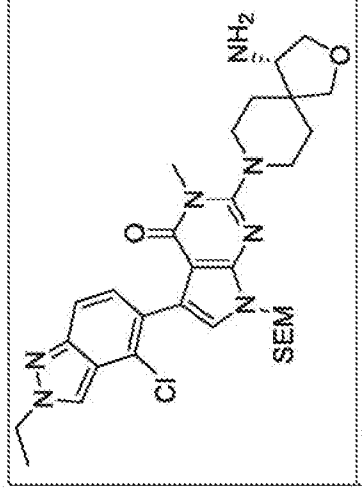
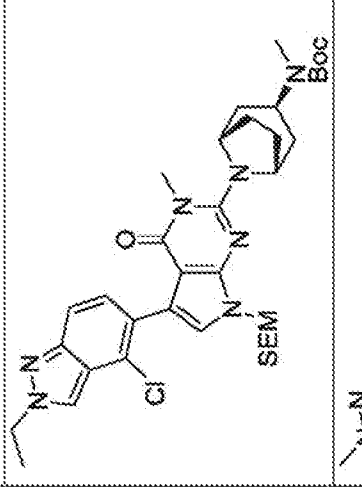
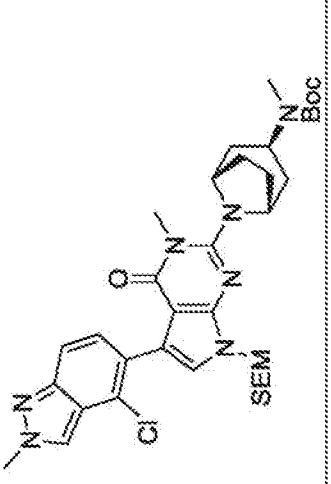
	(*endo*-8-(5-(7-氯-2-乙基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	699, 701	根据上述通用方法1，利用2-氯-5-(7-氯-2-乙基苯并[*d*]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	(*endo*-8-(5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	685, 687	根据上述通用方法1，利用2-氯-5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	(*endo*-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	668, 670	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备

[1507]

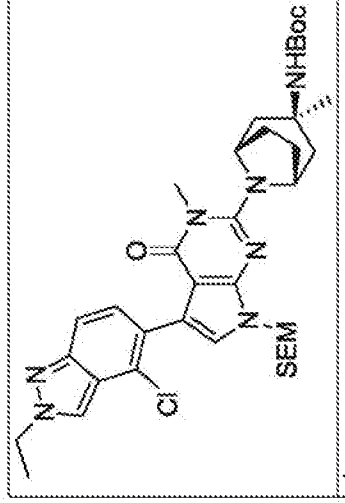
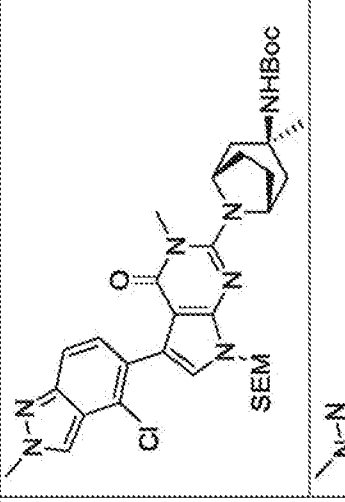
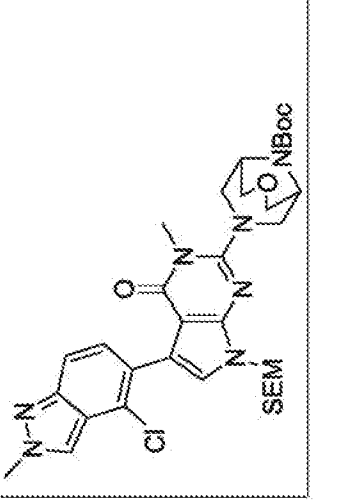
	(*endo*-8-(5-(2-(叔丁基)-4-氯-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	710, 712
	(*exo*-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	668, 670
	*N*-((*R*)-8-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂螺[4.5]癸烷-1-基)-2-甲基丙烷-2-亚磺酰胺	714, 716

根据上述通用方法 1，利用 5-(2-(叔丁基)-4-氯-2*H*-吲唑-5-基)-2-氯-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备	
根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*exo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备	
根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 2-甲基-*N*-((*R*)-8-氮杂螺[4.5]癸烷-1-基)丙烷-2-亚磺酰胺制备	

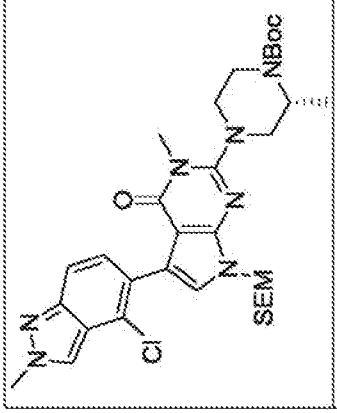
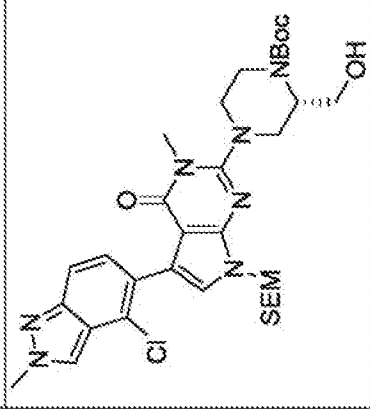
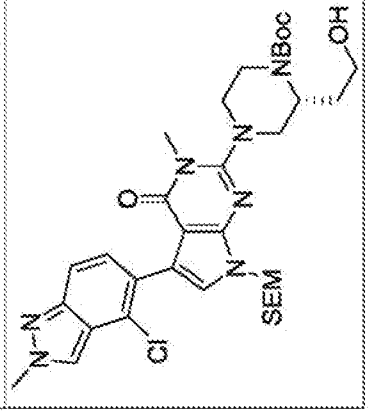
[1508]

	(*S*)-2-(4-氯基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	612, 614	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备
	(*endo*-8-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)(甲基)氨基甲酸叔丁酯	696, 698	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)(甲基)氨基甲酸叔丁酯制备
	(*endo*-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)(甲基)氨基甲酸叔丁酯	682, 684	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)(甲基)氨基甲酸叔丁酯制备

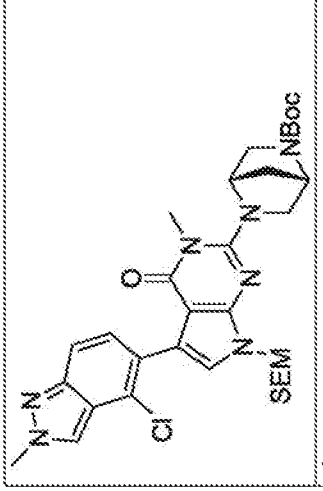
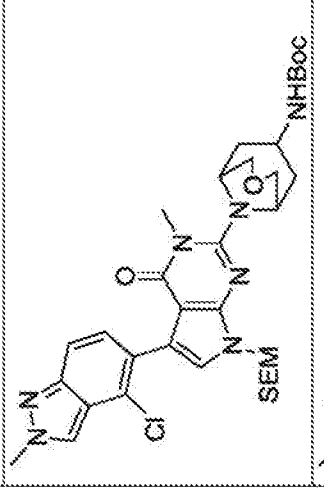
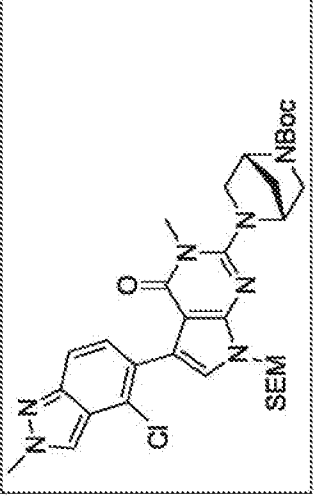
[1509]

	(*endo*-8-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	696, 698	根据上述通用方法1，利用2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	(*endo*-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	682, 684	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	670, 672	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯制备

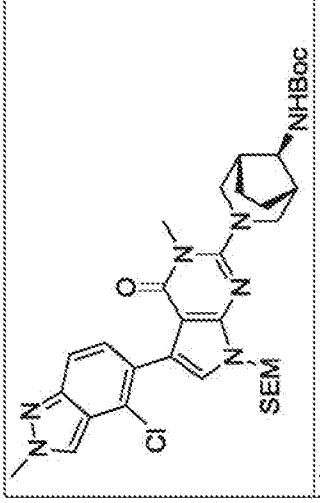
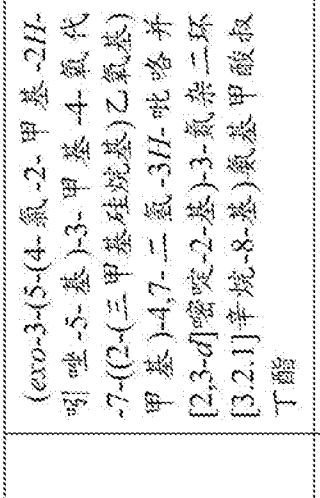
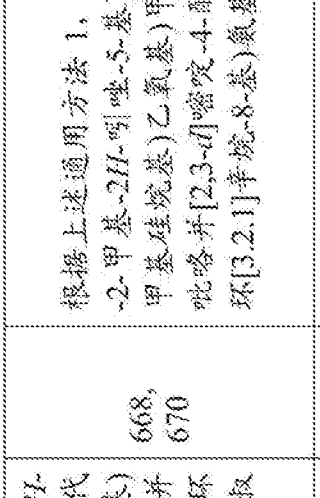
[1510]

	(*R*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-甲基哌嗪-1-甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-2-甲基哌嗪-1-甲酸叔丁酯制备。
	(*S*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-(羟基甲基)哌嗪-1-甲酸叔丁酯	658, 660	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-2-(羟基甲基)哌嗪-1-甲酸叔丁酯制备。
	(*R*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-(2-羟基乙基)哌嗪-1-甲酸叔丁酯	672, 674	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-2-(2-羟基乙基)哌嗪-1-甲酸叔丁酯制备。

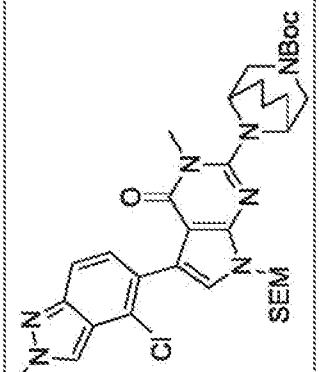
[1511]

	(1*S*,4*S*)-5-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2,5-二氮杂二环[2.2.1]庚烷-2-甲酸叔丁酯	640, 642	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(1*S*,4*S*)-2,5-二氮杂二环[2.2.1]庚烷-2-甲酸叔丁酯制备
	(9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-9-氮杂二环[3.3.1]壬烷-7-基)氨基甲酸叔丁酯	684, 686	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(3-氧杂-9-氮杂二环[3.3.1]壬烷-7-基)氨基甲酸叔丁酯制备
	(1*R*,4*R*)-5-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2,5-二氮杂二环[2.2.1]庚烷-2-甲酸叔丁酯	640, 642	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(1*R*,4*R*)-2,5-二氮杂二环[2.2.1]庚烷-2-甲酸叔丁酯制备

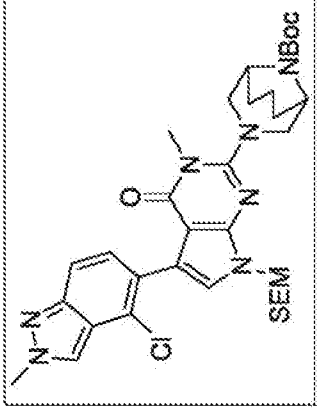
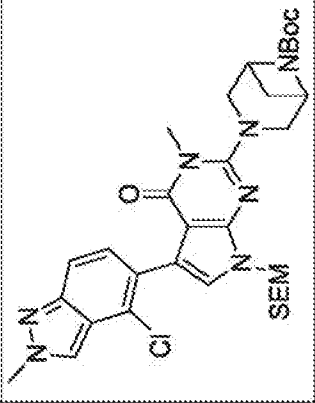
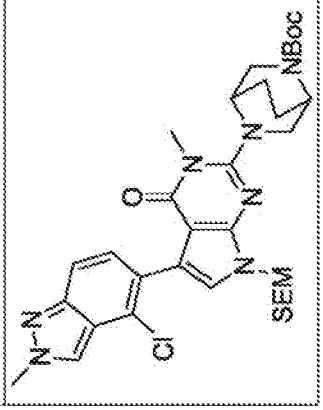
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	(*exo*-3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.2.1]辛烷-8-基)氨基甲酸叔丁酯	668, 670	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*exo*-3-氮杂二环[3.2.1]辛烷-8-基)氨基甲酸叔丁酯制备
	(*endo*-3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.2.1]辛烷-8-基)氨基甲酸叔丁酯	668, 670	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-3-氮杂二环[3.2.1]辛烷-8-基)氨基甲酸叔丁酯制备
	*rac*-((1*S*,2*R*,3*R*,5*R*)-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯	720, 722	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *rac*-((1*S*,2*S*,3*R*,5*R*)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯盐酸盐制备

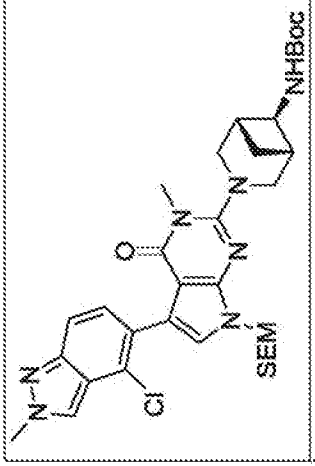
[1513]

	9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	668, 670	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯制备
	3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯	654, 656	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,8-二氮杂二环[3.2.1]辛烷-8-甲酸叔丁酯制备
	6-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,6-二氮杂二环[3.1.1]庚烷-3-甲酸叔丁酯	640, 642	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,6-二氮杂二环[3.1.1]庚烷-3-甲酸叔丁酯制备

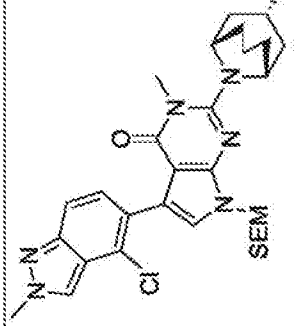
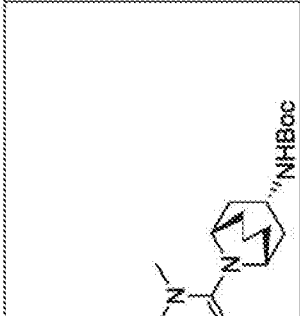
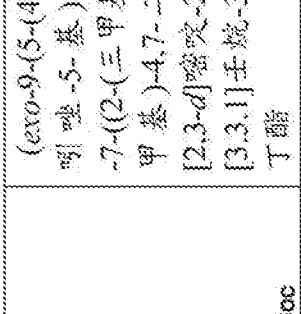
[1514]

	3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	668, 670	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯制备
	3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,6-二氮杂二环[3.1.1]庚烷-6-甲酸叔丁酯	640, 642	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,6-二氮杂二环[3.1.1]庚烷-6-甲酸叔丁酯制备
	5-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2,5-二氮杂二环[2.2.2]辛烷-2-甲酸叔丁酯	654, 656	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 2,5-二氮杂二环[2.2.2]辛烷-2-甲酸叔丁酯制备

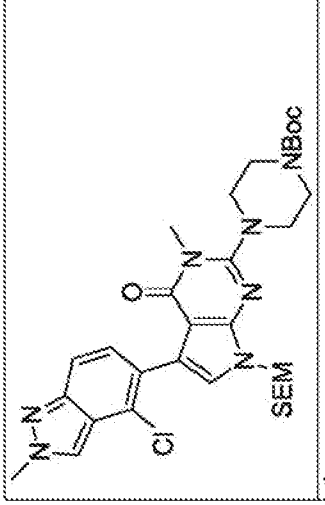
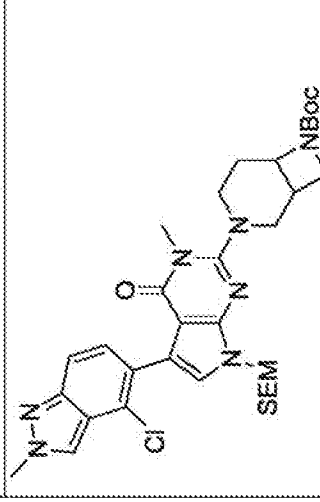
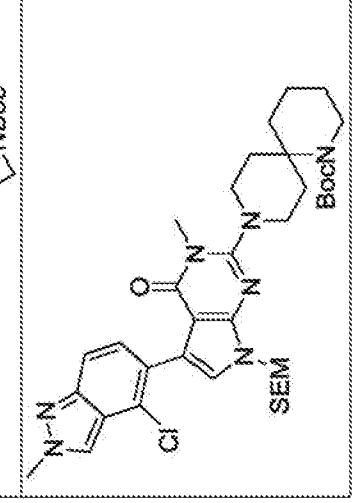
[1515]

	(*exo*-3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.1.1]庚烷-6-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*exo*-3-氮杂二环[3.1.1]庚烷-6-基)氨基甲酸叔丁酯制备。
	(*endo*-3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.1.1]庚烷-6-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-3-氮杂二环[3.1.1]庚烷-6-基)氨基甲酸叔丁酯制备
	(2-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-5-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(2-氮杂二环[2.2.1]庚烷-5-基)氨基甲酸叔丁酯制备

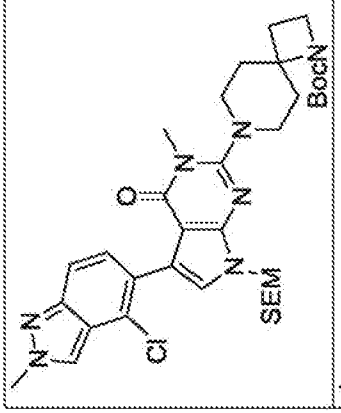
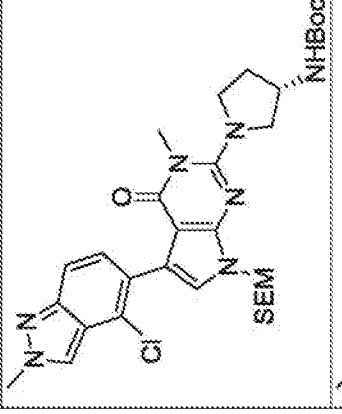
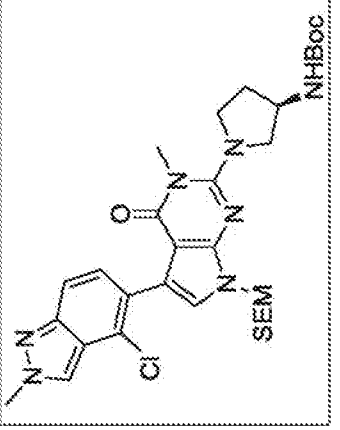
[1516]

	(*exo*-9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-9-氮杂二环[3.3.1]壬烷-3-基)氨基甲酸叔丁酯	682, 684	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*exo*-9-氮杂二环[3.3.1]壬烷-3-基)氨基甲酸叔丁酯制备。
	(*endo*-9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-9-氮杂二环[3.3.1]壬烷-3-基)氨基甲酸叔丁酯	682, 684	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*endo*-9-氮杂二环[3.3.1]壬烷-3-基)氨基甲酸叔丁酯制备。
	8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-1,8-二氮杂螺[4.5]癸烷-1-甲酸叔丁酯	682, 684	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和1,8-二氮杂螺[4.5]癸烷-1-甲酸叔丁酯制备。

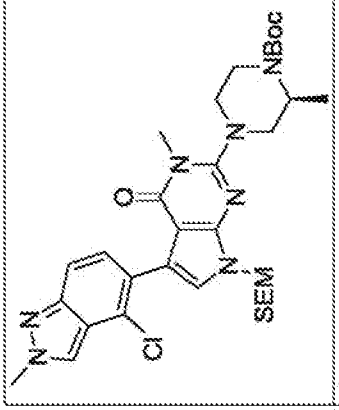
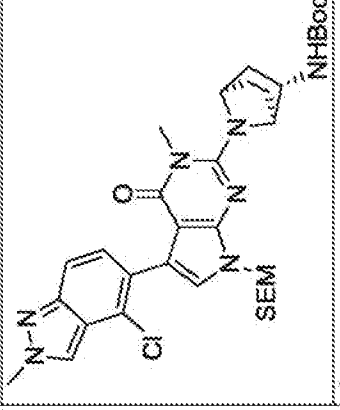
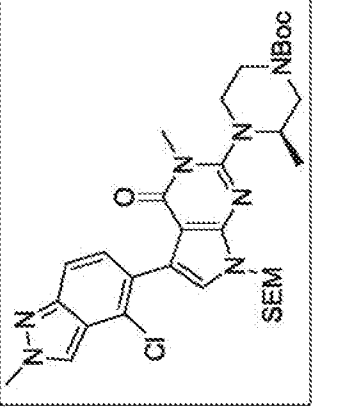
[1517]

	4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)哌嗪-1-甲酸叔丁酯	628, 630	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和哌嗪-1-甲酸叔丁酯制备
	3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,7-二氮杂二环[4.2.0]辛烷-7-甲酸叔丁酯	654, 656	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 3,7-二氮杂二环[4.2.0]辛烷-7-甲酸叔丁酯制备
	9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-1,9-二氮杂螺[5.5]十一烷-1-甲酸叔丁酯	696, 698	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 1,9-二氮杂螺[5.5]十一烷-1-甲酸叔丁酯制备

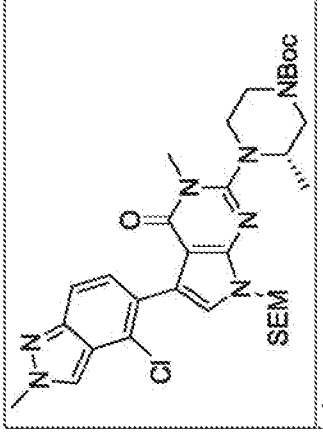
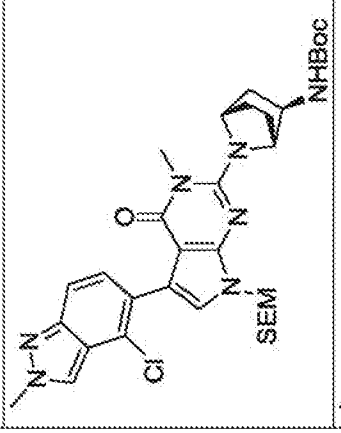
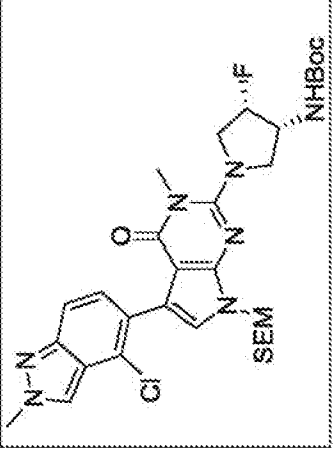
[1518]

	7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-1,7-二氮杂螺[3.5]壬烷-1-甲酸叔丁酯	668, 670	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 1,7-二氮杂螺[3.5]壬烷-1-甲酸叔丁酯制备
	(*S*)-(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)吡咯烷-3-基)氨基甲酸叔丁酯	628, 630	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-吡咯烷-3-基氨基甲酸叔丁酯制备
	(*R*)-(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)吡咯烷-3-基)氨基甲酸叔丁酯	628, 630	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-吡咯烷-3-基氨基甲酸叔丁酯制备

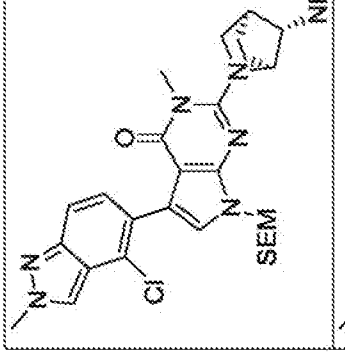
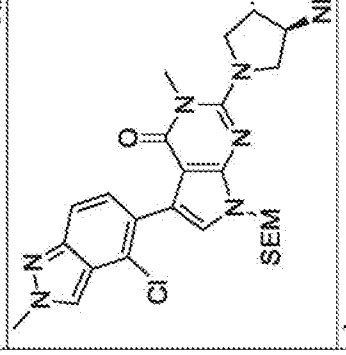
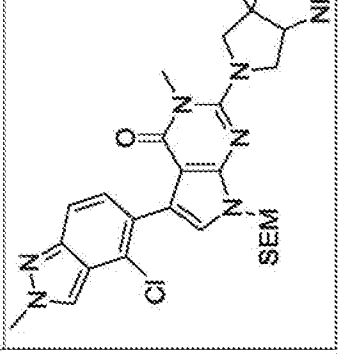
[1519]

	(*S*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-甲基哌嗪-1-甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-2-甲基哌嗪-1-甲酸叔丁酯制备
	((1*S*,2*S*,4*R*)-7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*S*,2*S*,4*R*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	(*R*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基哌嗪-1-甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-3-甲基哌嗪-1-甲酸叔丁酯制备

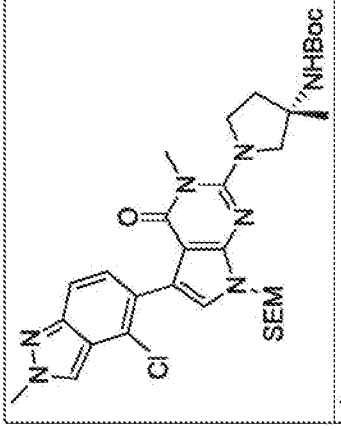
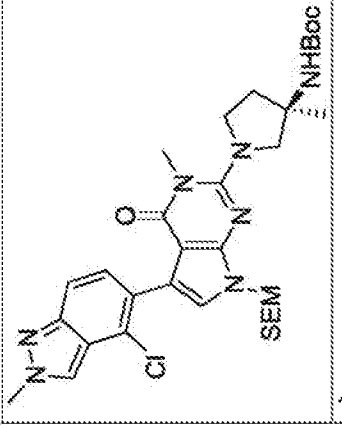
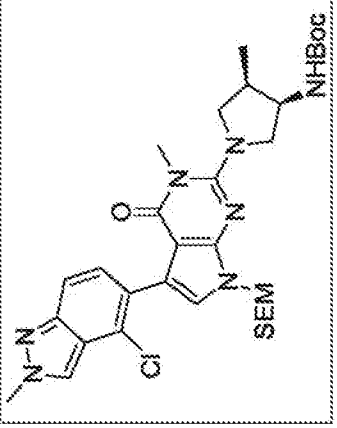
[1520]

	(*S*)-4-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基哌嗪-1-甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-3-甲基哌嗪-1-甲酸叔丁酯制备
	((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	((3*R*,4*S*)-1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-氟吡咯烷-3-基)氨基甲酸叔丁酯	646, 648	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((3*R*,4*S*)-4-氟吡咯烷-3-基)氨基甲酸叔丁酯制备

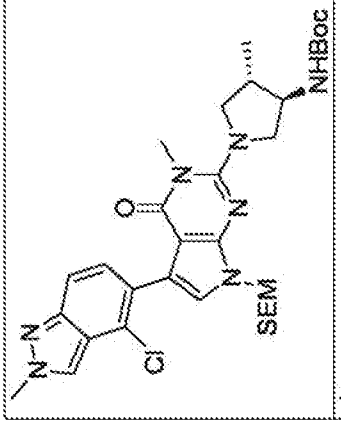
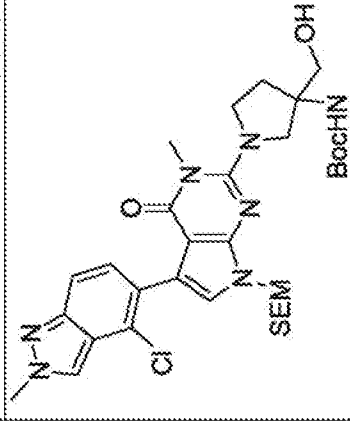
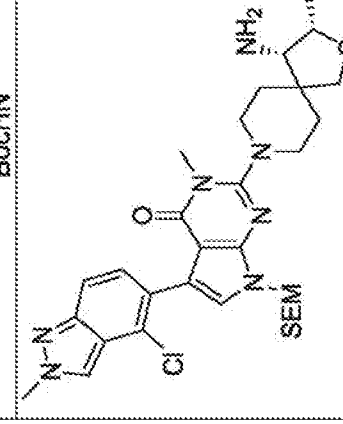
[1521]

	*rac*-((1*S*,4*S*,7*S*)-2-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *rac*-((1*S*,4*S*,7*S*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备
	((3*S*,4*S*)-1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-氟吡咯烷-3-基)氨基甲酸叔丁酯	646, 648	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((3*S*,4*S*)-4-氟吡咯烷-3-基)氨基甲酸叔丁酯制备
	(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4,4-二氟吡咯烷-3-基)氨基甲酸叔丁酯	664, 666	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(4,4-二氟吡咯烷-3-基)氨基甲酸叔丁酯制备

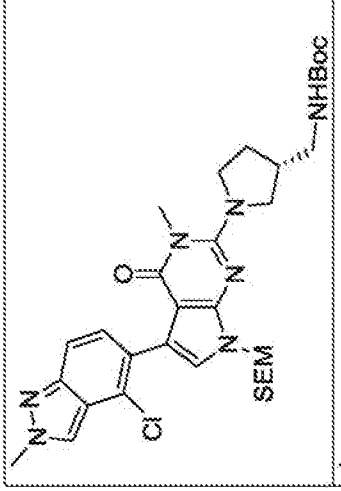
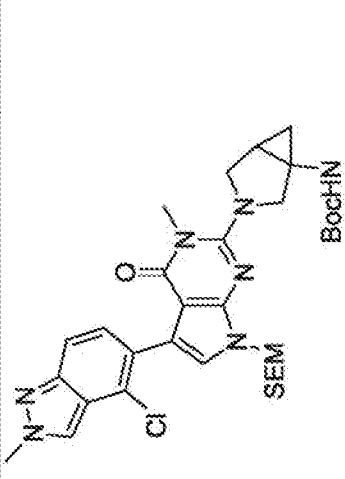
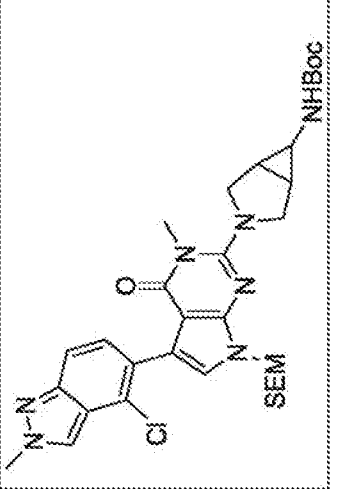
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	(*S*)-(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基吡咯烷-3-基)氨基甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-(3-甲基吡咯烷-3-基)氨基甲酸叔丁酯制备
	(*R*)-(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基吡咯烷-3-基)氨基甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-(3-甲基吡咯烷-3-基)氨基甲酸叔丁酯制备
	((3*R*,4*R*)-1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-甲基吡咯烷-3-基)氨基甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((3*R*,4*R*)-4-甲基吡咯烷-3-基)氨基甲酸叔丁酯制备

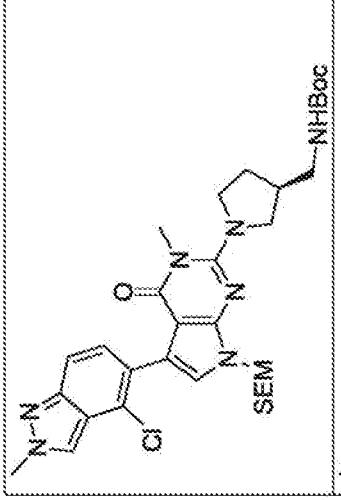
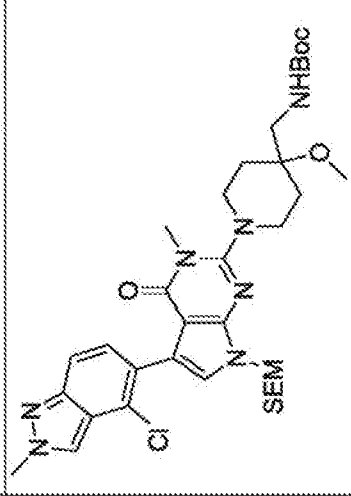
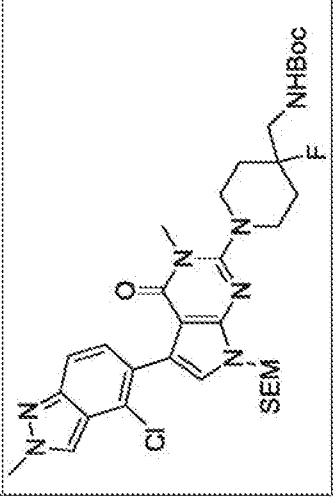
[1523]

	((3*R*,4*S*)-1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-甲基吡咯烷-3-基)氨基甲酸叔丁酯	642, 644	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((3*R*,4*S*)-4-甲基吡咯烷-3-基)氨基甲酸叔丁酯制备
	(1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-(羟基甲基)吡咯烷-3-基)氨基甲酸叔丁酯	658, 660	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(3-(羟基甲基)吡咯烷-3-基)氨基甲酸叔丁酯制备
	2-((3*S*,4*S*)-4-氨基-3-甲基-2-氮杂-8-氧杂螺[4.5]癸烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	612, 614	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(3*S*,4*S*)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备

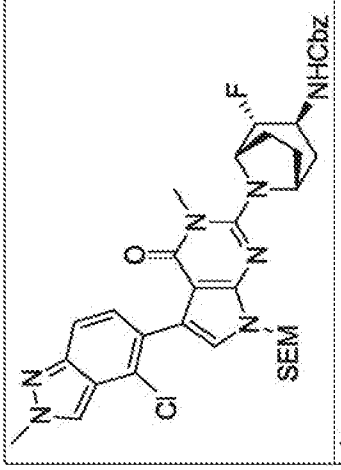
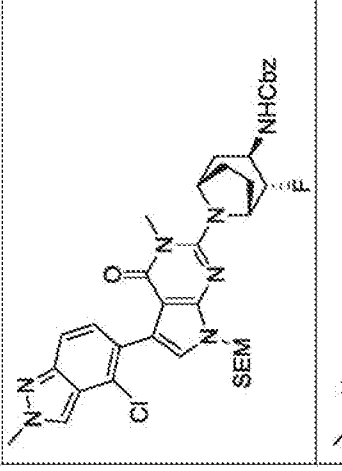
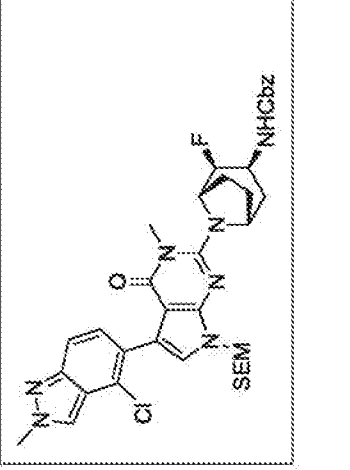
[1524]

	(*R*)-((1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)吡咯烷-3-基)甲基)氨基甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*S*)-(吡咯烷-3-基甲基)氨基甲酸叔丁酯制备
	(3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.1.0]己烷-1-基)氨基甲酸叔丁酯	640, 642	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(3-氮杂二环[3.1.0]己烷-1-基)氨基甲酸叔丁酯制备
	(3-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氮杂二环[3.1.0]己烷-6-基)氨基甲酸叔丁酯	640, 642	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(3-氮杂二环[3.1.0]己烷-6-基)氨基甲酸叔丁酯制备

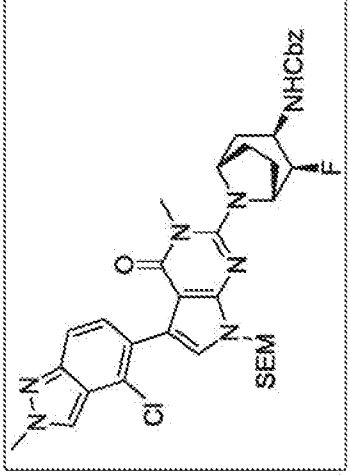
[1525]

	(*S*)-((1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)吡咯烷-3-基)甲基)氨基甲酸叔丁酯	642, 644	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和(*R*)-(吡咯烷-3-基甲基)氨基甲酸叔丁酯制备
	(((1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-甲氧基哌啶-4-基)甲基)氨基甲酸叔丁酯	686, 688	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((4-甲氧基哌啶-4-基)甲基)氨基甲酸叔丁酯制备
	(((1-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-4-氟哌啶-4-基)甲基)氨基甲酸叔丁酯	674, 676	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((4-氟哌啶-4-基)甲基)氨基甲酸叔丁酯制备

[1526]

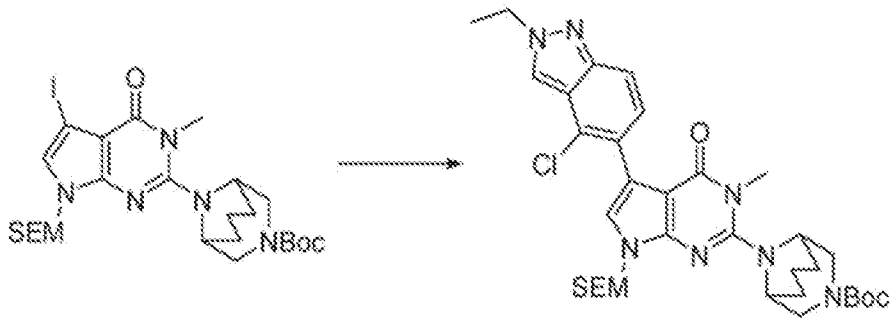
	(((1*S*,2*R*,3*S*,5*R*)-8-(5-(4- 氯 -2-甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -4- 氧代 -7-((2-(三甲基硅烷基) 乙氧基)甲基)-4,7- 二氢 -3*H*- 吡咯并[2,3-*d*]嘧啶 -2- 基)-2- 氟 -8-氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯	720, 722	根据上述通用方法 1，利用 2-氯 -5-(4-氯 -2- 甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7- 二氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮 和 (((1*S*,2*S*,3*S*,5*R*)-2- 氟 -8- 氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯制备
	(((1*R*,2*S*,3*R*,5*S*)-8-(5-(4- 氯 -2-甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -4- 氧代 -7-((2-(三甲基硅烷基) 乙氧基)甲基)-4,7- 二 氢 -3*H*- 吡咯并[2,3-*d*]嘧啶 -2- 基)-2- 氟 -8-氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯	720, 722	根据上述通用方法 1，利用 2-氯 -5-(4-氯 -2- 甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7- 二氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮 和 (((1*R*,2*R*,3*R*,5*S*)-2- 氟 -8- 氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯制备
	(((1*S*,2*S*,3*S*,5*R*)-8-(5-(4- 氯 -2-甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -4- 氧代 -7-((2-(三甲基硅烷基) 乙氧基)甲基)-4,7- 二 氢 -3*H*- 吡咯并[2,3-*d*]嘧啶 -2- 基)-2- 氟 -8-氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯	720, 722	根据上述通用方法 1，利用 2-氯 -5-(4-氯 -2- 甲基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7- 二氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮 和 (((1*S*,2*R*,3*S*,5*R*)-2- 氟 -8- 氮杂二环[3.2.1]辛烷 -3- 基) 氨基甲酸苄酯制备

[1527]

	((1*R*,2*R*,3*R*,5*S*)-8-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯	720, 722	根据上述通用方法1，利用2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,2*S*,3*R*,5*S*)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯制备

[1528] 通用方法2：9-(5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯

[1529] [化学式147]

[1530] 

[1531] 将9-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯(500mg,0.794mmol)、4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(365mg,1.19mmol)、K_3PO_4(337mg,1.58mmol)、[1,1′-二(二苯基膦基)二茂铁]合二氯钯(II)与二氯甲烷的络合物(64.8mg,0.0794mmol)、1,4-二氧六环(8mL)和水(2mL)的混合物在70℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(375mg)。MS:$[M+H]^+$=682,684.

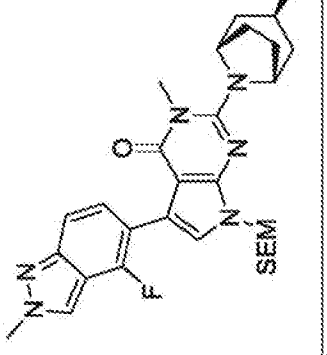
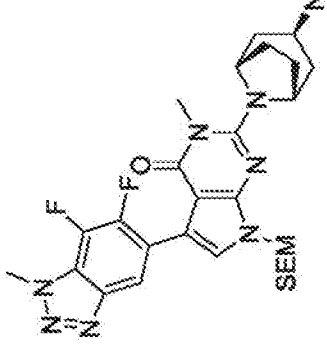
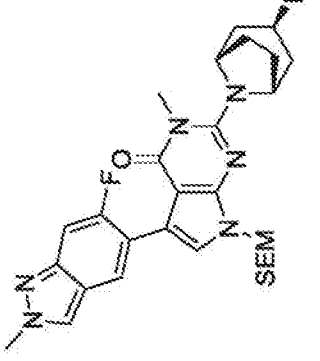
[1532] 利用与通用方法2中所述的类似方法,从适当取代、保护的吡咯并嘧啶酮开始,并利用不同硼酸酯或硼酸,制备下表6的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1533]

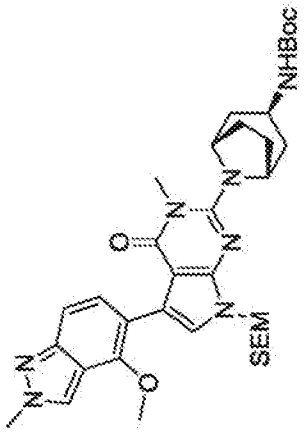
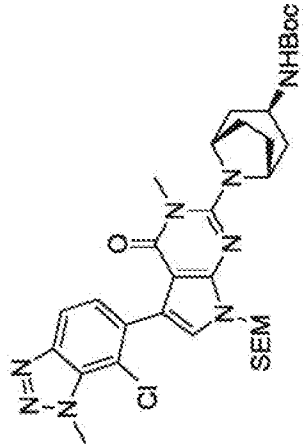
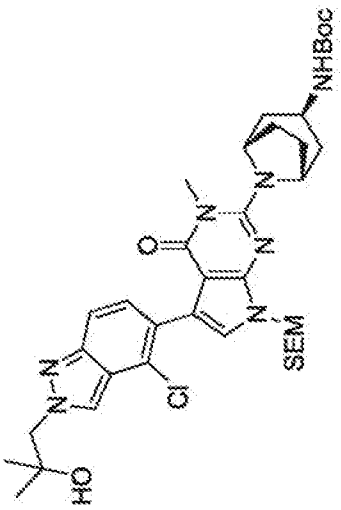
表 6

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	(*endo*-8-(3-甲基-5-(2-甲基-2*H*-吲唑-5-基)-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	634	根据上述通用方法 2，利用(*endo*-8-(5-溴-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(*endo*-8-[5-(7-氯-2-甲基苯并[*d*]噁唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)吡啶并[2,3-*d*]嘧啶-2-基]-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯	669, 671	根据上述通用方法 2，利用(*endo*-8-(6-溴-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噁唑制备
	(*endo*-8-(5-(7-氯-2-乙基苯并[*d*]噁唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	683, 685	根据上述通用方法 2，利用(*endo*-8-(5-溴-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 7-氯-2-乙基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噁唑制备

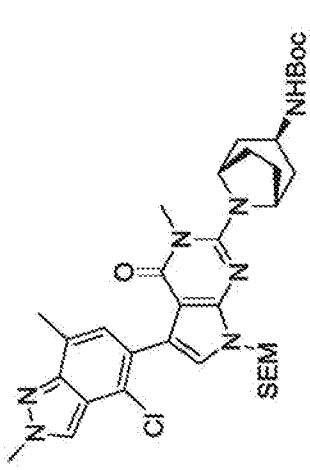
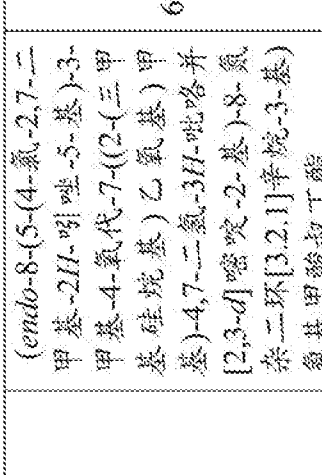
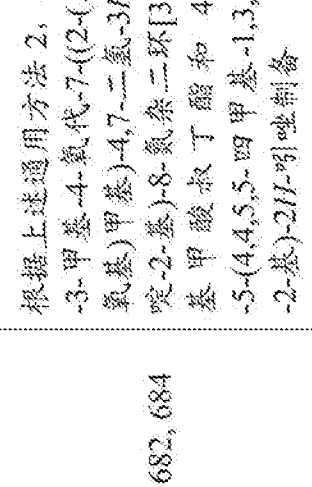
[1534]

	(*endo*-8-(5-(4- 氟 -2- 甲基 -2*H*- 吲 唑 -5- 基)-3- 甲基 -4- 氧代 -7-((2-(三 甲 基 硅 烷 基) 乙 氧 基) 甲基)-4,7- 二氢 -3*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -2- 基)-8- 氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	652	根据上文通过方法 2，利用(*endo*-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 4-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(*endo*-8-(5-(6,7- 二 氟 -1- 甲 基 -1*H*- 苯 并 [*d*][1,2,3] 三 唑 -5- 基)-3- 甲 基 -4- 氧代 -7-((2-(三 甲 基 硅 烷 基) 乙 氧 基) 甲 基)-4,7- 二氢 -3*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -2- 基)-8- 氮 杂 二 环 [3.2.1] 辛 烷 -3- 基) 氨 基 甲酸叔丁酯	671	根据上述通用方法 2，利用 *endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 6,7-二氟-1-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-苯并[*d*][1,2,3]三唑制备
	(*endo*-8-(5-(6- 氟 -2- 甲基 -2*H*- 吲 唑 -5- 基)-3- 甲基 -4- 氧代 -7-((2-(三 甲 基 硅 烷 基) 乙 氧 基) 甲 基)-4,7- 二氢 -3*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -2- 基)-8- 氮 杂 二 环 [3.2.1] 辛 烷 -3- 基) 氨基甲酸叔丁酯	652	根据上述通用方法 2，利用 *endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 6-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

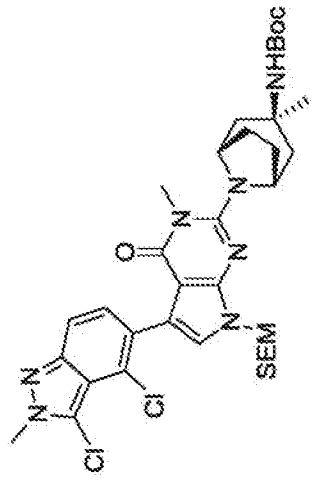
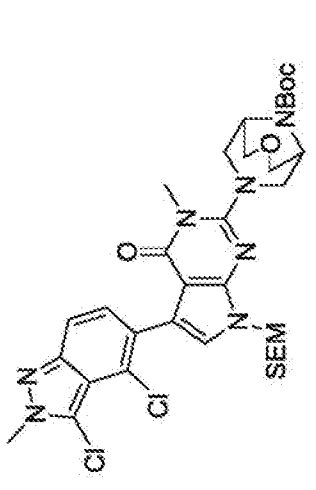
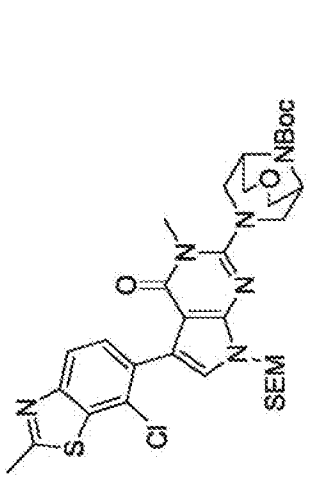
[1535]

	(*endo*-8-(5-(4-甲氧基-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	664	根据上述通用方法2，利用*endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和4-甲氧基-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(*endo*-8-(5-(7-氯-1-甲基-1*H*-苯并[*d*][1,2,3]三唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	669, 671	根据上述通用方法2，利用*endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和7-氯-1-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-苯并[*d*][1,2,3]三唑制备
	(*endo*-8-(5-(4-氯-2-(2-羟基-2-甲基丙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	726, 728	根据上述通用方法2，利用*endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和1-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-2-甲基丙烷-2-醇制备

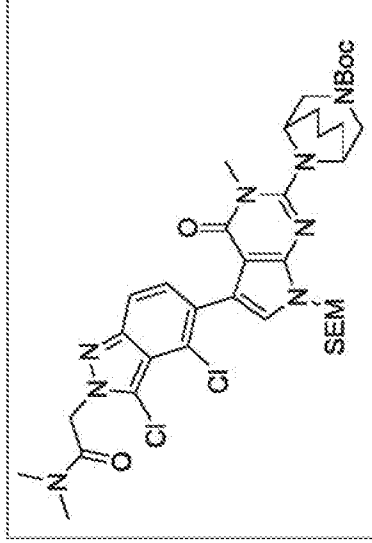
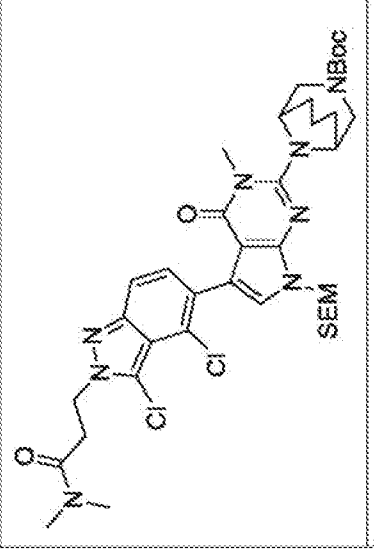
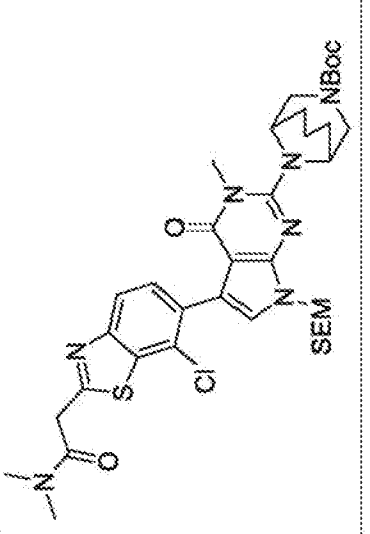
[1536]

	(*endo*-8-(5-(4-氯-2,7-二甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	682, 684	根据上述通用方法 2，利用(*endo*-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 4-氯-2,7-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(*endo*-8-(5-(4-氯-1*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	654，656	根据上述通用方法 2，利用 *endo*-(8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1*H*-吲唑制备
	(*endo*-8-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	702, 704	根据上述通用方法 2，利用(*endo*-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

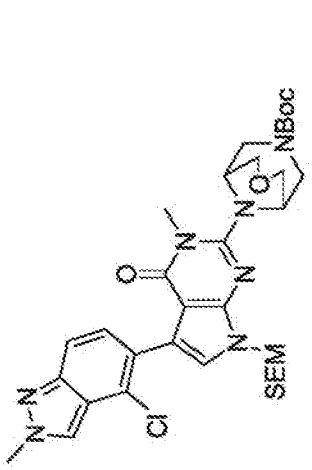
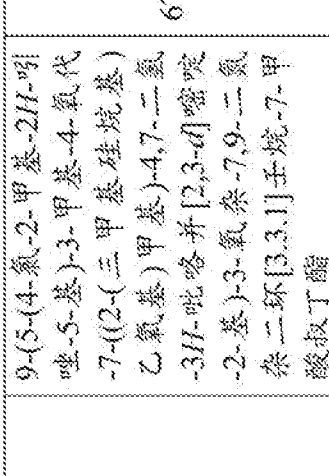
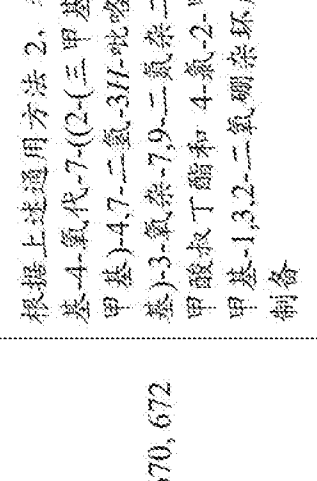
[1537]

	(*endo*-8-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	716, 718	根据上述通用方法 2，利用(*endo*-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	7-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-d]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	704, 706	根据上述通用方法 2，利用 7-(5-碘-3-甲基-4-氧代-7-(2-三甲基硅烷基乙氧基甲基)吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	7-(5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	687, 689	根据上述通用方法 2，利用 7-(5-碘-3-甲基-4-氧代-7-(2-三甲基硅烷基乙氧基甲基)吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯和 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-1,3-苯并噻唑制备

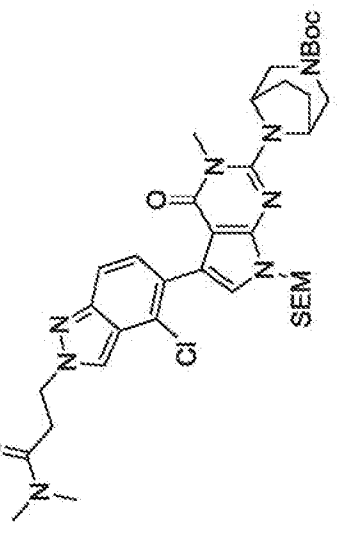
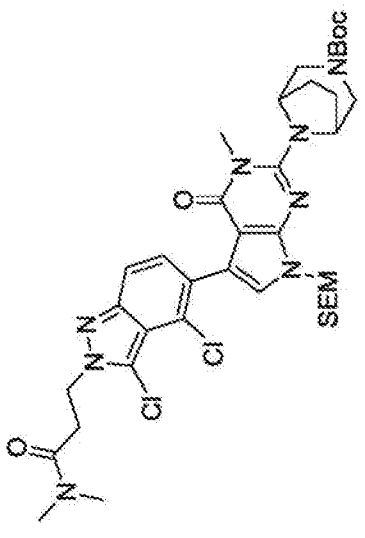
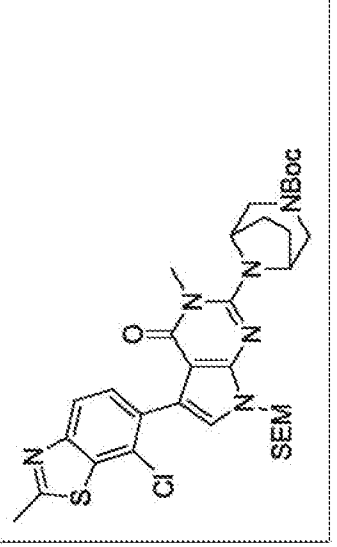
[1538]

	9-(5-(3,4-二氯-2-(2-(二甲氨基)-2-氧代乙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	773, 775	根据上述通用方法 2，利用 2-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基乙酰胺制备
	9-(5-(3,4-二氯-2-(3-(二甲氨基)-3-氧代丙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	787, 789	根据上述通用方法 2，利用 3-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基丙酰胺制备
	9-(5-(7-氯-2-(2-(二甲氨基)-2-氧代乙基)苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	756, 758	根据上述通用方法 2，利用 2-(7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑-2-基)-*N*,*N*-二甲基乙酰胺制备

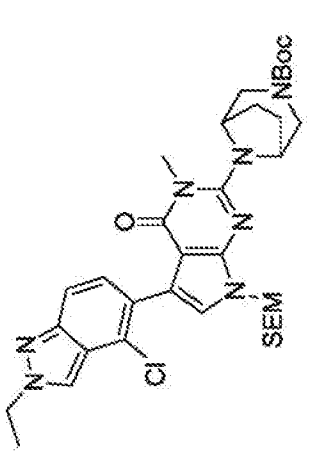
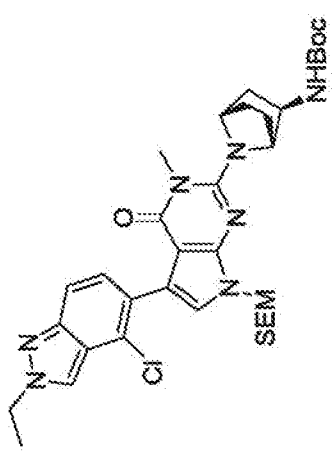
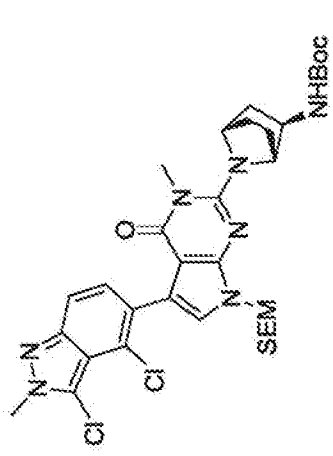
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	9-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-甲酸叔丁酯	670, 672	根据上述通用方法 2，利用 9-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-甲酸叔丁酯和 4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	8-(5-(4-氯-2-(2-(二甲氨基)-2-氧代乙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	725, 727	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 2-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基乙酰胺制备
	8-(5-(4-氯-2-甲基-2*H*-苯并[*d*][1,2,3]三唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	655, 657	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-苯并[*d*][1,2,3]三唑制备

[1540]

	8-(5-(4-氯-2-(3-(二甲氨基)-3-氧代丙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	739, 741	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 3-(4-氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基丙酰胺制备
	8-(5-(3,4-二氯-2-(3-(二甲氨基)-3-氧代丙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	773, 775	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 3-(3,4-二氯-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-2-基)-*N*,*N*-二甲基丙酰胺制备
	8-(5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	671, 673	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

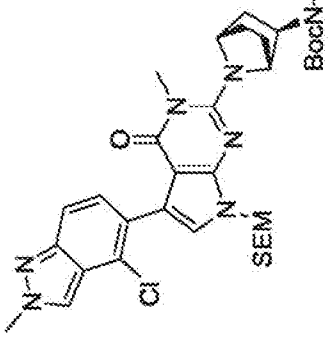
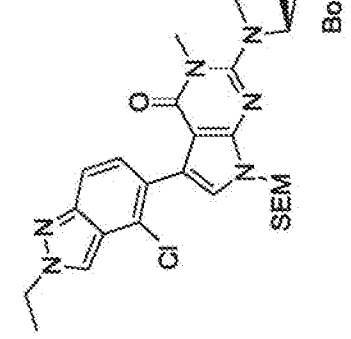
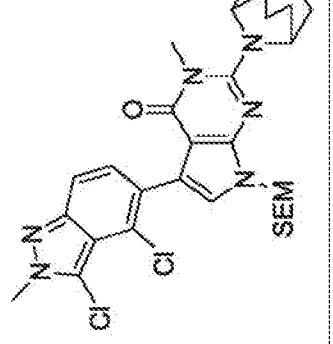
[1541]

	8-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	668, 670	根据上述通用方法 2，利用 8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯和 4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	668, 670	根据上述通用方法 2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	688, 690	根据上述通用方法 2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

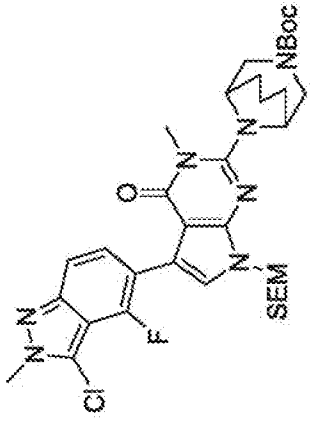
[1542]

	(((1*R*,2*R*,4*S*)-7-(5-(4-氯-2,3-二甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯	668, 670	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯和4-氯-2,3-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯	671, 673	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)氧基甲酸叔丁酯和7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯	672, 674	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯和3-氯-4-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

[1543]

	(((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	668, 670	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	682, 684	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氯代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯制备
	9-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	702, 704	根据上述通用方法2，利用-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

[1544]

	9-(5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	686, 688	根据上述通用方法 2，利用 9-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和 3-氯-4-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(7-氯苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	657, 659	根据上述通用方法 2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-乙基-3-甲氧基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	698, 700	根据上述通用方法 2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 4-氯-2-乙基-3-甲氧基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

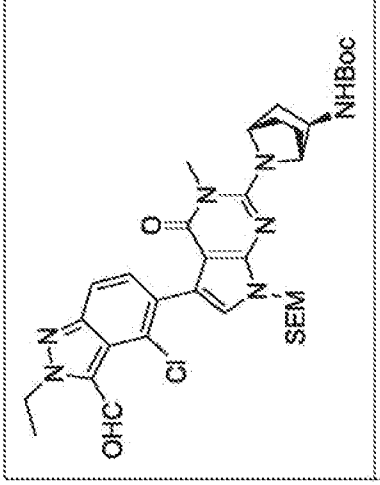
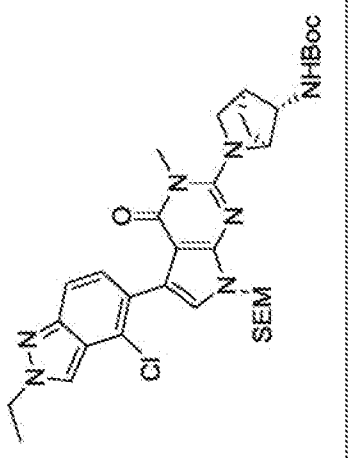
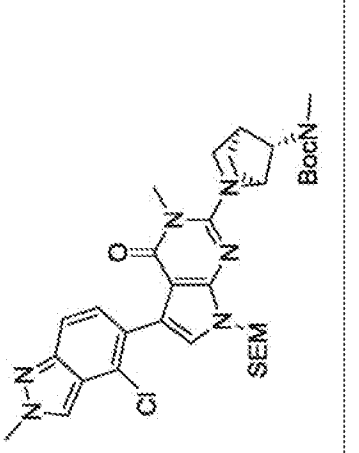
[1545]

	(((1*R*,2*R*,4*S*)-7-(5-(3,4-二氯-2-(氟甲基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯	706, 708	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氧基甲酸叔丁酯和3,4-二氟-2-(氟甲基)-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	702, 704	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和3,4-二氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(7-氯苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	671, 673	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

[1546]

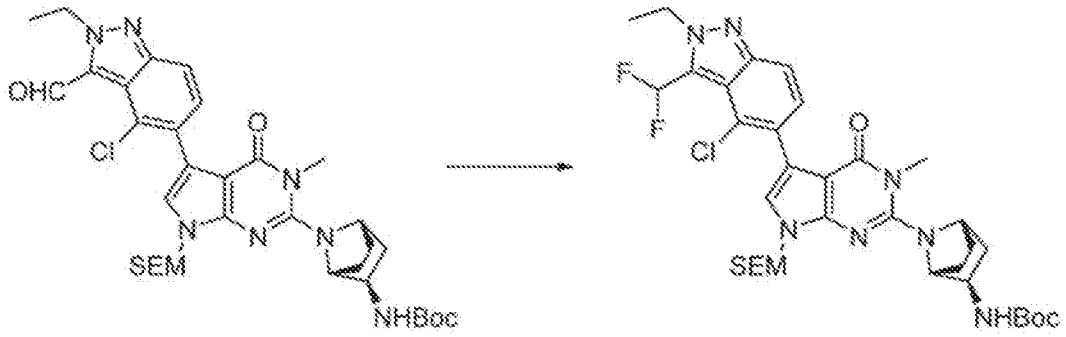
	(((1*R*,2*R*,4*S*)-7-(5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	686, 688	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和3-氯-4-氟-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	(((1*R*,2*R*,4*S*)-7-(5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	685, 687	根据上述通用方法2，利用(((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	9-(5-(苯并[*d*]噻唑-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	685, 687	根据上述通用方法2，利用9-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

[1547]

	((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-乙基-3-甲酰基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	696, 698	根据上述通用方法2，利用((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和4-氯-3-甲酰基-5-碘-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑-3-甲酸制备
	*rac*-((1*S*,4*S*,7*S*)-2-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	668, 670	根据上述通用方法2，利用*rac*-((1*S*,4*S*,7*S*)-2-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯和4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	*rac*-((1*S*,4*S*,7*S*)-2-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-7-基)(甲基)氨基甲酸叔丁酯	668, 670	根据上述通用方法2，利用*rac*-((1*S*,4*S*,7*S*)-2-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯和2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

[1548] 制备112：((1R,2R,4S)-7-(5-(4-氯-3-(二氟甲基)-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

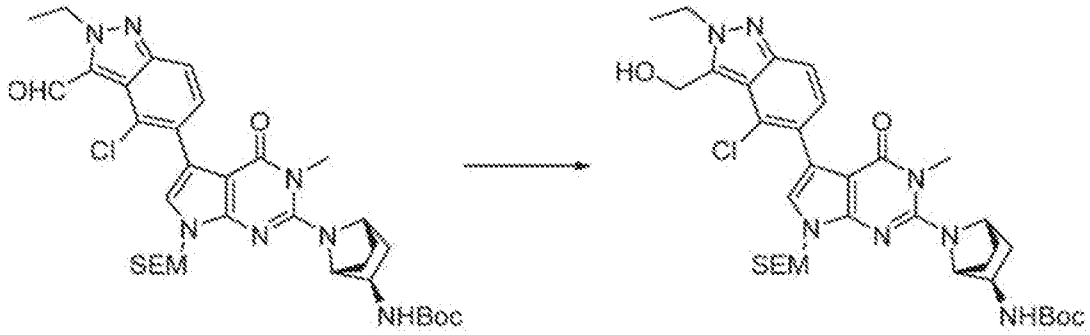
[1549] [化学式148]

[1550] 

[1551] 向((1R,2R,4S)-7-(5-(4-氯-2-乙基-3-甲酰基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(220mg,0.32mmol)的1,2-二氯乙烷(1.3mL)溶液中,加入双(2-甲氧基乙基)氨基三氟化硫(290mg,1.3mmol)。将混合物在50℃搅拌过夜。将混合物用sat.$NaHCO_3$淬灭,并用EtOAc萃取。将有机层真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-80%EtOAc/己烷),得到标题化合物(54mg)。MS:$[M+H]^+$=718,720.

[1552] 制备113:((1R,2R,4S)-7-(5-(4-氯-2-乙基-3-(羟基甲基)-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

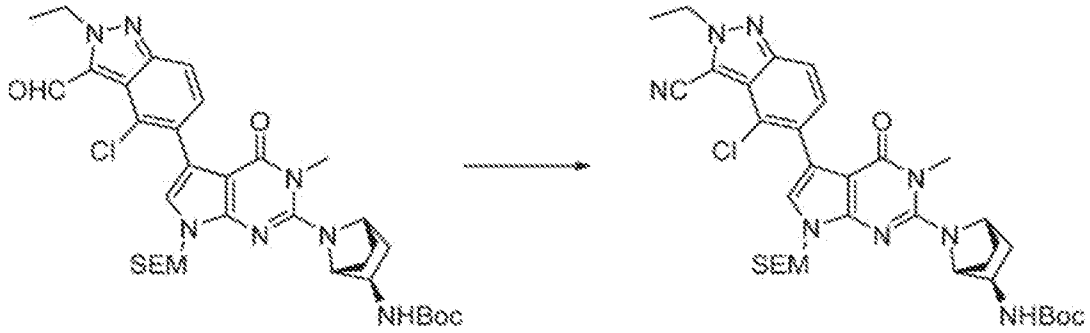
[1553] [化学式149]

[1554] 

[1555] 向((1R,2R,4S)-7-(5-(4-氯-2-乙基-3-甲酰基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(240mg,0.34mmol)的甲醇溶液(3.0mL)中,加入硼氢化钠(21mg,0.56mmol)。将混合物在RT搅拌1h。将混合物用sat.NH_4Cl aq.淬灭,用EtOAc萃取。将有机层用水和盐水洗涤,并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱,0-10%MeOH/$CHCl_3$)纯化,得到标题化合物(215mg)。MS:$[M+H]^+$=698,700.

[1556] 制备114:((1R,2R,4S)-7-(5-(4-氯-3-氰基-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

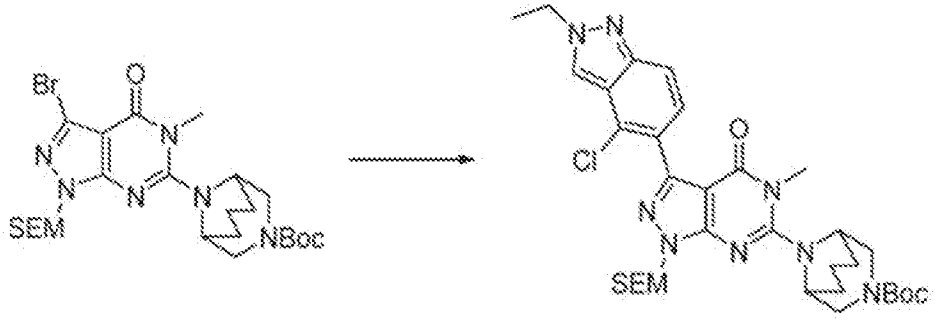
[1557] [化学式150]

[1558] 

[1559] 向((1R,2R,4S)-7-(5-(4-氯-2-乙基-3-甲酰基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(314mg,0.45mmol)和碳酸钠(75mg,0.71mmol)混合物的乙醇(0.9mL)溶液中,加入羟胺盐酸盐(49mg,0.71mmol)。将混合物在RT搅拌过夜。将混合物用EtOAc稀释,用水和盐水洗涤,并真空浓缩。向残留物中,加入乙腈(2.4ml)和乙酸铜(II)(8.1mg,0.045mmol)。将混合物在80℃搅拌5h,然后真空浓缩。将残留物经NH-硅胶色谱(梯度洗脱,0-10%MeOH/$CHCl_3$)纯化,得到标题化合物(245mg)。MS:$[M+H]^+$=693,695.

[1560] 通用方法3:9-(3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-4-氧代-1-((2-(三甲基硅烷基)乙氧基)甲基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯

[1561] [化学式151]

[1562] 

[1563] 将9-(3-溴-5-甲基-4-氧代-1-((2-(三甲基硅烷基)乙氧基)甲基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯(300mg,0.475mmol)、4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(315mg,1.02mmol)、K_3PO_4(327mg,1.54mmol)、[1,1′-二(二苯基膦基)二茂铁]合二氯钯(II)与二氯甲烷的络合物(41.9mg,0.0514mmol)、1,4-二氧六环(6mL)和水(1.5mL)的混合物在90℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱,0-100%EtOAc/己烷)纯化,得到标题化合物(200mg)。MS:$[M+H]^+$=683,685.

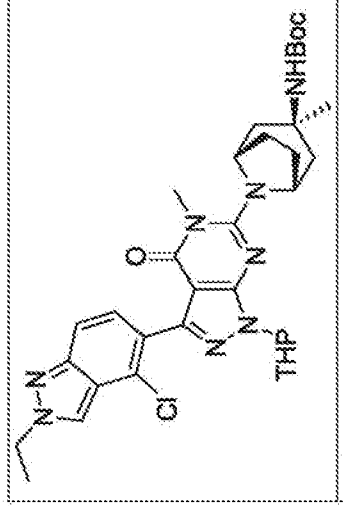
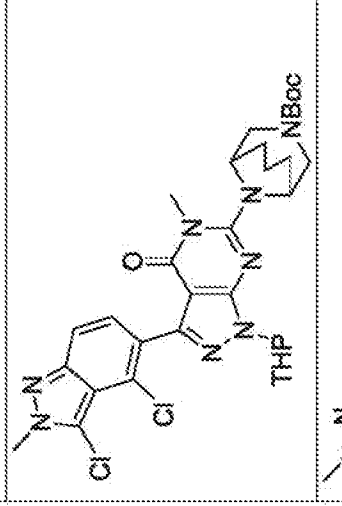
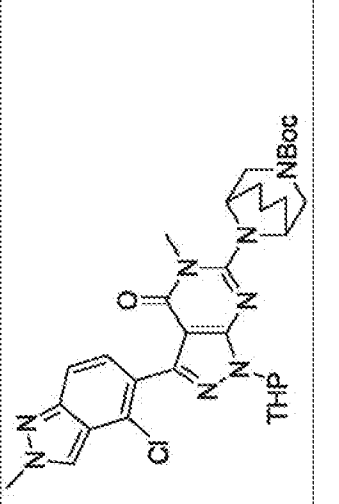
[1564] 利用与通用方法3中所述的类似方法,从适当取代、保护的吡咯并嘧啶酮和不同硼酸酯或硼酸开始,制备下表7的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1565]

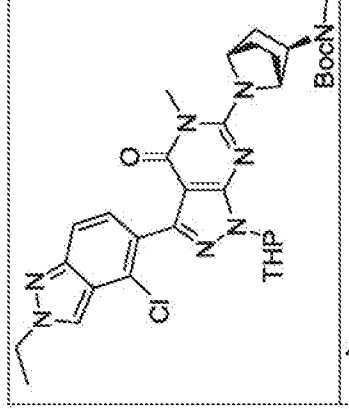
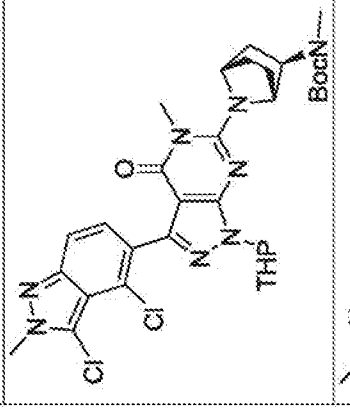
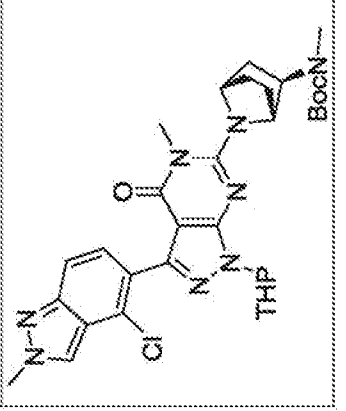
表 7

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	((1*R*,2*R*,4*S*)-7-(3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	623, 625	根据上述通用方法 3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	((1*R*,2*R*,4*S*)-7-(3-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	626, 628	根据上述通用方法 3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	((1*R*,2*R*,4*S*)-7-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	643, 645	根据上述通用方法 3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

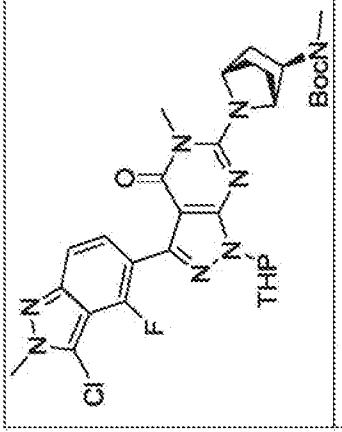
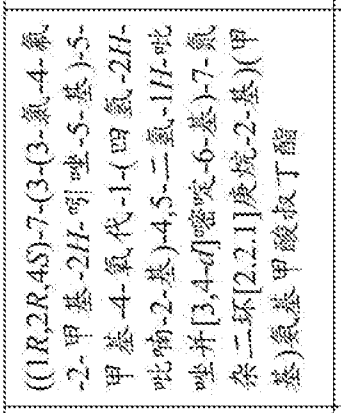
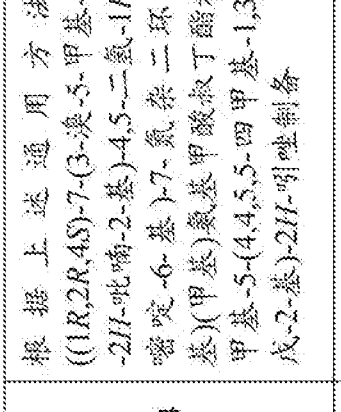
[1566]

	(*endo*-8-(3-(4- 氯 -2- 乙 基 -2*H*- 吲 唑 -5- 基)-5- 甲 基 -4- 氧代 -1-(四 氢 -2*H*- 吡 喃 -2- 基)-4,5- 二氢 -1*H*- 吡 唑 并 [3,4-*d*] 嘧 啶 -6- 基)-3- 甲 基 -8- 氮 杂 二 环 [3.2.1] 辛 烷 -3- 基) 氨基甲酸叔丁酯	651, 653	根据上述通用方法 3，利用 (*endo*-8-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和 4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备。
	9-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四 氢 -2*H*- 吡 喃 -2- 基)-4,5- 二氢 -1*H*- 吡 唑 并 [3,4-*d*] 嘧 啶 -6- 基)-3,9- 二 氮 杂 二 环 [3.3.1] 壬 烷 -3- 甲 酸叔丁酯	657, 659	根据上述通用方法 3，利用 9-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	9-(3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	623, 625	根据上述通用方法 3，利用 9-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和 4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备。

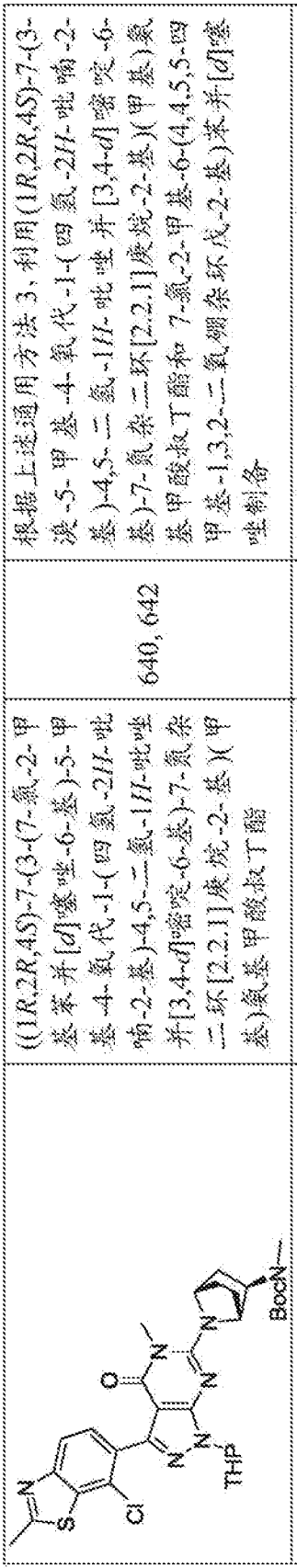
[1567]

	((1*R*,2*R*,4*S*)-7-(3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	637, 639	根据上述通用方法3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯制备
	((1*R*,2*R*,4*S*)-7-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	657, 659	根据上述通用方法3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)-3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	((1*R*,2*R*,4*S*)-7-(3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯	623, 625	根据上述通用方法3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

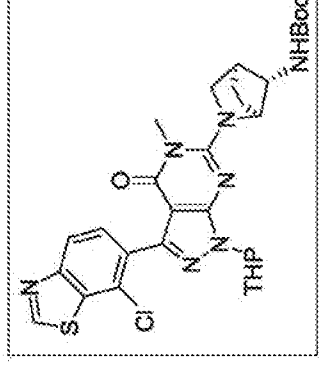
[1568]

	((1*R*,2*R*,4*S*)-7-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]吡嗪-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲氧基甲酸叔丁酯	642, 644	根据上述通用方法3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和3-氯-4-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	9-(3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯	626, 628	根据上述通用方法3，利用9-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯和7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	((1*R*,2*R*,4*S*)-7-(3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲氧基甲酸叔丁酯	626, 628	根据上述通用方法3，利用((1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

[1569]

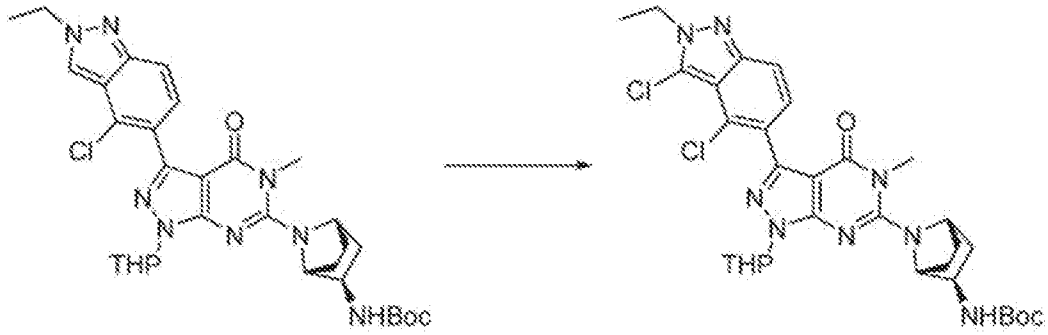
	((1*R*,2*R*,4*S*)-7-(3-氯-2-甲基苯并[*d*]噻唑-6-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-7-基)氨基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑-2-胺	640, 642	根据上述通用方法 3，利用(1*R*,2*R*,4*S*)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-7-氨基)-2-(甲基)氨基甲酸叔丁酯和 7-氯-2-甲基-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备
	rac-((1*S*,4*S*,7*S*)-2-(3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	623, 625	根据上述通用方法 3，利用 *rac*-((1*S*,4*S*,7*S*)-2-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯和 4-氯-2-乙基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备
	rac-((1*S*,4*S*,7*S*)-2-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	643, 645	根据上述通用方法 3，利用 *rac*-((1*S*,4*S*,7*S*)-2-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯和 3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

[1570]

	*rac*-((1*S*,4*S*,7*S*)-2-(3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-4-氧代-1-((2-(三甲基硅烷基)乙氧基)甲基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	612, 614	根据上述通用方法3，利用*rac*-((1*S*,4*S*,7*S*)-2-(3-溴-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯和7-氯-6-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)苯并[*d*]噻唑制备

[1571] 制备115：((1R,2R,4S)-7-(3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

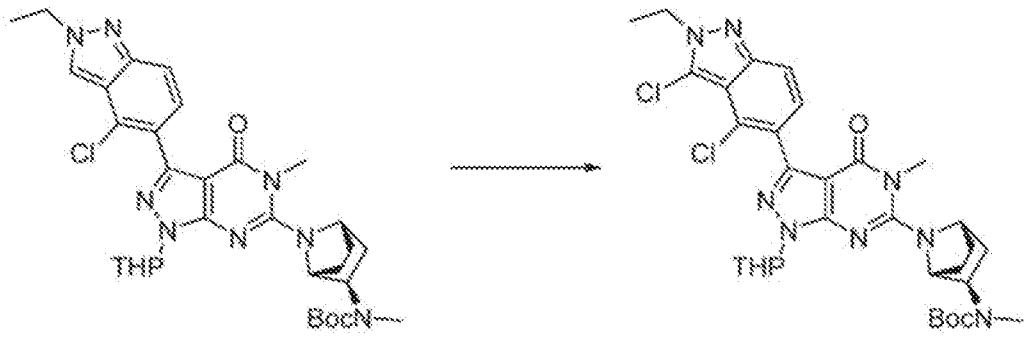
[1572] [化学式152]

[1573] 

[1574] 在RT下,向((1R,2R,4S)-7-(3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(140mg,0.225mmol)的DMF(1.4mL)溶液中,加入NCS(36mg,0.270mmol)。将混合物在60℃搅拌5h。将反应混合物冷却至RT,并用NCS(15mg,0.112mmol)在RT处理。将混合物在60℃搅拌1h,用水稀释,并用EtOAc萃取。将有机层用水(x3)和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱,50-80%EtOAc/己烷)纯化,得到标题化合物(81mg)。MS:$[M+H]^+$=657,659.

[1575] 制备116:((1R,2R,4S)-7-(3-(3,4-二氯-2-乙基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯

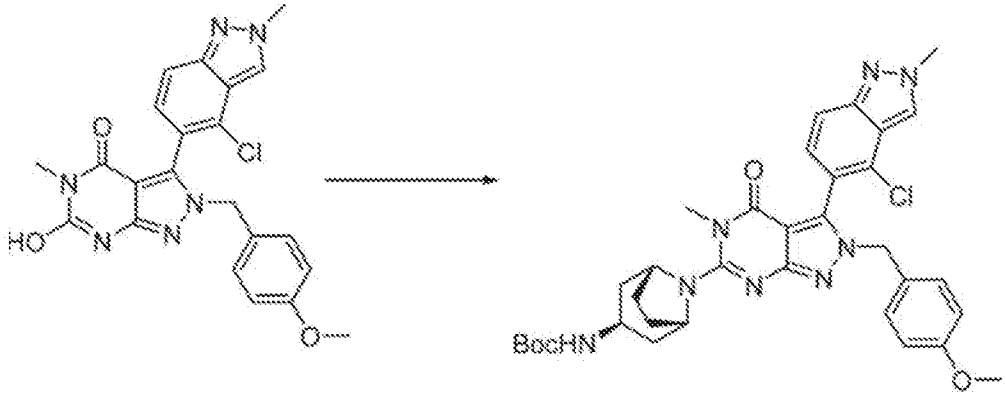
[1576] [化学式153]

[1577] 

[1578] 在RT,向((1R,2R,4S)-7-(3-(4-氯-2-乙基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯(177mg,0.278mmol)的DMF溶液(1.4mL)中,加入NCS(55.6mg,0.417mmol)。将混合物在60℃搅拌30min,用水稀释,并用EtOAc萃取。将有机层用水(x3)和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,40-80%EtOAc/己烷),得到标题化合物(115mg)。MS:$[M+H]^+$=671,673.

[1579] 通用方法4:N-[endo-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯

[1580] [化学式154]

[1581] 

[1582] 将DBU(0.0677mL,0.45mmol)在环境温度下滴加至3-(4-氯-2-甲基-2H-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮(135mg,0.3mmol)和PyBOP(172mg,0.33mmol)的DMF(2.5mL)溶液中。将混合物搅拌10分钟,然后用N-(endo-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯(102mg,0.45mmol)处理。将混合物搅拌过夜,保持20小时-一些原料剩余。将混合物用水(40mL)处理。然后,将细的沉淀萃取至EtOAc(50mL)中,然后将有机层用(2x20mL)洗涤、干燥(Na_2SO_4),并真空浓缩。将粗产物经硅胶色谱(12g柱,0-100%EtOAc/异己烷)纯化,得到标题化合物(128mg,0.19mmol,产率65%),作为透明无色玻璃状。MS:$[M+H]^+$=659.

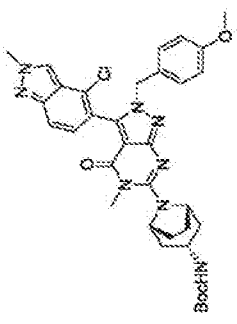
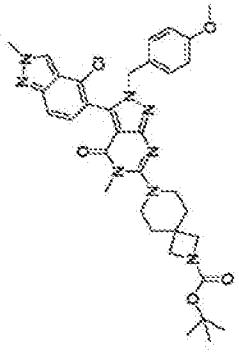
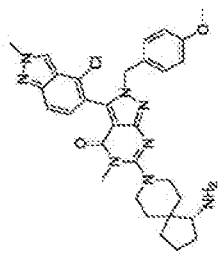
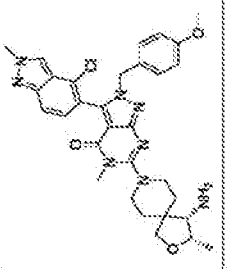
[1583] 利用与通用方法4中所述的类似方法,从适当取代、保护的吡咯并嘧啶酮和不同的胺开始,制备下表8的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1584]

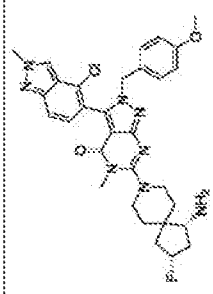
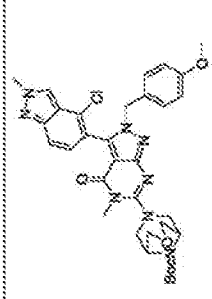
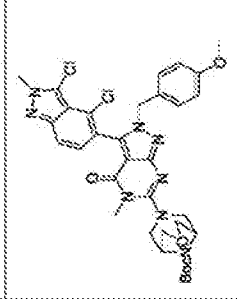
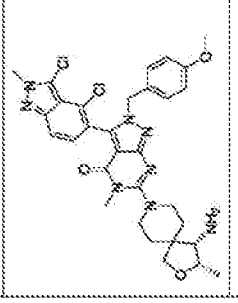
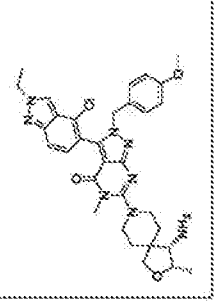
表 8

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	8-[3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	645	根据通用方法 4，利用 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯，搅拌 48 h 制备。
	N-[(1*R*,3*S*)-8-[3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-3-羟基-8-氮杂螺[4.5]癸烷-1-基]-2-甲基丙烷-2-亚磺酰胺	707	根据通用方法 4，利用 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 *N*-[(1*R*,3*S*)-3-羟基-8-氮杂螺[4.5]癸烷-1-基]-2-甲基丙烷-2-亚磺酰胺，在室温下搅拌 24 h，在 40 °C 搅拌 24 h，并在 50 °C 搅拌 24 h 制备。
	6-[(4*S*)-4-氨基-2-氮杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	589	根据通用方法 4，利用 3.5 eq. DBU 并搅拌 2 h，由 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(*S*)-2-氨基-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备。

[1585]

	*N*-[*exo*-8-[3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯	659	根据通用方法 4，利用 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 *N*-(*exo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备。
	7-[3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-2,7-二氮杂螺[3.5]壬烷-2-甲酸叔丁酯	659	根据通用方法 4，利用 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 2,7-二氮杂螺[3.5]壬烷-2-甲酸叔丁酯，搅拌 48 h 制备。
	6-[(1*R*)-1-氨基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	587	根据通用方法 4，利用 3.5 eq. DBU，由 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(*R*)-8-氮杂螺[4.5]癸烷-1-胺二盐酸盐制备。
	6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	603	根据通用方法 4，利用 4.5 eq. DBU，由 3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(3*S*,4*S*)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备。

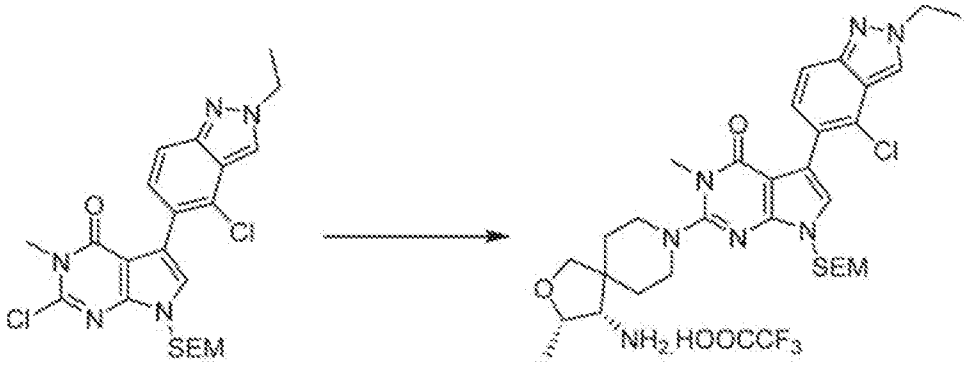
[1586]

	6-[(1*R*,3*R*)-1-氨基-3-氟-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	605	根据通用方法4，利用4.5 eq. DBU，由3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(1*R*,3*R*)-3-氟-8-氮杂螺[4.5]癸烷-1-胺二盐酸盐制备。
	7-[3-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-3-氟-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	661	根据通用方法4，由3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和3-氟-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯制备。
	7-[3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-6-基]-3-氟-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯	695	根据通用方法4，由3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和3-氟-7,9-二氮杂二环[3.3.1]壬烷-9-甲酸叔丁酯制备。
	6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	637	根据通用方法4，利用4.5 eq. DBU，由3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(3*S*,4*S*)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备。
	6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	617	根据通用方法4，利用4.5 eq. DBU，由3-(4-氯-2-乙基-2*H*-吲唑-5-基)-6-羟基-2-[(4-甲氧基苯基)甲基]-5-甲基-2*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(3*S*,4*S*)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐制备。

[1587] 通用方法5：2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-

吡咯并[2,3-d]嘧啶-4-酮

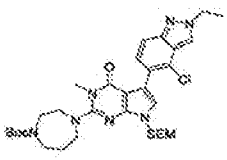
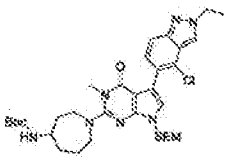
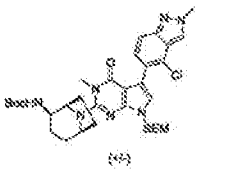
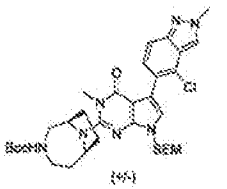
[1588] [化学式155]

[1589] 

[1590] 将2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮(250mg,0.51mmol)、(3S,4S)-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-4-胺二盐酸盐(148mg,0.61mmol)和三乙胺(0.21mL,1.52mmol)混合物的NMP(1mL)溶液在100℃加热2h。冷却至环境温度,并在EtOAc和水之间分配,相分离,并将水相用EtOAc萃取。将合并的有机相用50%饱和盐水洗涤,然后用盐水洗涤,干燥($MgSO_4$+疏水性玻璃料),并浓缩。将残留物经反相C18硅胶色谱纯化,用加0.1%TFA的5-100%MeCN/H_2O洗脱,得到标题化合物,作为TFA盐(256mg,0.346mmol,68%)。^1H NMR(400MHz,DMSO-d_6)δ:8.48(1H,s),7.98(3H,s),7.54(1H,dd),7.31(1H,d),7.25(1H,s),5.48(2H,s),4.50(2H,q),4.29-4.18(1H,m),3.70-3.66(1H,m),3.62(2H,t),3.53-3.33(7H,m),3.03-2.73(2H,m),1.98-1.86(2H,m),1.82-1.77(1H,m),1.66(1H,d),1.53(3H,t),1.24(3H,d),0.93-0.82(2H,m),0.02-0.08(9H,m).MS:$[M+H]^+$=626.

[1591] 利用与通用方法5中所述的类似方法,从适当取代、保护的吡咯并嘧啶酮和不同的胺开始,制备下表9的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1592] 表9

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	4-[5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基]-1,4-二氮杂环庚烷-1-甲酸叔丁酯	656	根据通用方法5，由2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和1,4-二氮杂环庚烷-1-甲酸叔丁酯制备，通过正相硅胶色谱纯化。
	*N*-{1-[5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基]氮杂环庚烷-4-基}氨基甲酸叔丁酯	670	根据通用方法5，用2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和*N*-(氮杂环庚烷-4-基)氨基甲酸叔丁酯制备，通过正相硅胶色谱纯化。
	*rac*-*N*-[(1*R*,2*R*,5*R*)-8-[5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基]-8-氮杂二环[3.2.1]辛烷-2-基]氨基甲酸叔丁酯	668	根据通用方法5，利用DIPEA，并加热16h，由2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-{[(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和*rac*-*N*-[(1*R*,2*R*,5*S*)-8-氮杂二环[3.2.1]辛烷-2-基]氨基甲酸叔丁酯制备。将粗产品通过正相硅胶色谱纯化。
	*rac*-(1*R*,6*S*)-9-[5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基]-3,9-二氮杂二环[4.2.1]壬烷-3-甲酸叔丁酯	668	根据通用方法5，利用DIPEA，并加热16h，由2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-{[(三甲基硅烷基)甲氧基]甲基}-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和*rac*-(1*R*,6*S*)-3,9-二氮杂二环[4.2.1]壬烷-3-甲酸叔丁酯制备。将粗产品通过正相硅胶色谱纯化。

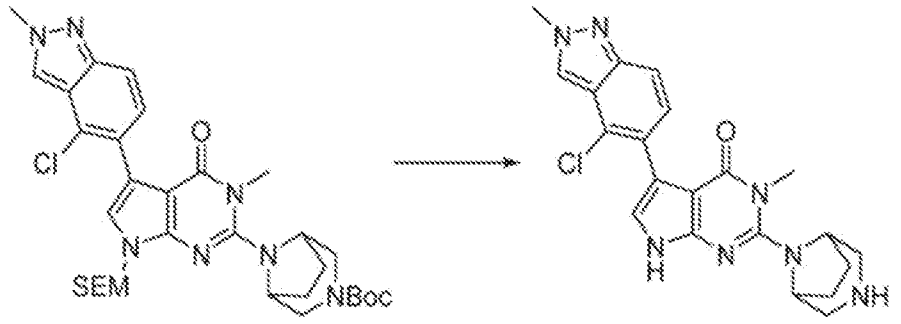
[1593]

[1594] 用于制备式(I)化合物的通用方法

[1595] 下述方法用于解释说明下面表10中列出的实施例1-135制备中所用的通用方法。

[1596] 方法1：2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

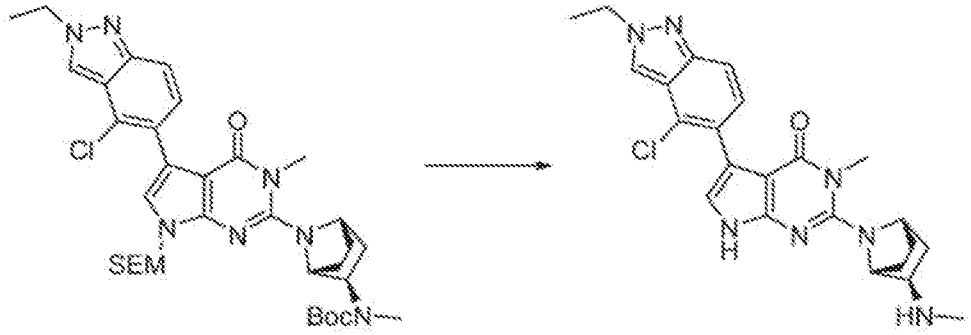
[1597] [化学式156]

[1598] 

[1599] 在RT下，向8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-3,8-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯(140mg,0.214mmol)的$CHCl_3$(2mL)溶液中，加入TFA(2mL)。将混合物在RT搅拌3h，并真空浓缩。将残留物溶于MeOH(4mL)中。在RT下，加入4M NaOH(1mL)。将混合物在RT搅拌1h，倒入水中，并用$CHCl_3$-MeOH萃取。将有机层用无水Na_2SO_4干燥，过滤，并真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱，0-10%MeOH/$CHCl_3$)纯化。将级分(fraction)真空浓缩，并经r-HPLC纯化。将级分用sat.$NaHCO_3$碱化，并用$CHCl_3$-MeOH萃取。将有机层经无水Na_2SO_4干燥，过滤，并真空浓缩，得到标题化合物(24mg)。

[1600] 方法2:5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-2-((1R,2R,4S)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

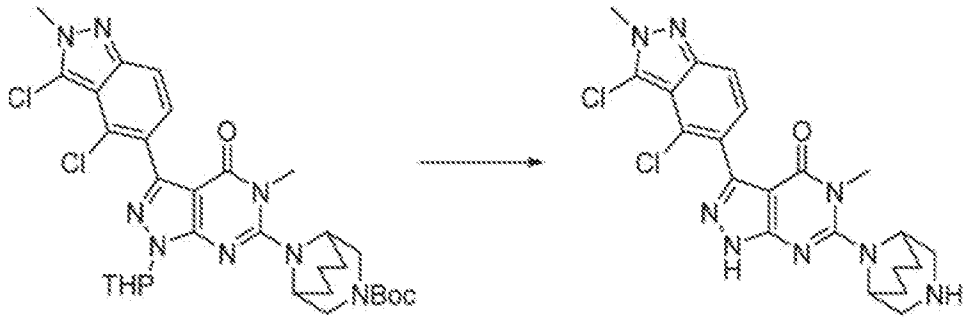
[1601] [化学式157]

[1602] 

[1603] 将((1R,2R,4S)-7-(5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯(150mg,0.219mmol)和TFA(3mL)的混合物在RT搅拌2h，并真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱，0-15%MeOH/$CHCl_3$)纯化。将残留物溶于MeOH(3mL)中。在RT下加入乙二胺(0.2mL,2.99mmol)。将混合物在RT搅拌2h，并真空浓缩。浓缩后，将残留物经r-HPLC纯化。将得到的级分经Vari-Pure纯化，并真空浓缩。将得到的固体悬浮于EtOAc-己烷中。收集沉淀，并将其在60℃减压干燥，得到标题化合物(48mg)。

[1604] 方法3:6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

[1605] [化学式158]

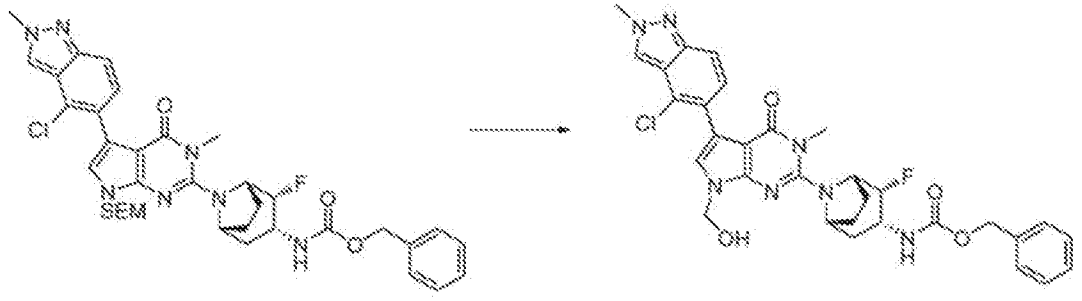
[1606] 

[1607] 在RT下，向9-(3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-3,9-二氮杂二环[3.3.1]壬烷-3-甲酸叔丁酯(120mg,0.182mmol)混合物的MeOH(1mL)溶液中，加入4M HCl的1,4-二氧六环溶液(2mL,8mmol)。将混合物在RT搅拌2h，并真空浓缩。将残留物经r-HPLC纯化。将得到的级

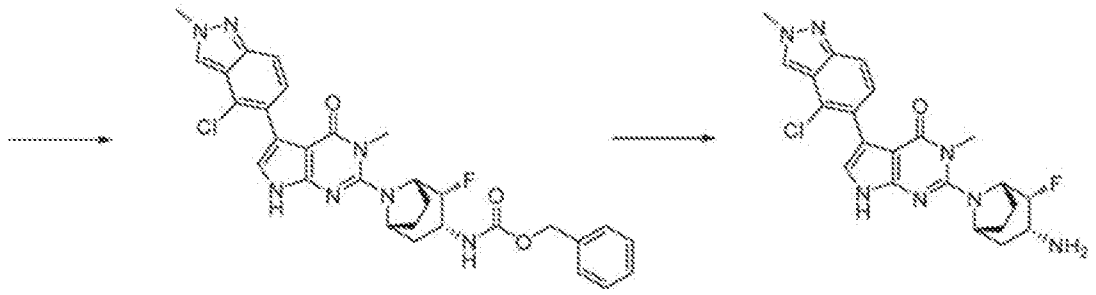
分通过Vari-Pure纯化，并真空浓缩。将得到的固体悬浮于EtOAc-己烷中。收集沉淀，并将其在60℃减压干燥，得到标题化合物(38mg)。

[1608] 方法4：rac-2-((1S,2R,3R,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[1609] [化学式159]



[1610]



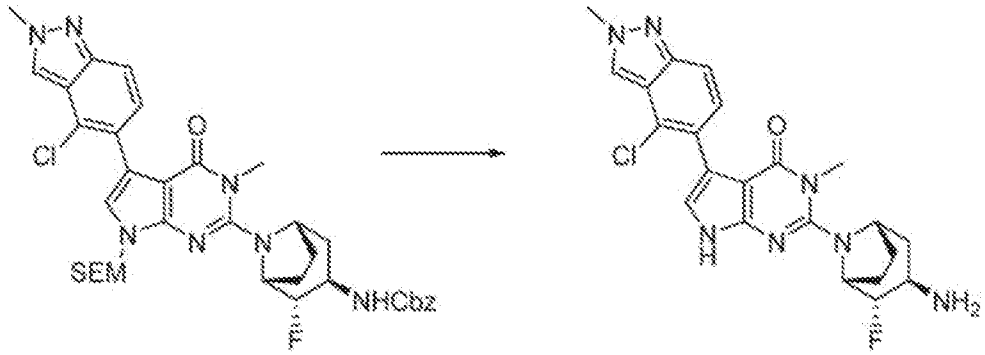
[1611] 在RT下，向rac-((1S,2R,3R,5R)-8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(129mg,0.179mmol)的$CHCl_3$溶液(0.5mL)中，加入TFA(0.5mL)。将混合物在RT搅拌6h，并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱，0-10%MeOH/$CHCl_3$)纯化。将级分真空浓缩，得到rac-((1S,2R,3R,5R)-8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-7-(羟基甲基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(106mg,0.17mmol,产率95%)。

[1612] 将残留物(106mg,0.17mmol)溶解于MeOH(0.40mL)和THF(0.40mL)中。在RT下，加入乙二胺(0.2mL,2.99mmol)。将混合物在RT搅拌1h，并真空浓缩。将残留物经NH硅胶柱色谱(梯度洗脱，0-10%MeOH/$CHCl_3$)纯化。将级分真空浓缩，得到rac-((1S,2R,3R,5R)-8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(97mg,0.16mmol,产率96%)。

[1613] 在RT、N_2气氛下，向残留物(97mg,0.16mmol)、三乙基硅烷(0.42mL,2.6mmol)、三乙胺(0.073mL,0.52mmol)的CH_2Cl_2(2.0mL)混悬液中，加入乙酸钯(II)(18mg,0.082mmol)，并将混悬液在RT搅拌2.5h。通过用硅藻土垫过滤，除去固体。将滤液浓缩，得到粗油-固体，将其经NH硅胶柱色谱(梯度洗脱，0-15%MeOH/$CHCl_3$)纯化，得到粗固体-油。将粗固体-油经r-HPLC纯化。将得到的级分浓缩，并将几乎浓缩的残留物用1N NaOH碱化，并用$CHCl_3$萃取，得到标题化合物(27mg,0.059mmol,产率36%)。

[1614] 方法5：2-((1R,2S,3R,5S)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

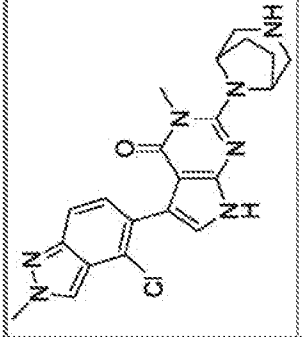
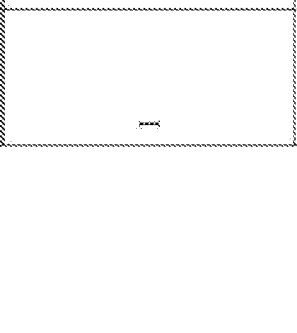
[1615] [化学式160]

[1616] 

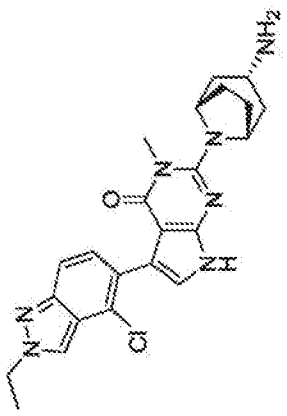
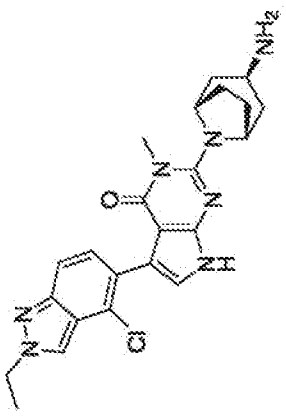
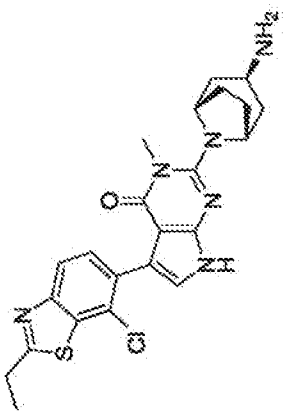
[1617] 将((1R,2S,3R,5S)-8-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸苄酯(61mg,0.085mmol)溶解于甲磺酸(1.0mL)中,并在RT搅拌3h。在0℃,将混合物倒入饱和$NaHCO_3$水溶液中,并用$CHCl_3$萃取。将有机层真空浓缩。将残留物溶解于THF(1mL)中。在0℃,向混合物中加入5M NaOH aq.(0.085mL,0.43mmol),并在RT搅拌1h。将混合物真空蒸发。将残留物经NH硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/$CHCl_3$),得到标题化合物(35mg)。

[1618]

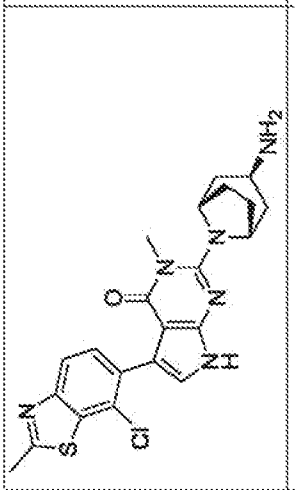
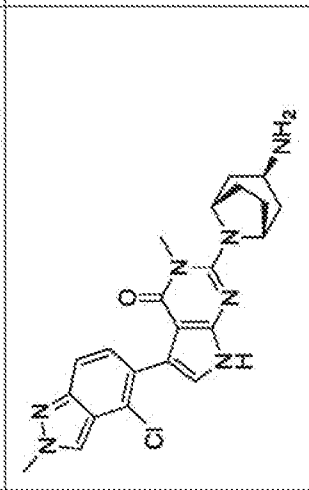
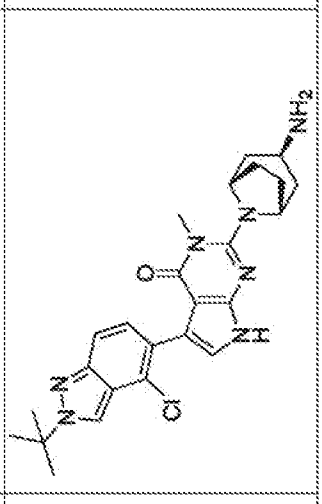
表 10：实施例 1 - 135

实施例	结构	名称	NMR 数据	MS: $[M+H]^+$ m/z	方法
1		2-(3,8- 二 氮 杂 二 环 [3.2.1] 辛 烷 -8- 基)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.96 (1H, d, J = 2.2 Hz), 4.19 (3H, s), 3.98 (2H, br s), 3.46 (3H, s), 2.99-2.96 (2H, m), 2.66-2.63 (2H, m), 1.97-1.80 (4H, m).	424, 426	1
2		2-(4-(氨基甲基)-4- 甲基哌啶 -1- 基)-5-(4- 氯 -2- 乙 基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 8.52 (1H, s), 7.57 (1H, d, J = 8.8 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.06 (1H, s), 4.54 (2H, q, J = 7.3 Hz), 3.43 (3H, s), 3.24-3.17 (2H, m), 3.08-2.99 (2H, m), 1.66-1.56 (6H, m), 1.46-1.39 (2H, m), 1.09 (2H, d, J = 6.1 Hz), 0.98 (3H, s).	454, 456	2
3		2-(4-氨基-4-甲基哌啶 -1- 基)-5-(4- 氯 -2- 乙 基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4*H*- 吡 咯 并 [2,3-*d*] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.75 (1H, br s), 8.45 (1H, s), 7.50 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.00 (1H, s), 4.48 (2H, q, J = 7.3 Hz), 3.37 (3H, s), 3.21-3.16 (2H, m), 3.11-3.05 (2H, m), 1.63-1.43 (7H, m), 1.11 (3H, s).	440, 442	2

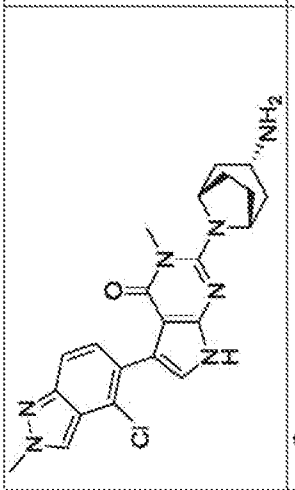
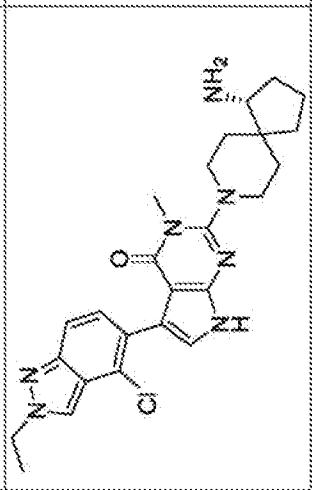
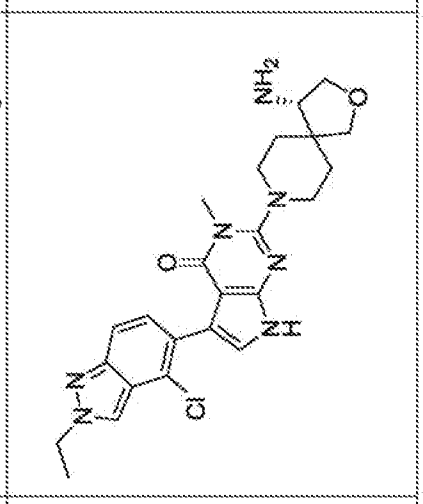
[1619]

4		2-(*exo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.45 (1H, s), 7.49 (1H, d, J = 8.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, s), 4.48 (2H, q, J = 7.2 Hz), 4.11 (2H, br s), 3.43 (3H, s), 3.06-2.94 (1H, m), 2.04-1.92 (2H, m), 1.85-1.78 (2H, m), 1.71-1.63 (2H, m), 1.56-1.46 (6H, m).	452, 454	1
5		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 6.94 (1H, s), 4.48 (2H, q, J = 7.3 Hz), 4.12-4.05 (2H, m), 3.41 (3H, s), 2.27-2.22 (2H, m), 2.17-2.09 (2H, m), 2.00-1.92 (2H, m), 1.59-1.50 (7H, m).	452, 454	1
6		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, s), 7.82 (1H, d, J = 8.4 Hz), 7.54 (1H, d, J = 8.4 Hz), 6.98 (1H, s), 4.06 (2H, br s), 3.38 (3H, s), 3.13 (2H, q, J = 7.6 Hz), 2.24-2.19 (2H, m), 2.13-2.08 (2H, m), 1.93-1.92 (3H, m), 1.56-1.52 (3H, m), 1.37 (3H, t, J = 7.6 Hz).	469, 471	1

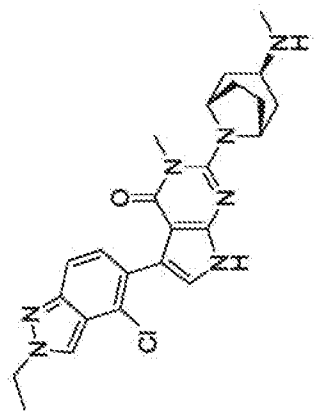
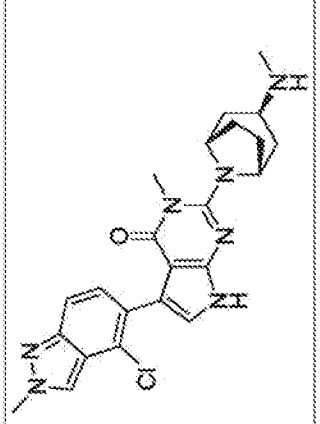
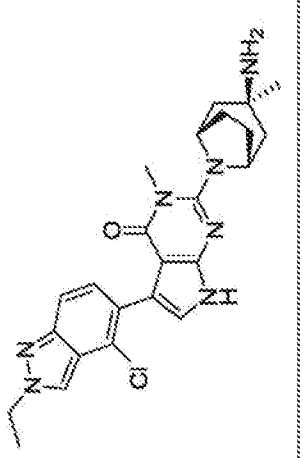
[1620]

7		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.81 (1H, d, J = 8.2 Hz), 7.56 (1H, d, J = 8.4 Hz), 6.99 (1H, s), 4.16-4.03 (1H, m), 3.42-3.32 (5H, m), 2.82 (3H, s), 2.29-2.19 (1H, m), 2.18-2.07 (2H, m), 2.02-1.89 (2H, m), 1.65-1.50 (2H, m).	455, 457	1
8		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.96 (1H, s), 4.19 (3H, s), 4.08-4.00 (2H, br s), 3.41 (3H, s), 2.24-2.19 (2H, m), 2.15-2.06 (2H, m), 2.05-1.97 (3H, m), 1.61-1.55 (3H, m).	438, 440	1
9		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(2-(叔丁基)-4-氯-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR ($CDCl_3$) δ: 8.58 (1H, br s), 8.09 (1H, s), 7.64 (1H, d, J = 8.8 Hz), 7.45 (1H, d, J = 8.8 Hz), 6.89 (1H, br s), 4.09 (2H, br s), 3.54 (3H, s), 3.44 (1H, br s), 2.40-2.25 (2H, m), 2.20-2.06 (4H, m), 1.73 (9H, s), 1.62 (2H, br d, J = 13.9 Hz).	480, 482	1

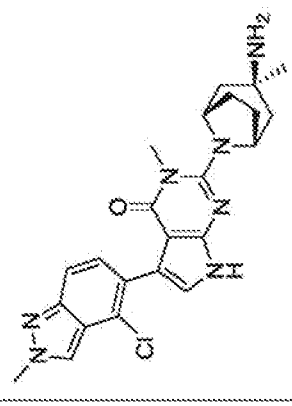
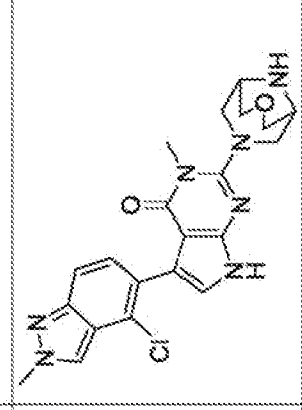
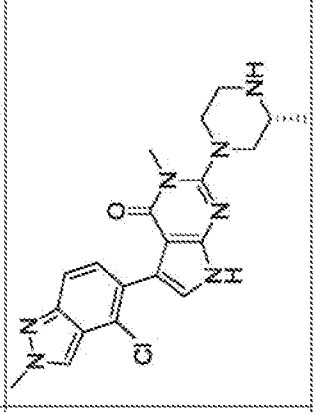
[1621]

10		2-(*exo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74-11.56 (1H, m), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 8.8 Hz), 6.95 (1H, s), 4.23-4.15 (6H, m), 3.42 (3H, s), 2.09-1.64 (8H, m).	438, 440	1
11		(*R*)-2-(1-氨基-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.45 (1H, s), 7.50 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.01 (1H, s), 4.48 (2H, q, J = 7.2 Hz), 3.39 (3H, s), 3.35-3.27 (1H, m), 2.88-2.83 (2H, m), 2.73-2.71 (1H, m), 1.88-1.50 (10H, m), 1.39-1.15 (5H, m).	480, 482	1
12		(*S*)-2-(4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.45 (1H, s), 7.50 (1H, d, J = 9.0 Hz), 7.31 (1H, d, J = 9.0 Hz), 7.01 (1H, s), 4.48 (2H, q, J = 7.2 Hz), 3.97-3.93 (1H, m), 3.70-3.68 (1H, m), 3.60-3.58 (1H, m), 3.40 (3H, s), 3.32-3.24 (1H, m), 3.18-3.13 (1H, m), 3.09-3.06 (1H, m), 2.90-2.83 (2H, m), 1.84-1.69 (4H, m), 1.60-1.45 (5H, m).	482, 484	1

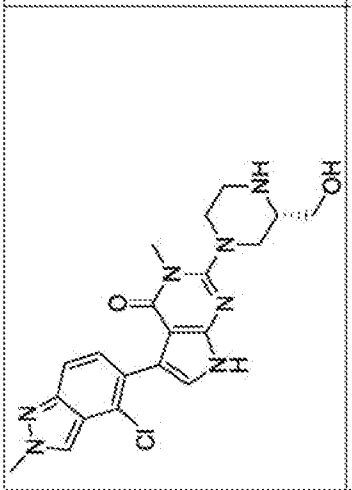
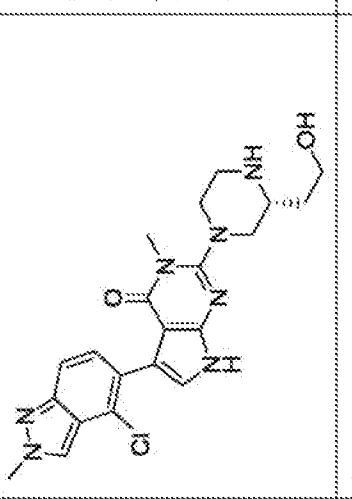
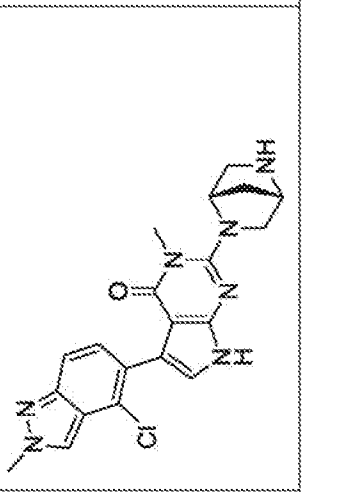
[1622]

13		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-2-(*endo*-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 6.94 (1H, s), 4.48 (2H, q, J = 7.3 Hz), 4.07 (2H, br s), 3.42 (3H, s), 2.78-2.74 (1H, m), 2.29 (3H, s), 2.11-2.03 (4H, m), 1.93-1.92 (2H, m), 1.75-1.71 (2H, m), 1.52 (3H, t, J = 7.3 Hz).	466, 468	1
14		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(*endo*-3-(甲基氨基)-8-氮杂二环[3.2.1]辛烷-8-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, J = 4.9 Hz), 7.32 (1H, d, J = 9.2 Hz), 6.95 (1H, s), 4.19 (3H, s), 4.08 (2H, br s), 3.42 (3H, s), 2.82-2.80 (1H, m), 2.31 (3H, s), 2.14-2.03 (4H, m), 1.97-1.89 (2H, m), 1.77-1.70 (2H, m).	452, 454	1
15		2-(*endo*-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, s), 8.42 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 6.92 (1H, s), 4.47 (2H, q, J = 7.2 Hz), 4.08 (2H, br s), 3.40 (3H, s), 2.29-2.23 (2H, m), 1.94-1.85 (4H, m), 1.64-1.58 (2H, m), 1.51 (3H, t, J = 7.2 Hz), 1.09 (3H, s).	466, 468	1

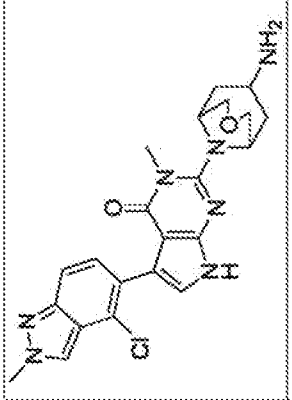
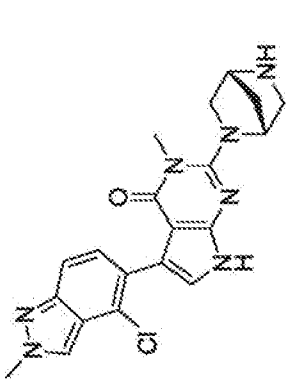
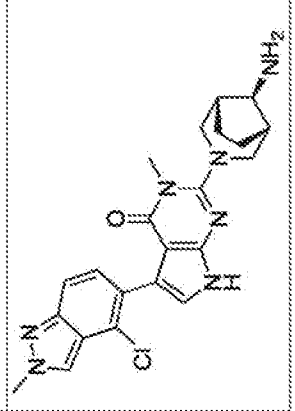
[1623]

16		2-(*endo*-3- 氨基 -3- 甲基 -8- 氮杂二环 [3.2.1] 辛烷 -8- 基)-5-(4- 氯 -2- 甲基 -2*H*- 吲唑 -5- 基)-3- 甲基 -3,7- 二氢 -4*H*- 吡咯并 [2,3-*d*] 嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.94 (1H, s), 4.19 (3H, s), 4.09 (2H, br s), 3.41 (3H, s), 2.34-2.27 (2H, m), 1.93-1.86 (4H, m), 1.67-1.59 (2H, m), 1.47-1.33 (1H, m), 1.09 (3H, s).	452, 454	1
17		2-(3- 氧杂 -7,9- 二氮杂二环 [3.3.1] 壬烷 -7- 基)-5-(4- 氯 -2- 甲基 -2*H*- 吲唑 -5- 基)-3- 甲基 -3,7- 二氢 -4*H*- 吡咯并 [2,3-*d*] 嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.41 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.96-3.79 (4H, m), 3.54-3.43 (5H, m), 3.23-3.14 (2H, m), 2.87-2.80 (2H, m).	440, 442	1
18		(*R*)-5-(4- 氯 -2- 甲基 -2*H*- 吲唑 -5- 基)-3- 甲基 -2-(3- 甲基哌嗪 -1- 基)-3,7- 二氢 -4*H*- 吡咯并 [2,3-*d*] 嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.80 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.41-3.22 (5H, m), 2.97-2.65 (4H, m), 2.46-2.36 (1H, m), 1.01 (3H, d, J = 6.0 Hz).	412, 414	1

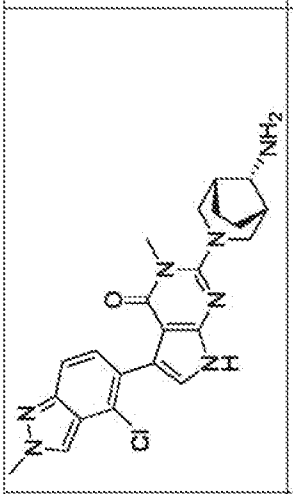
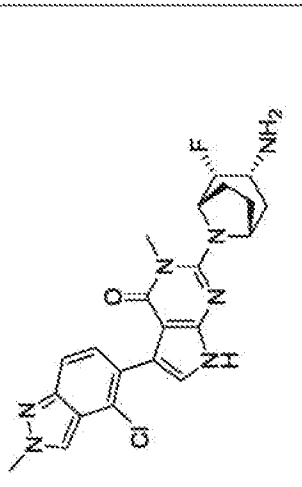
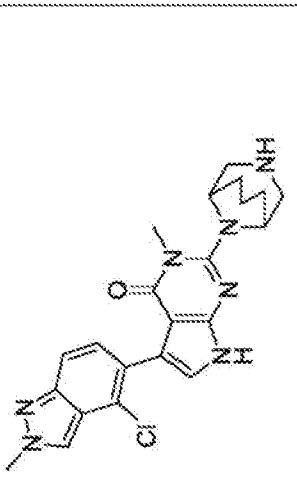
[1624]

19		(*S*)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-2-(3-(羟基甲基)吡咯 -1- 基)-3- 甲 基 -3,7- 二 氢 -4*H*- 吡 哆 并 [2,3-*d*]嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J*= 8.8 Hz), 7.31 (1H, d, *J*= 8.8 Hz), 7.01 (1H, s), 4.18 (3H, s), 3.39 (3H, s), 3.39-3.21 (4H, m), 3.06-2.72 (4H, m), 2.65-2.52 (1H, m).	428, 430	2
20		(*R*)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-2-(3-(2-羟基乙基) 吡 咯 -1- 基)-3- 甲 基 -3,7-二氢-4*H*-吡哆并 [2,3-*d*]嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.79 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 7.02 (1H, s), 4.18 (3H, s), 3.39 (3H, s), 3.39-3.21 (4H, m), 3.07-2.98 (2H, m), 2.94 (1H, t, *J* = 10.8 Hz), 2.81 (1H, t, *J* = 10.4 Hz), 2.58 (1H, t, *J* = 11.5 Hz), 1.63-1.51 (2H, m).	442, 444	2
21		2-((1*S*,4*S*)-2,5-二氮杂二环 [2.2.1] 庚 烷 -2- 基)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-3- 甲 基 -3,7-二氢-4*H*-吡哆并[2,3-*d*]嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.54 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.91 (1H, s), 4.43 (1H, br s), 4.20 (3H, s), 3.67-3.61 (2H, m), 3.33-3.30 (4H, m), 3.19-3.14 (1H, m), 2.91-2.85 (1H, m), 1.77-1.73 (1H, m), 1.65-1.62 (1H, m).	410, 412	1

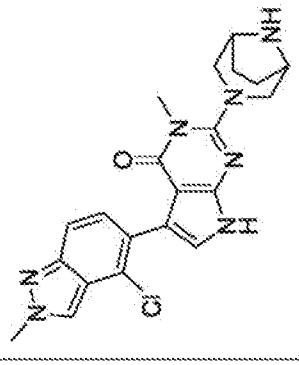
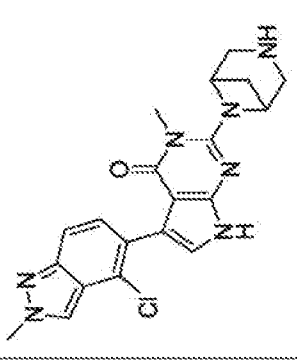
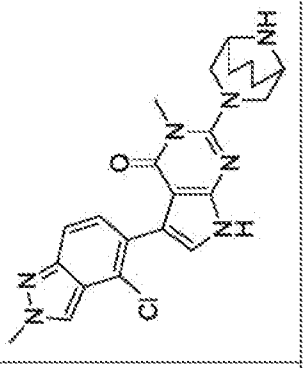
[1625]

22		2-(7-氯基-3-氧杂-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.38 (1H, s), 7.52-7.26 (2H, m), 6.97 (1H, s), 4.18 (3H, s), 4.01-3.08 (9H, m), 2.18-2.01 (4H, m).	454, 456	2
23		2-((1*R*,4*R*)-2,5-二氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.54 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.33 (1H, d, *J* = 8.8 Hz), 6.91 (1H, s), 4.43 (1H, br s), 4.20 (3H, s), 3.67-3.61 (2H, m), 3.33-3.30 (4H, m), 3.19-3.14 (1H, m), 2.91-2.85 (1H, m), 1.77-1.73 (1H, m), 1.65-1.62 (1H, m).	410, 412	1
24		2-(*exo*-8-氨基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.38 (1H, s), 7.48 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 4.18 (3H, s), 3.43 (3H, s), 3.43-3.39 (1H, m), 3.31-3.17 (4H, m), 2.95 (2H, d, *J* = 11.6 Hz), 2.29-2.23 (2H, m), 1.94-1.74 (4H, m).	438, 440	2

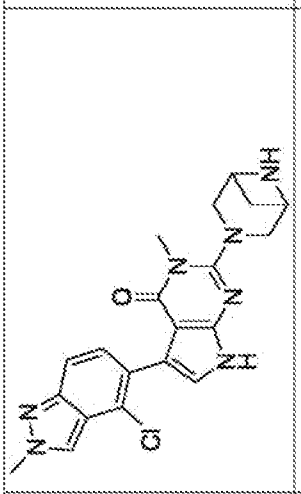
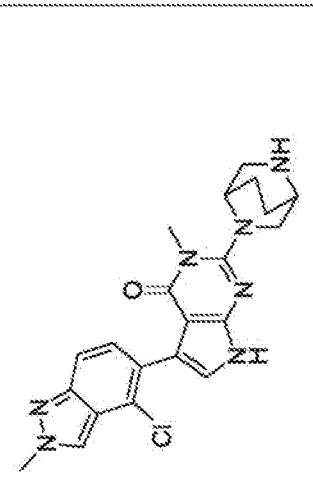
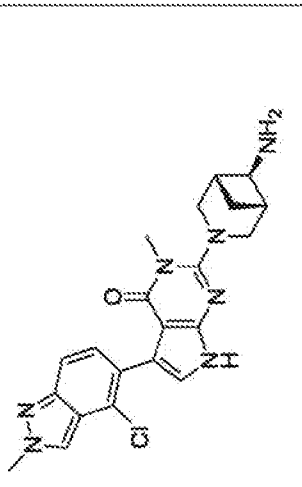
[1626]

25		2-(*endo*-8-氮基-3-氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.69 (1H, br s), 8.38 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.00 (1H, s), 4.18 (3H, s), 3.42 (3H, s), 3.42-3.36 (1H, m), 3.15-3.00 (4H, m), 2.13-2.06 (2H, br s), 1.85-1.70 (4H, m).	438, 440	1
26		*rac*-2-((1*S*,2*R*,3*R*,5*R*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, s), 8.38 (1H, s), 7.47 (1H, dd, J = 8.8, 0.9 Hz), 7.31 (1H, d, J = 8.8 Hz), 6.96-6.94 (1H, m), 4.56-4.38 (2H, m), 4.18 (3H, s), 4.14-4.09 (1H, m), 3.44 (3H, s), 3.06-2.89 (1H, m), 2.07-1.92 (2H, m), 1.89-1.79 (1H, m), 1.77-1.57 (5H, m).	456, 458	4
27		2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.94 (1H, s), 4.19 (3H, s), 3.65 (2H, br s), 3.34-3.32 (4H, m), 3.27-3.25 (1H, m), 2.92-2.88 (2H, m), 2.80-2.70 (1H, m), 2.16-2.10 (2H, m), 1.76-1.71 (2H, m), 1.62-1.55 (1H, m).	438, 440	1

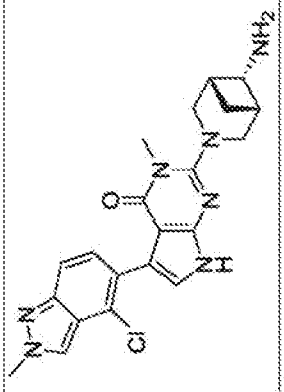
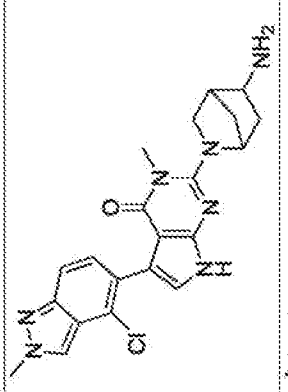
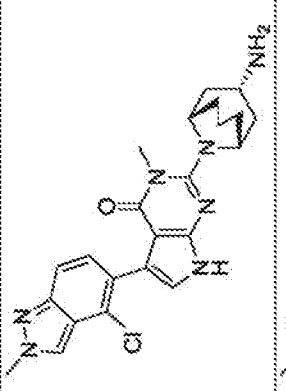
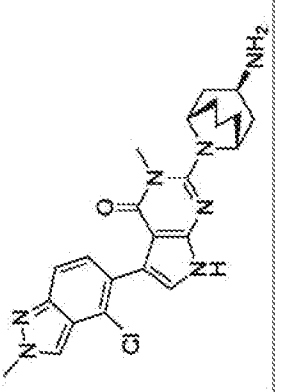
[1627]

28		2-(3,8-二氮杂二环[3.2.1]辛烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.81 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 8.8 Hz), 7.02 (1H, s), 4.18 (3H, s), 3.72 (2H, br s), 3.42 (3H, s), 3.21 (2H, d, J = 12.3 Hz), 3.09 (2H, d, J = 12.1 Hz), 2.02-1.95 (2H, m), 1.86-1.78 (2H, m).	424, 426	1
29		2-(3,6-二氮杂二环[3.1.1]庚烷-6-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.55 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.93 (1H, s), 4.48 (2H, d, J = 6.2 Hz), 4.19 (3H, s), 3.68-3.41 (2H, m), 3.28 (3H, s), 3.08 (2H, d, J = 12.1 Hz), 2.79-2.72 (1H, m), 1.84 (1H, d, J = 8.8 Hz).	410, 412	1
30		2-(3,9-二氮杂二环[3.3.1]壬烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.46 (3H, s), 3.39-3.36 (2H, m), 3.14-3.11 (2H, m), 3.05-3.03 (2H, m), 2.51-2.49 (1H, m), 1.89-1.76 (4H, m), 1.65-1.58 (1H, m).	438, 440	1

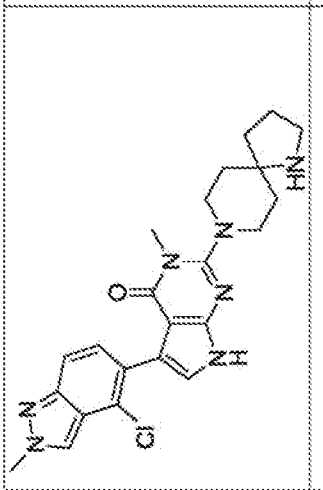
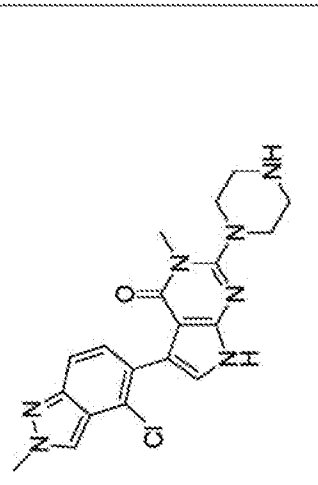
[1628]

31		2-(3,6-二氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.69 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.00 (1H, s), 4.19 (3H, s), 3.90 (2H, d, J = 5.6 Hz), 3.83-3.73 (4H, m), 3.39 (3H, s), 2.63-2.56 (1H, m), 1.84 (1H, d, J = 8.7 Hz).	410, 412	1
32		2-(2,5-二氮杂二环[2.2.2]辛烷-2-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.3 Hz), 6.93 (1H, s), 4.18 (3H, s), 3.78-3.74 (1H, m), 3.65 (1H, d, J = 10.1 Hz), 3.53-3.45 (3H, m), 3.32 (1H, s), 3.30-3.27 (1H, m), 3.08 (1H, br s), 2.98 (1H, d, J = 10.9 Hz), 2.28-2.13 (1H, m), 1.94-1.67 (3H, m).	424, 426	1
33		2-(*exo*-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.97 (1H, s), 4.18 (3H, s), 3.84 (2H, d, J = 11.3 Hz), 3.62-3.59 (2H, m), 3.37 (3H, s), 3.18-3.15 (1H, m), 2.67-2.59 (1H, m), 2.34-2.29 (2H, m), 1.66-1.60 (1H, m).	424, 426	1

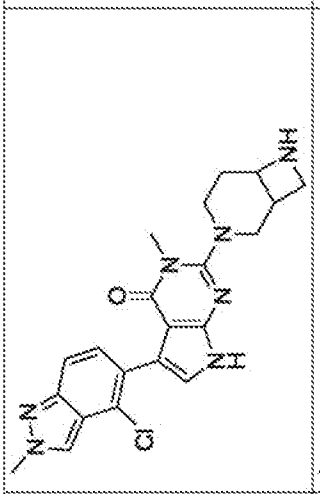
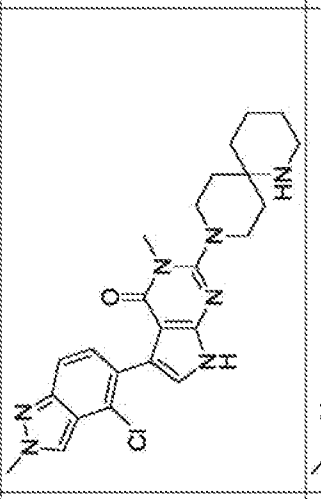
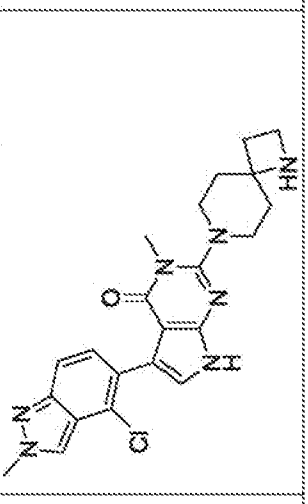
[1629]

34		2-(*endo*-6-氨基-3-氮杂二环[3.1.1]庚烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.96 (1H, s), 4.18 (3H, s), 3.80-3.27 (7H, m), 2.44-2.39 (2H, m), 1.75-1.61 (1H, m), 1.46 (1H, d, J = 9.0 Hz).	424, 426	1
35		2-(5-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.53 (1H, br s), 8.37 (1H, s), 7.48-7.45 (1H, m), 7.32 (1H, d, J = 8.7 Hz), 6.88 (1H, s), 4.23-4.14 (5H, m), 3.39-3.21 (5H, m), 2.65-2.60 (1H, m), 2.09-2.00 (1H, m), 1.82-1.59 (2H, m).	424, 426	1
36		2-(*exo*-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.38 (1H, s), 7.52-7.28 (2H, m), 6.94 (1H, s), 4.18 (3H, s), 4.00-3.87 (3H, m), 3.33 (3H, s), 2.17-1.59 (10H, m).	452, 454	2
37		2-(*endo*-3-氨基-9-氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 8.8 Hz), 6.94 (1H, s), 4.18 (3H, s), 4.11-4.04 (2H, m), 3.31 (3H, s), 2.55-2.36 (1H, m), 2.12-1.76 (2H, m), 1.61-1.37 (6H, m).	452, 454	1

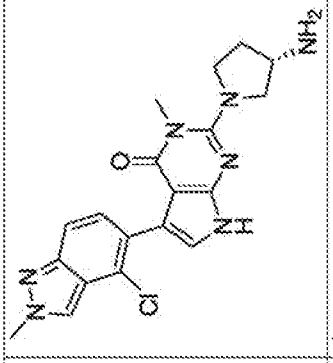
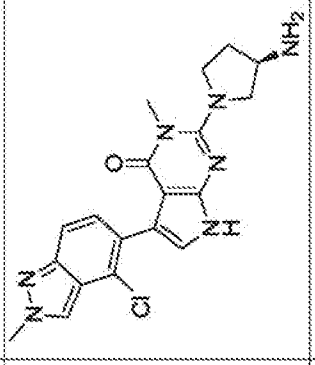
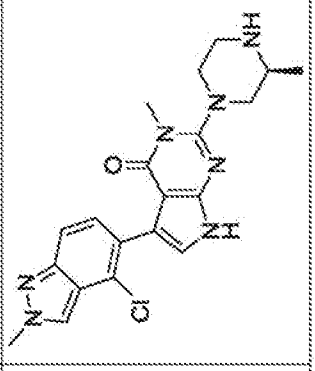
[1630]

38		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(1,8-二氮杂螺[4.5]癸烷-8-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.71 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.99 (1H, s), 4.18 (3H, s), 3.37 (3H, s), 3.21-3.14 (2H, m), 3.08-3.00 (2H, m), 2.85-2.81 (2H, m), 1.80-1.49 (8H, m).	452, 454	1
39		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(哌嗪-1-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.78 (1H, s), 8.38 (1H, s), 7.46 (1H, d, J = 8.8 Hz), 7.29 (1H, d, J = 8.8 Hz), 6.99 (1H, s), 4.17 (3H, s), 3.36 (3H, s), 3.02-2.96 (4H, m), 2.86-2.78 (4H, m).	398, 400	2, 通过r-HPLC纯化后，将所得级分用饱和$NaHCO_3$碱化，并用$CHCl_3$-MeOH萃取，有机层经无水Na_2SO_4干燥，过滤，并真空浓缩，将残余物悬浮于EtOAc-己烷中。

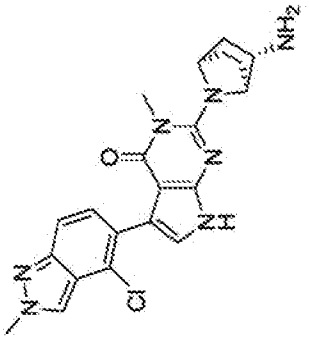
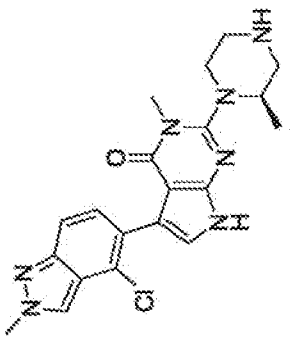
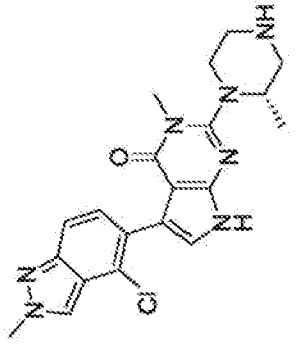
[1631]

40		2-(3,7-二氮杂二环[4.2.0]辛烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氮-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.9 Hz), 7.01 (1H, d, J = 2.7 Hz), 4.23-4.14 (4H, m), 3.75-3.66 (2H, m), 3.36 (3H, s), 3.21-3.01 (2H, m), 2.94-2.87 (2H, m), 2.53-2.50 (1H, m), 1.81-1.73 (2H, m).	424, 426	1
41		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(1,9-二氮杂螺[5.5]十一烷-9-基)-3,7-二氮-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.40 (1H, s), 7.55-7.30 (2H, m), 7.03-7.01 (1H, m), 4.19 (3H, s), 3.37 (3H, s), 3.09-2.86 (4H, m), 1.95-1.76 (4H, m), 1.68-1.48 (6H, m).	466, 468	1
42		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(1,7-二氮杂螺[3.5]壬烷-7-基)-3,7-二氮-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.82 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 9.2 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.78-3.14 (9H, m), 2.95-2.89 (2H, m), 2.35-2.20 (4H, m).	438, 440	1,用 4 M HCl 的二氧六环溶液代替 TFA 和 $CHCl_3$

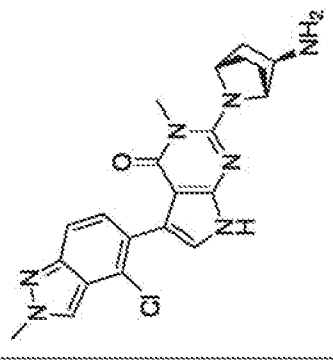
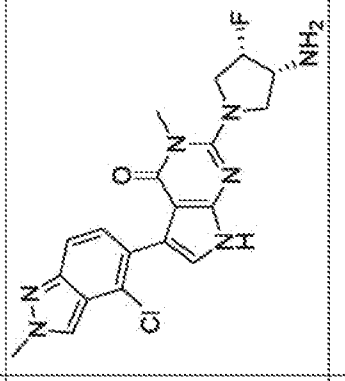
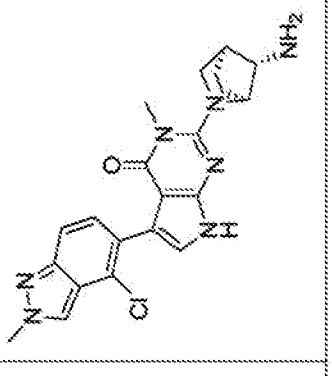
[1632]

43		(*S*)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 4.19 (3H, s), 3.66-3.41 (4H, m), 3.33 (3H, s), 3.13-3.06 (1H, m), 2.04-1.58 (4H, m).	398, 400	1
44		(*R*)-2-(3-氨基吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 4.19 (3H, s), 3.66-3.39 (4H, m), 3.33 (3H, s), 3.13-3.07 (1H, m), 2.05-1.59 (4H, m).	398, 400	1
45		(*S*)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-(3-甲基哌嗪-1-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.77 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.00 (1H, s), 4.19 (3H, s), 3.51-3.45 (1H, m), 3.38 (3H, s), 2.96-2.79 (3H, m), 2.74-2.65 (1H, m), 2.42-2.35 (2H, m), 1.00 (3H, d, J = 6.6 Hz).	412, 414	1

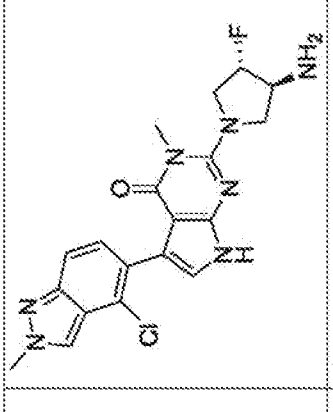
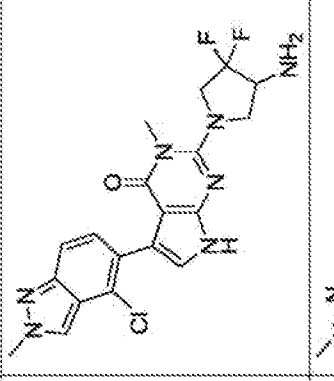
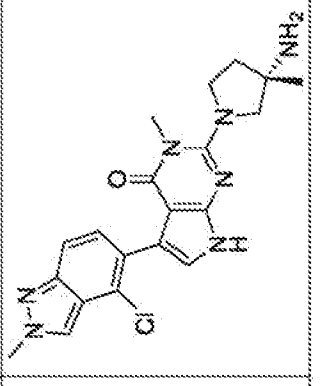
[1633]

46		2-((1*S*,2*S*,4*R*)-2- 氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2- 甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 9.0 Hz), 6.94 (1H, d, J = 9.0 Hz), 7.32 (1H, s), 4.19 (3H, s), 4.15-4.12 (1H, m), 4.01-3.98 (1H, m), 3.49-3.42 (1H, m), 3.39 (3H, s), 2.30-2.24 (1H, m), 2.19-2.14 (1H, m), 2.00-1.79 (2H, m), 1.72-1.64 (1H, m), 1.54-1.45 (1H, m), 0.90-0.85 (1H, m).	424, 426	1
47		(*R*)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-3- 甲基 -2-(2- 甲基哌嗪 -1-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.88 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 9.0 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.06 (1H, s), 4.19 (3H, s), 3.48-3.43 (1H, m), 3.42 (3H, s), 3.23-3.15 (1H, m), 3.10-3.02 (1H, m), 3.00-2.87 (2H, m), 2.85-2.77 (1H, m), 2.70-2.61 (1H, m), 1.04 (3H, d, J = 6.2 Hz).	412, 414	1
48		(*S*)-5-(4- 氯 -2- 甲 基 -2*H*- 吲 唑 -5- 基)-3- 甲基 -2-(2- 甲基哌嗪 -1-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.84 (1H, br s), 8.39 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.9 Hz), 7.05 (1H, s), 4.18 (3H, s), 3.42 (3H, s), 3.42-3.35 (1H, m), 3.17-3.09 (1H, m), 2.99-2.93 (1H, m), 2.77-2.69 (2H, m), 2.58-2.51 (1H, m), 1.02 (3H, d, J = 6.1 Hz).	412, 414	1

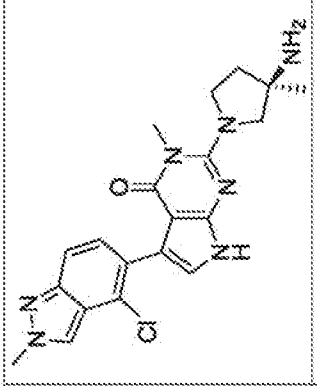
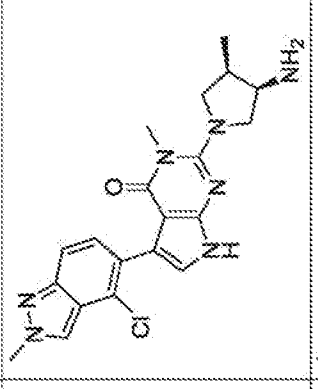
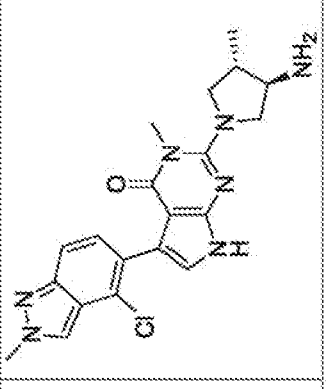
[1634]

49		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 6.93 (1H, s), 4.18 (3H, s), 4.15-4.10 (1H, m), 4.02-3.97 (1H, m), 3.50-3.42 (1H, m), 3.38 (3H, s), 2.34-2.07 (2H, m), 1.97-1.79 (1H, m), 1.78-1.60 (1H, m), 1.57-1.40 (1H, m), 0.91-0.83 (1H, m).	424, 426	1
50		2-((3*R*,4*S*)-3-氨基-4-氟吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.52 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.91 (1H, d, *J* = 2.3 Hz), 5.05-4.88 (1H, m), 4.18 (3H, s), 4.07-3.90 (1H, m), 3.56-3.35 (4H, m), 3.32 (3H, s), 1.77 (2H, br s).	416, 418	1
51		*rac*-2-(((1*S*,4*S*,7*S*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.37 (1H, s), 7.46 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 6.88 (1H, s), 4.18 (3H, s), 3.84 (1H, s), 3.73-3.65 (1H, m), 3.28-3.23 (4H, m), 3.02 (1H, d, *J* = 8.8 Hz), 2.15 (1H, s), 2.01-1.83 (3H, m), 1.74-1.49 (2H, m), 1.42-1.31 (1H, m).	424, 426	1

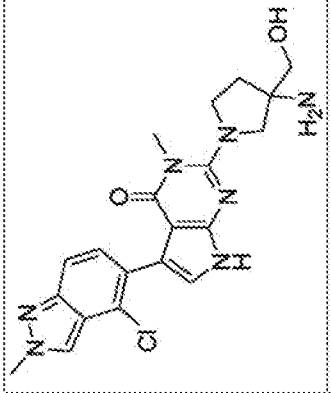
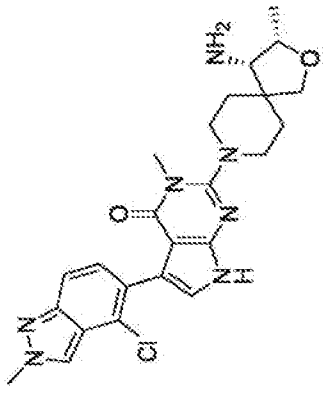
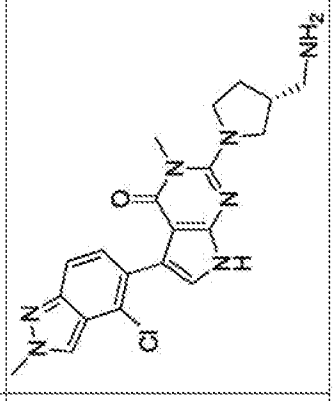
[1635]

52		2-((3S,4S)-3- 氟 基 -4- 氟 吡 咯 烷 -1- 基)-5-(4- 氟 -2- 甲 基 -2H- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4H- 吡 咯 并 [2,3-d] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.52 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.92 (1H, d, J = 2.2 Hz), 5.07-4.87 (1H, m), 4.22-3.99 (4H, m), 3.90-3.84 (1H, m), 3.62-3.40 (2H, m), 3.36 (3H, s), 3.16 (1H, d, J = 10.7 Hz).	416, 418	1
53		2-(4- 氟 基 -3,3- 二 氟 吡 咯 烷 -1- 基)-5-(4- 氟 -2- 甲 基 -2H- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4H- 吡 咯 并 [2,3-d] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, br s), 8.41 (1H, s), 7.50 (1H, d, J = 8.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 6.98 (1H, d, J = 2.4 Hz), 4.21 (3H, s), 3.98-3.88 (2H, m), 3.82-3.76 (1H, m), 3.69-3.59 (1H, m), 3.36 (3H, s), 3.33-3.27 (1H, m), 2.09-1.93 (2H, br s).	434, 436	1
54		(S)-2-(3- 氟 基 -3- 甲 基 吡 咯 烷 -1- 基)-5-(4- 氟 -2- 甲 基 -2H- 吲 唑 -5- 基)-3- 甲 基 -3,7- 二 氢 -4H- 吡 咯 并 [2,3-d] 嘧 啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 11.47 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.7 Hz), 6.89 (1H, s), 4.20-4.16 (3H, m), 3.75-3.65 (2H, m), 3.53-3.43 (2H, m), 3.33 (3H, s), 3.30-3.13 (2H, m), 2.02-1.76 (4H, m), 1.22 (3H, s).	412, 414	1

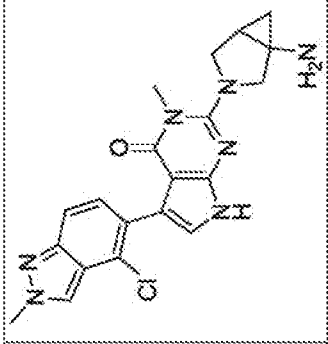
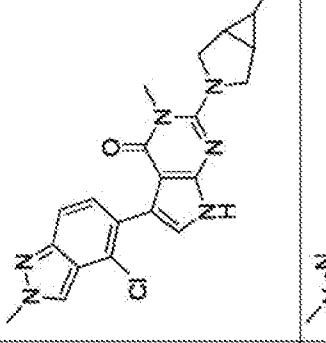
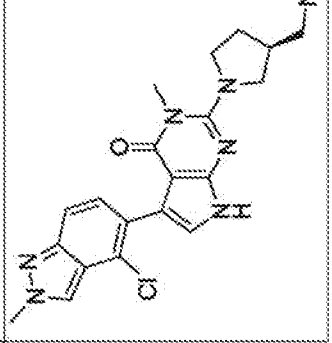
[1636]

55		(*R*)-2-(3-氯基-3-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, br s), 8.40 (1H, s), 7.50 (1H, d, J = 8.7 Hz), 7.35 (1H, d, J = 8.8 Hz), 6.92 (1H, s), 4.21 (3H, s), 3.78-3.67 (1H, m), 3.56-3.45 (1H, m), 3.39-3.29 (4H, m), 3.20 (1H, d, J = 10.1 Hz), 1.83-1.75 (4H, m), 1.25 (3H, s).	412, 414	1
56		2-((3*R*,4*R*)-3-氯基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.48 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.35 (1H, d, J = 8.8 Hz), 6.91 (1H, s), 4.21 (3H, s), 3.69 (1H, q, J = 5.2 Hz), 3.47-3.28 (5H, m), 3.20-3.12 (2H, m), 2.26-2.13 (1H, m), 1.01 (1H, d, J = 7.0 Hz).	412, 414	1
57		2-((3*R*,4*S*)-3-氯基-4-甲基吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.55 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.8 Hz), 6.92 (1H, s), 4.21 (3H, s), 3.61-3.51 (2H, m), 3.34 (3H, s), 3.28-3.17 (2H, m), 2.95-2.87 (1H, m), 1.92-1.76 (1H, m), 1.05 (3H, d, J = 6.6 Hz).	412, 414	1

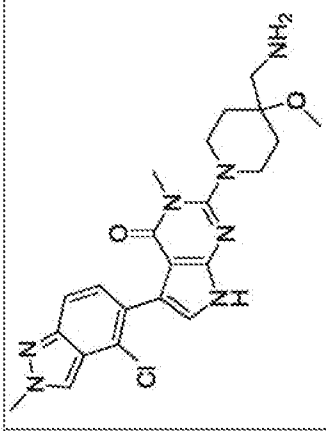
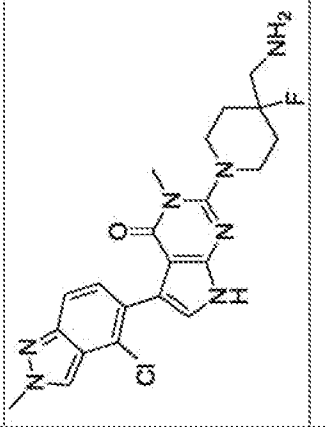
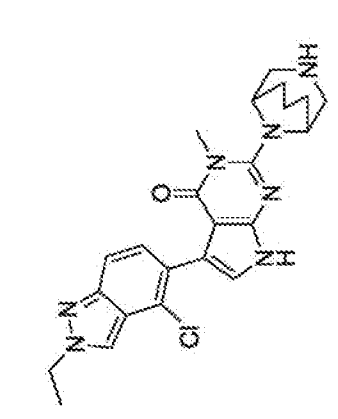
[1637]

58		2-(3-氨基-3-(羟基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.47 (1H, br s), 8.37 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.7 Hz), 6.89 (1H, s), 4.86 (1H, br s), 4.18 (3H, s), 3.76-3.67 (1H, m), 3.51-3.01 (8H, m), 1.93-1.83 (1H, m), 1.67-1.54 (1H, m).	428, 430	1
59		2-((3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 8.40 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.01 (1H, d, J = 2.0 Hz), 4.19 (3H, s), 4.09-4.02 (1H, m), 3.66 (1H, d, J = 8.3 Hz), 3.49 (1H, d, J = 8.5 Hz), 3.40 (3H, s), 3.27-3.19 (1H, m), 3.00-2.85 (3H, m), 1.90-1.84 (1H, m), 1.80-1.73 (1H, m), 1.66-1.55 (2H, m), 1.36-1.24 (2H, m), 1.09 (3H, d, J = 6.3 Hz).	482, 484	1
60		(*R*)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.91 (1H, s), 4.18 (3H, s), 3.55-3.26 (7H, m), 2.87-2.76 (2H, m), 2.45-2.36 (1H, m), 2.13-2.00 (1H, m), 1.76-1.61 (1H, m).	412, 414	1

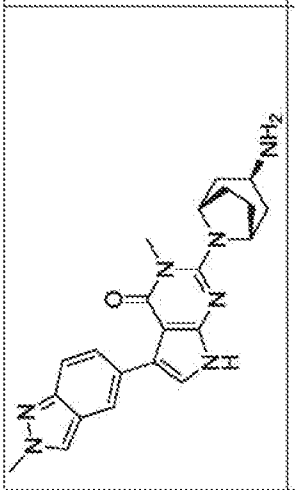
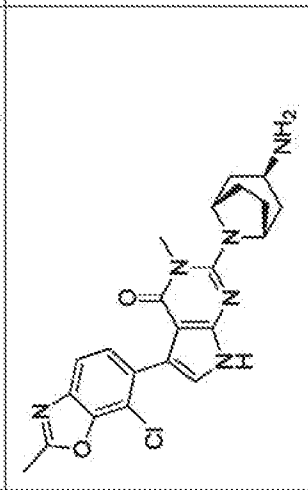
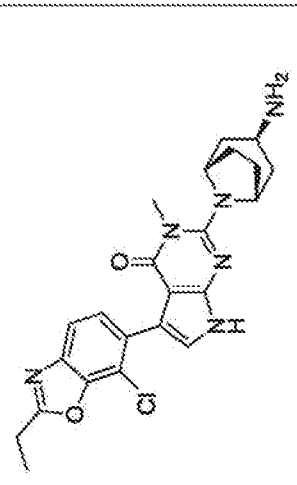
[1638]

61		2-(1-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, d, J = 2.3 Hz), 4.18 (3H, s), 3.73 (1H, d, J = 9.9 Hz), 3.58-3.46 (2H, m), 3.36-3.25 (4H, m), 1.39-1.31 (1H, m), 0.81-0.74 (1H, m), 0.69-0.62 (1H, m).	410, 412	1
62		2-(6-氨基-3-氮杂二环[3.1.0]己烷-3-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.59 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, d, J = 2.3 Hz), 4.18 (3H, s), 3.73 (1H, d, J = 9.9 Hz), 3.58-3.46 (2H, m), 3.36-3.25 (4H, m), 1.39-1.31 (1H, m), 0.81-0.74 (1H, m), 0.69-0.62 (1H, m).	410, 412	1
63		(*S*)-2-(3-(氨基甲基)吡咯烷-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.38 (1H, s), 7.47 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 4.18 (3H, s), 3.51-3.22 (7H, m), 2.64-2.53 (2H, m), 2.26-2.12 (1H, m), 2.03-1.92 (1H, m), 1.68-1.54 (1H, m).	412, 414	1

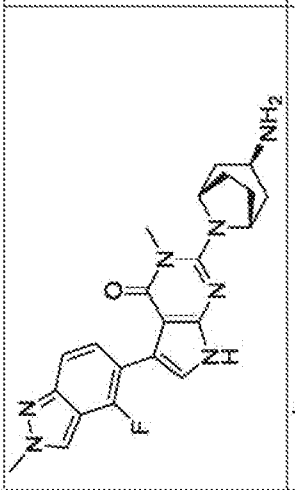
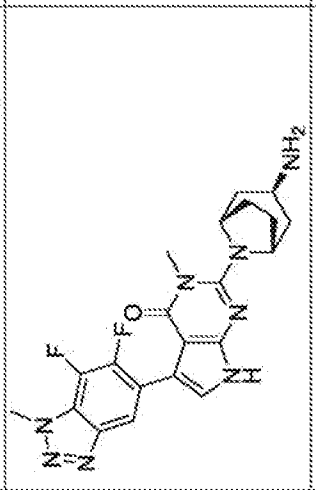
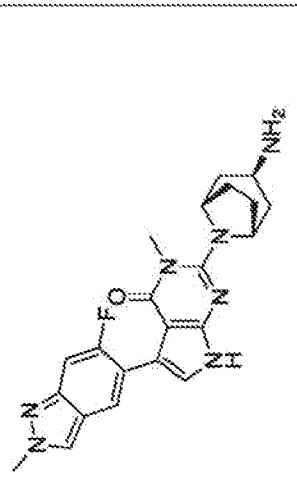
[1639]

64		2-(4-(氨基甲基)-4-甲氧基哌啶-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.01 (1H, s), 4.19 (3H, s), 3.39 (3H, s), 3.17-3.14 (5H, m), 3.01-2.98 (2H, m), 2.60 (2H, s), 1.83-1.80 (2H, m), 1.65-1.59 (2H, m).	456, 458	2
65		2-(4-(氨基甲基)-4-氟哌啶-1-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, s), 7.48 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.9 Hz), 7.02 (1H, s), 4.19 (3H, s), 3.40 (3H, s), 3.01-2.99 (2H, m), 2.72 (2H, d, J = 19.8 Hz), 2.54 (2H, s), 1.90-1.80 (4H, m).	444, 446	2
66		2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 8.43 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.93 (1H, d, J = 2.4 Hz), 4.48 (2H, q, J = 7.2 Hz), 3.65 (2H, br s), 3.37-3.33 (4H, m), 3.28-3.25 (1H, m), 2.92-2.89 (2H, m), 2.79-2.67 (1H, m), 2.20-2.07 (2H, m), 1.76-1.70 (2H, m), 1.63-1.56 (1H, m), 1.52 (3H, t, J = 7.2 Hz).	452, 454	1

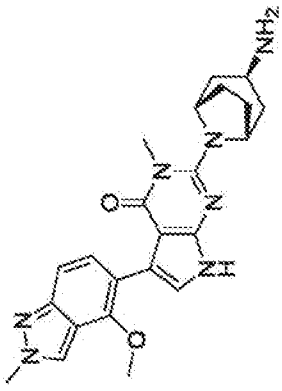
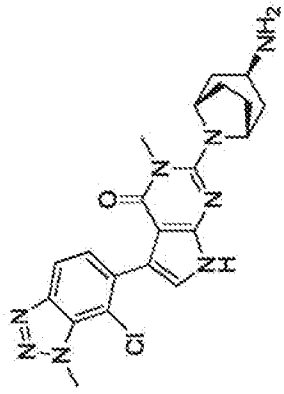
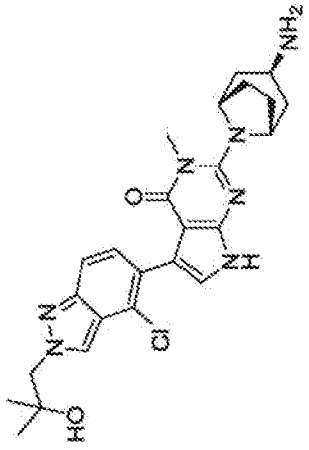
[1640]

67		2-(*endo*-3-氮杂二环[3.2.1]辛烷-8-基)-3-甲基-5-(2-甲基-2H-吲唑-5-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, br s), 8.26 (1H, s), 7.75-7.46 (2H, m), 7.14 (1H, s), 4.16-4.06 (5H, m), 3.51-3.40 (4H, m), 2.27-2.10 (4H, m), 2.00-1.90 (2H, m), 1.58 (2H, d, J = 13.6 Hz).	404	1
68		2-(*endo*-3-氮杂-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[*d*]噁唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.65 (1H, br s), 7.55 (1H, d, J = 8.3 Hz), 7.40 (1H, d, J = 8.3 Hz), 6.96 (1H, s), 4.08 (2H, br s), 3.40 (3H, s), 3.35-3.31 (1H, m), 2.65 (3H, s), 2.26-2.20 (2H, m), 2.17-2.09 (2H, m), 1.98-1.90 (2H, m), 1.60-1.53 (2H, m).	439, 441	2
69		2-(*endo*-3-氮杂-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-乙基苯并[*d*]噁唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (CD_3OD) δ: 7.52 (1H, d, J = 8.4 Hz), 7.46 (1H, d, J = 8.4 Hz), 6.96 (1H, s), 4.22 (2H, br s), 3.55 (3H, s), 3.37-3.33 (1H, m), 3.03 (2H, q, J = 7.7 Hz), 2.56-2.44 (2H, m), 2.27-2.17 (2H, m), 2.06-1.98 (2H, m), 1.68 (2H, br d, J = 13.6 Hz), 1.46 (3H, t, J = 7.7 Hz).	453, 455	1

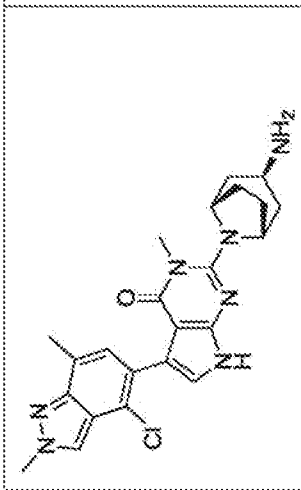
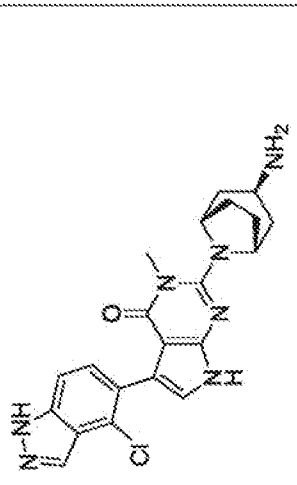
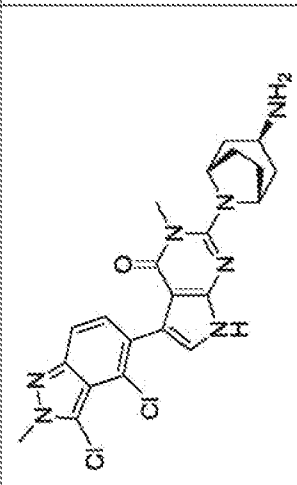
[1641]

70		2-(*endo*-3-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.60-7.31 (2H, m), 6.99 (1H, s), 4.19-4.09 (5H, m), 3.55-3.32 (4H, m), 2.33-2.19 (2H, m), 2.13-1.95 (4H, m), 1.67-1.55 (2H, m).	422	2
71		2-(*endo*-3-氮杂-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6,7-二氟-1-甲基-1*H*-苯并[*d*][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-d]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.78 (1H, s), 8.29 (1H, d, J = 4.6 Hz), 7.16 (1H, d, J = 1.8 Hz), 4.42 (3H, s), 4.17-4.03 (2H, m), 3.45 (3H, s), 2.63-2.61 (1H, m), 2.27-2.21 (2H, m), 2.18-2.12 (2H, m), 1.98-1.92 (2H, m), 1.61-1.56 (2H, m).	441	2
72		2-(*endo*-3-氮杂-8-氮杂二环[3.2.1]辛烷-8-基)-5-(6-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.57 (1H, s), 8.34 (1H, s), 8.06 (1H, d, J = 7.9 Hz), 7.28 (1H, d, J = 11.9 Hz), 6.97 (1H, d, J = 2.4 Hz), 4.14 (3H, s), 4.11-4.06 (2H, m), 3.44 (3H, s), 2.63-2.59 (1H, m), 2.25-2.21 (2H, m), 2.17-2.11 (2H, m), 1.98-1.92 (2H, m), 1.61-1.54 (2H, m).	422	2

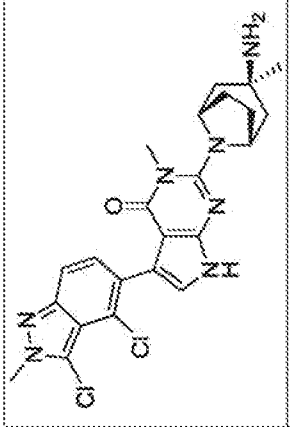
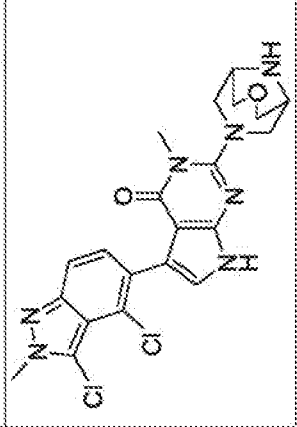
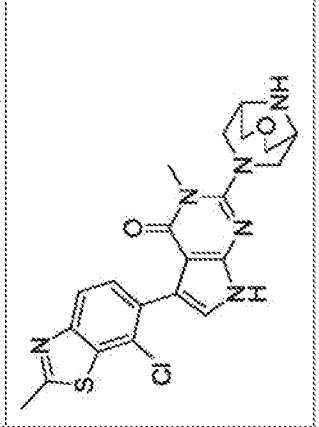
[1642]

73		2-(*endo*-3-氧基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-甲氧基-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.43 (1H, s), 8.51 (1H, s), 7.42 (1H, d, J = 8.9 Hz), 7.17 (1H, dd, J = 8.7, 1.1 Hz), 6.90 (1H, d, J = 2.4 Hz), 4.15 (3H, s), 4.11-4.07 (2H, m), 3.89 (3H, s), 3.43 (3H, s), 2.55-2.53 (1H, m), 2.23-2.12 (4H, m), 2.00-1.93 (2H, m), 1.61-1.55 (2H, m).	434	2
74		2-(*endo*-3-氧基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-1-甲基-1*H*-苯并[*d*][1,2,3]三唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, s), 7.92 (1H, d, J = 8.5 Hz), 7.44 (1H, d, J = 8.5 Hz), 7.02 (1H, d, J = 1.5 Hz), 4.53 (3H, s), 4.11-4.08 (2H, m), 3.41 (3H, s), 2.53-2.51 (1H, m), 2.27-2.22 (2H, m), 2.16-2.10 (2H, m), 1.99-1.92 (2H, m), 1.60-1.55 (2H, m).	439, 441	2
75		2-(*endo*-3-氧基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-(2-羟基-2-甲基丙基)-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.60 (1H, s), 8.30 (1H, d, J = 0.9 Hz), 7.51 (1H, dd, J = 8.9, 0.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, s), 4.88 (1H, s), 4.36 (2H, s), 4.11-4.07 (2H, m), 3.41 (3H, s), 2.69-2.65 (1H, m), 2.25-2.20 (2H, m), 2.18-2.11 (2H, m), 1.99-1.92 (2H, m), 1.60-1.55 (2H, m), 1.13 (6H, s).	496, 498	2

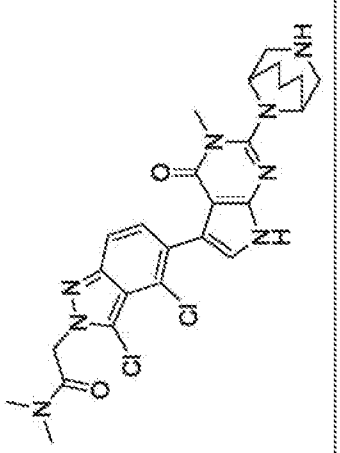
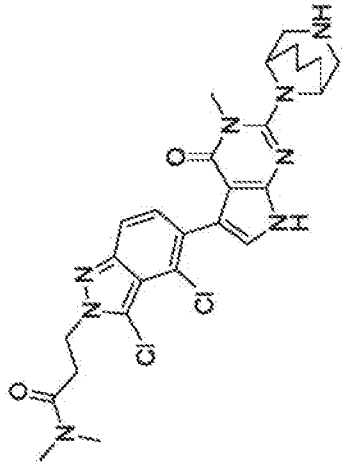
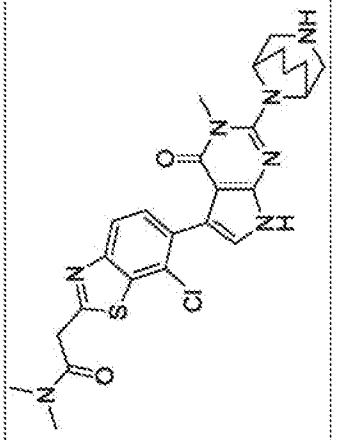
[1643]

76		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2,7-二甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR ($CDCl_3$) δ: 8.46 (1H, br s), 7.93 (1H, s), 7.25 (1H, s), 6.90 (1H, d, J = 2.2 Hz), 4.23 (3H, s), 4.10 (2H, br s), 3.55 (3H, s), 3.43 (1H, br t, J = 6.1 Hz), 2.60 (3H, s), 2.38-2.26 (2H, m), 2.23-2.13 (2H, m), 2.13-2.04 (2H, m), 1.60 (2H, br d, J = 13.9 Hz).	452, 454	1
77		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(1*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.32 (1H, s), 11.58 (1H, s), 8.07 (1H, s), 7.45-7.42 (2H, m), 6.93 (1H, d, J = 1.5 Hz), 4.11-4.05 (2H, m), 3.28 (3H, s), 2.47-2.43 (1H, m), 2.25-2.20 (2H, m), 2.16-2.09 (2H, m), 1.98-1.91 (2H, m), 1.59-1.54 (2H, m).	424, 426	2
78		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR ($CDCl_3$) δ: 8.37 (1H, br s), 7.53 (1H, d, J = 8.8 Hz), 7.46 (1H, d, J = 8.8 Hz), 6.94 (1H, d, J = 2.2 Hz), 4.14 (3H, s), 4.13 - 4.07 (2H, m), 3.55 (3H, s), 3.48-3.38 (1H, m), 2.39-2.25 (2H, m), 2.25-2.07 (4H, m), 1.61 (2H, br d, J = 13.9 Hz).	472, 474	1

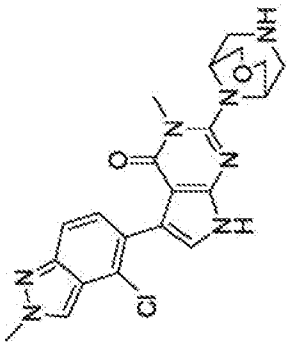
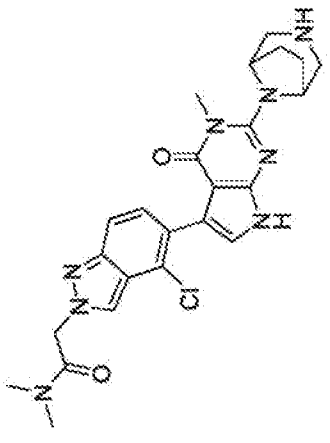
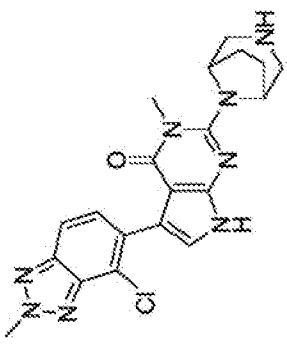
[1644]

79		2-(*endo*-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 7.50 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.97 (1H, s), 4.14 (3H, s), 4.09 (2H, br s), 3.41 (3H, s), 2.35-2.23 (2H, m), 1.96-1.81 (4H, m), 1.61 (2H, br d, J = 13.6 Hz), 1.09 (3H, s).	486, 488	1
80		2-(3-氯杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR ($CDCl_3$) δ: 8.45 (1H, br s), 7.54 (1H, d, J = 8.8 Hz), 7.46 (1H, d, J = 8.8 Hz), 7.00 (1H, d, J = 1.8 Hz), 4.15 (3H, s), 4.03 (4H, s), 3.67 (3H, s), 3.57 (2H, br d, J = 12.1 Hz), 3.37 (2H, br d, J = 12.1 Hz), 3.01 (2H, br s).	474, 476	1
81		2-(3-氯杂-7,9-二氮杂二环[3.3.1]壬烷-7-基)-5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.86 (1H, br s), 7.84 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 2.6 Hz), 3.91 (2H, d, J = 11.0 Hz), 3.83 (2H, br d, J = 11.0 Hz), 3.51 (3H, s), 3.48 (2H, br d, J = 11.7 Hz), 3.20 (2H, br d, J = 11.7 Hz), 2.88-2.81 (5H, m).	457, 459	1

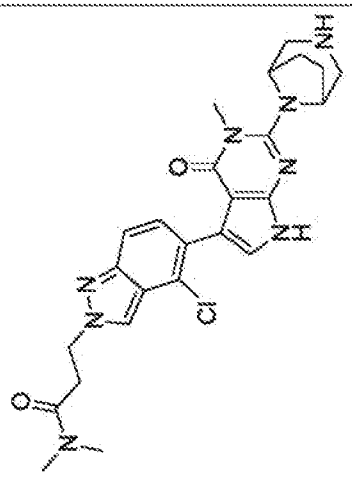
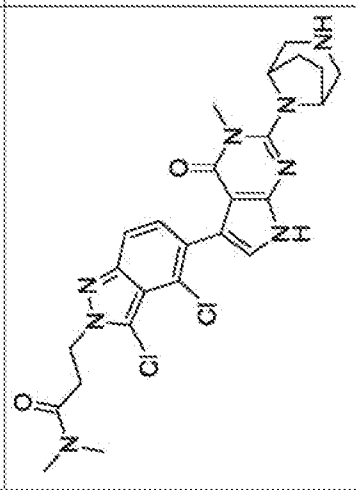
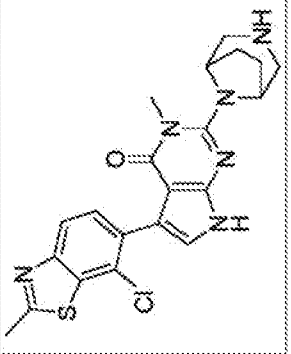
[1645]

82		2-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-5-基)-3,4-二氯-2*H*-吡唑-2-基)-*N*,*N*-二甲基乙酰胺	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, s), 7.51-7.48 (1H, m), 7.36-7.33 (1H, m), 6.97 (1H, d, J = 2.4 Hz), 5.52 (2H, s), 3.67-3.65 (2H, m), 3.28-3.24 (5H, m), 3.12 (3H, s), 2.93-2.88 (5H, m), 2.78-2.71 (1H, m), 2.17-2.06 (2H, m), 1.75-1.70 (2H, m), 1.61-1.54 (1H, m).	543, 545	2
83		3-(5-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-5-基)-3,4-二氯-2*H*-吡唑-2-基)-*N*,*N*-二甲基丙酰胺	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, s), 7.50 (1H, d, J = 8.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 6.96 (1H, d, J = 2.4 Hz), 4.63 (2H, t, J = 7.0 Hz), 3.68-3.63 (2H, m), 3.30-3.26 (5H, m), 3.07 (2H, t, J = 7.0 Hz), 2.96 (3H, s), 2.91 (2H, d, J = 11.3 Hz), 2.81 (3H, s), 2.76-2.70 (1H, m), 2.15-2.10 (2H, m), 1.75-1.71 (2H, m), 1.62-1.56 (1H, m).	557, 559	2
84		2-(6-(2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]噻唑-5-基)-7-氯苯并[*d*]噻唑-2-基)-*N*,*N*-二甲基乙酰胺		526, 528	2

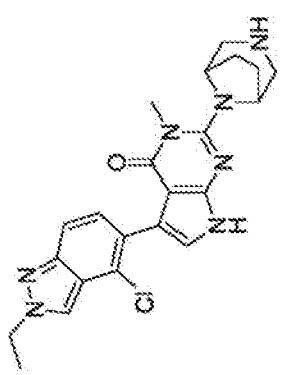
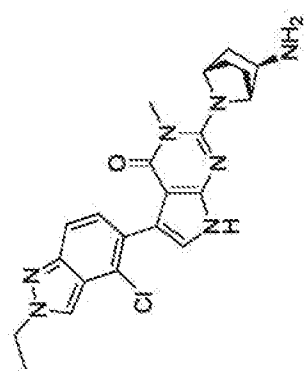
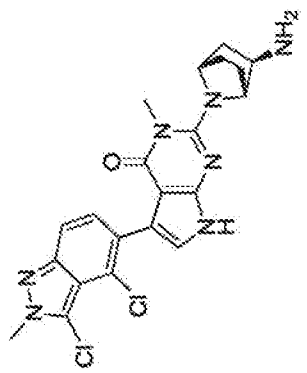
[1646]

85		2-(3-氟杂-7,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.38 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 9.6 Hz), 6.97 (1H, s), 4.18 (3H, s), 4.12 (2H, d, J = 11.3 Hz), 3.96 (2H, d, J = 10.9 Hz), 3.51-3.43 (2H, m), 3.33-3.24 (2H, m), 3.33 (3H, s), 3.09 (2H, d, J = 13.9 Hz).	440, 442	1
86		2-(6-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-5-基)-4-氯-2*H*-吲唑-2-基)-*N*,*N*-二甲基乙酰胺	^{1}H-NMR (DMSO-d6) δ: 11.64 (1H, s), 8.32 (1H, d, J = 0.9 Hz), 7.47 (1H, dd, J = 8.9, 0.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 6.96 (1H, d, J = 2.4 Hz), 5.47 (2H, s), 3.99-3.96 (2H, m), 3.45 (3H, s), 3.10 (3H, s), 3.01-2.96 (2H, m), 2.88 (3H, s), 2.66-2.63 (2H, m), 1.97-1.90 (2H, m), 1.86-1.82 (2H, m).	495, 497	2
87		2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-苯并[*d*][1,2,3]三唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.76 (1H, s), 7.79 (1H, d, J = 8.9 Hz), 7.53 (1H, d, J = 8.9 Hz), 7.07 (1H, d, J = 2.1 Hz), 4.53 (3H, s), 4.00-3.97 (2H, m), 3.46 (3H, s), 3.00-2.95 (2H, m), 2.67-2.63 (2H, m), 1.96-1.91 (2H, m), 1.86-1.82 (2H, m).	425, 427	2

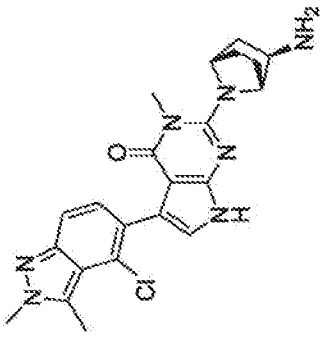
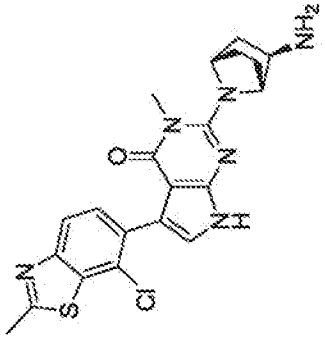
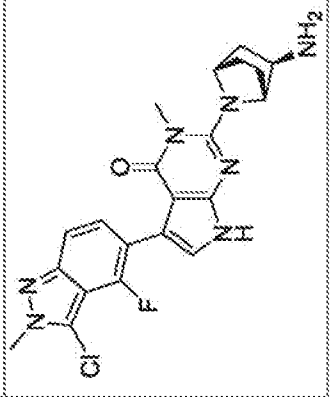
[1647]

88		3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-5-基)-4-氯-2*H*-吲唑-2-基)-*N*,*N*-二甲基丙酰胺	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, s), 8.42 (1H, d, J = 0.9 Hz), 7.48 (1H, dd, J = 8.5, 0.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, d, J = 2.1 Hz), 4.66 (2H, t, J = 6.9 Hz), 3.99-3.95 (2H, m), 3.45 (3H, s), 3.05 (2H, t, J = 6.9 Hz), 2.99-2.93 (2H, m), 2.94 (3H, s), 2.82 (3H, s), 2.66-2.63 (2H, m), 1.96-1.90 (2H, m), 1.86-1.82 (2H, m).	509, 511	2
89		3-(5-(2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-3-甲基-4-氧代-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-5-基)-3,4-二氯-2*H*-吲唑-2-基)-*N*,*N*-二甲基丙酰胺	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, s), 7.50 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.96 (1H, d, J = 2.4 Hz), 4.63 (2H, t, J = 7.0 Hz), 3.99-3.95 (2H, m), 3.45 (3H, s), 3.07 (2H, t, J = 7.0 Hz), 2.99-2.96 (5H, m), 2.81 (3H, s), 2.67-2.63 (2H, m), 1.96-1.90 (2H, m), 1.86-1.80 (2H, m).	543, 545	2
90		2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 7.83 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 8.5 Hz), 7.02 (1H, s), 3.98 (2H, br s), 3.45 (3H, s), 2.99-2.96 (2H, m), 2.83 (3H, s), 2.65-2.62 (2H, m), 1.94-1.82 (4H, m).	441, 443	1

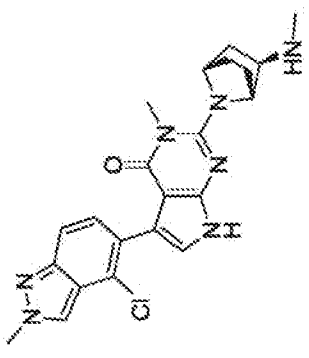
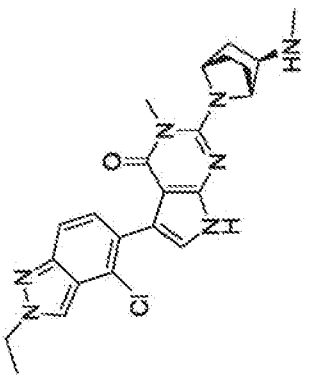
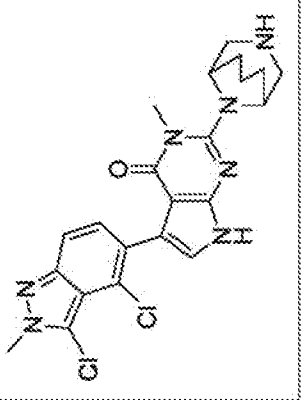
[1648]

91		2-(3,8-二氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.43 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.94 (1H, d, J = 2.4 Hz), 4.48 (2H, q, J = 7.2 Hz), 3.98 (2H, br s), 3.45 (3H, s), 3.00-2.96 (2H, m), 2.68-2.64 (2H, m), 1.97-1.81 (4H, m), 1.52 (3H, t, J = 7.2 Hz).	438, 440	1
92		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 8.44 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.93 (1H, s), 4.48 (2H, q, J = 7.2 Hz), 4.14-4.12 (1H, m), 4.00-3.98 (1H, m), 3.48-3.43 (1H, m), 3.39 (3H, s), 2.30-2.22 (1H, m), 2.21-2.14 (1H, m), 1.96-1.88 (1H, m), 1.71-1.63 (2H, m), 1.54-1.46 (5H, m), 0.89-0.84 (1H, m).	438, 440	1
93		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, br s), 7.50 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.97 (1H, s), 4.20-4.09 (4H, m), 4.01 (1H, br t, J = 4.0 Hz), 3.54-3.44 (1H, m), 3.39 (3H, s), 2.33-2.21 (1H, m), 2.20-2.07 (1H, m), 1.98-1.84 (1H, m), 1.80-1.61 (1H, m), 1.56-1.41 (1H, m), 0.90 (1H, br dd, J = 12.1, 4.0 Hz).	458, 460	1

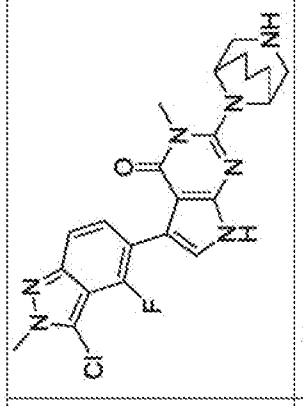
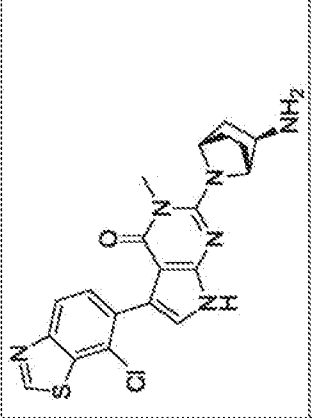
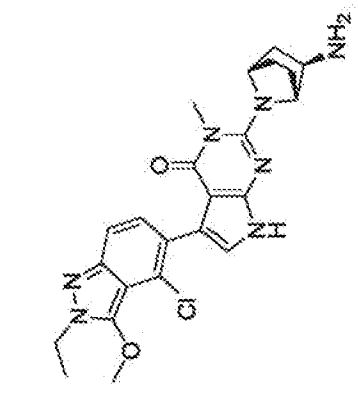
[1649]

94		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2,3-二甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.58 (1H, s), 7.38 (1H, d, J = 8.9 Hz), 7.20 (1H, d, J = 8.9 Hz), 6.88 (1H, d, J = 2.4 Hz), 4.15-4.12 (1H, m), 4.06 (3H, s), 4.02-3.98 (1H, m), 3.49-3.44 (1H, m), 3.38 (3H, s), 2.82 (3H, s), 2.29-2.23 (1H, m), 2.19-2.13 (1H, m), 1.94-1.86 (1H, m), 1.72-1.63 (1H, m), 1.52-1.46 (1H, m), 0.91-0.85 (1H, m).	438, 440	2
95		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.83 (1H, d, J = 8.3 Hz), 7.57 (1H, d, J = 8.3 Hz), 7.01 (1H, s), 4.16-4.14 (1H, m), 4.05-4.02 (1H, m), 3.52-3.48 (2H, m), 3.39 (3H, s), 2.83 (3H, s), 2.32-2.21 (1H, m), 2.17-2.10 (1H, m), 1.94-1.85 (1H, m), 1.74-1.65 (1H, m), 1.54-1.47 (1H, m), 0.94-0.90 (1H, m).	441, 443	2
96		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氟-4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, br s), 7.66-7.60 (1H, m), 7.35 (1H, d, J = 8.9 Hz), 7.02 (1H, s), 4.14-4.09 (4H, m), 4.01-3.97 (1H, m), 3.48-3.39 (4H, m), 2.33-2.10 (2H, m), 1.95-1.83 (2H, m), 1.74-1.60 (1H, m), 1.53-1.43 (1H, m), 0.91-0.80 (1H, m).	442, 444	2

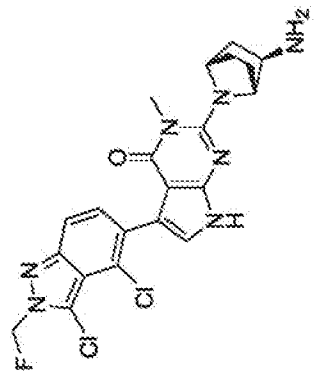
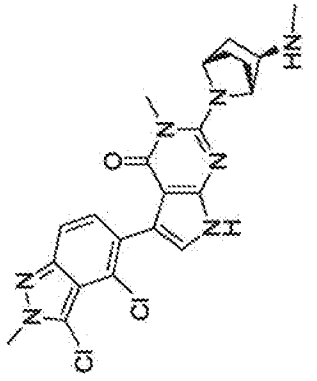
[1650]

97		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 8.40 (1H, s), 7.48 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.7 Hz), 6.95 (1H, s), 4.23-4.15 (5H, m), 3.40 (3H, s), 3.15-3.11 (1H, m), 2.26-2.19 (4H, m), 2.09-2.03 (1H, m), 1.92-1.86 (1H, m), 1.71-1.65 (1H, m), 1.47-1.42 (1H, m), 0.95-0.90 (1H, m).	438, 440	2
98		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 8.44 (1H, s), 7.49 (1H, d, J = 8.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 6.94 (1H, d, J = 2.4 Hz), 4.48 (2H, q, J = 7.3 Hz), 4.24-4.20 (1H, m), 4.18-4.14 (1H, m), 3.40 (3H, s), 3.16-3.12 (1H, m), 2.27-2.19 (4H, m), 2.08-2.03 (1H, m), 1.91-1.85 (1H, m), 1.72-1.65 (1H, m), 1.52 (3H, t, J = 7.3 Hz), 1.48-1.42 (1H, m), 0.95-0.90 (1H, m).	452, 454	2
99		2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.65-11.59 (1H, m), 7.50 (1H, br d, J = 8.8 Hz), 7.34 (1H, d, J = 8.8 Hz), 7.01-6.95 (1H, m), 4.14 (3H, s), 3.65 (2H, br s), 2.90 (2H, d, J = 12.1 Hz), 2.84-2.70 (1H, m), 2.21-2.05 (2H, m), 1.80-1.68 (2H, m), 1.65-1.51 (1H, m).	472, 474	1

[1651]

100		2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, br s), 7.68-7.62 (1H, m), 7.37 (1H, d, J = 8.8 Hz), 7.05 (1H, s), 4.12 (3H, s),3.66 (2H, br s), 3.52-3.14 (4H, m), 2.97-2.88 (2H, m), 2.18-2.06 (2H, m), 1.78-1.69 (2H, m), 1.64-1.54 (1H, m).	456, 458	1
101		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(7-氯苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, br s), 9.42 (1H, s), 8.00 (1H, d, J = 8.3 Hz), 7.64 (1H, d, J = 8.4 Hz), 7.03 (1H, s), 4.17-3.95 (2H, m), 3.48-3.41 (1H, m), 3.39 (3H, s), 2.34-2.09 (2H, m), 1.97-1.43 (5H, m), 0.91-0.80 (1H, m).	428, 430	2
102		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-乙基-3-甲氧基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, br s), 7.34 (1H, d, J = 8.8 Hz), 7.22 (1H, d, J = 8.8 Hz), 6.91 (1H, s), 4.30 (2H, q, J = 7.2 Hz), 4.14-4.09 (1H, m), 4.06 (3H, s), 4.01-3.96 (1H, m), 3.48-3.42 (1H, m), 3.37 (3H, s), 2.29-2.11 (2H,m), 1.94-1.85 (1H, m), 1.71-1.60 (1H, m), 1.52-1.41 (1H, m), 1.44 (3H, t, J = 7.2 Hz), 0.90-0.81 (1H,m).	468, 470	1

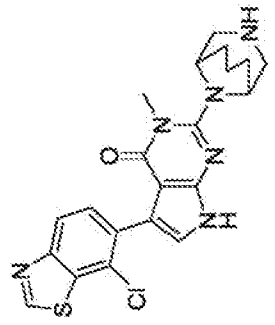
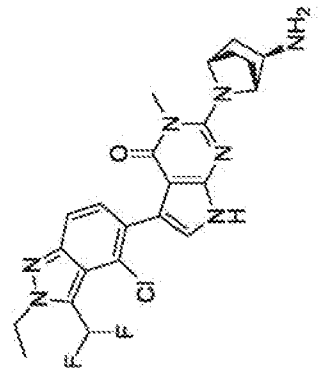
[1652]

103		2-((1*R*,2*R*,4*S*)-2-氟基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-(氟甲基)-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, br s), 7.57 (1H, d, J = 8.8 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.02 (1H, s), 6.51 (2H, d, J = 51.2 Hz), 4.15-4.10 (1H, m), 4.01-3.96 (1H, m), 3.48-3.42 (1H, m), 3.38 (3H, s), 2.28-2.13 (2H, m), 1.92-1.86 (1H, m), 1.75-1.65 (1H, m), 1.52-1.45 (1H, m), 0.89-0.82 (1H, m).	476, 478	1
104		5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br d, J = 2.2 Hz), 7.59 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 8.8 Hz), 6.97 (1H, d, J = 2.2 Hz), 4.22 (1H, t, J = 4.4 Hz), 4.18-4.11 (4H, m), 3.40 (3H, s), 3.19-3.07 (1H, m), 2.28-2.17 (4H, m), 2.11-1.98 (1H, m), 1.95-1.79 (1H, m), 1.75-1.61 (1H, m), 1.51-1.38 (1H, m), 0.92 (1H, dd, J = 11.7, 4.4 Hz).	472, 474	1

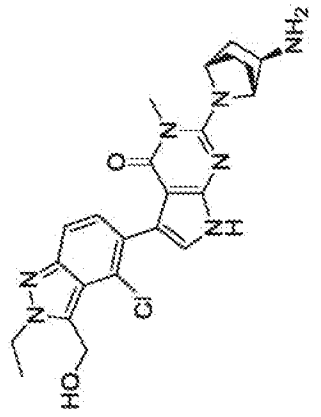
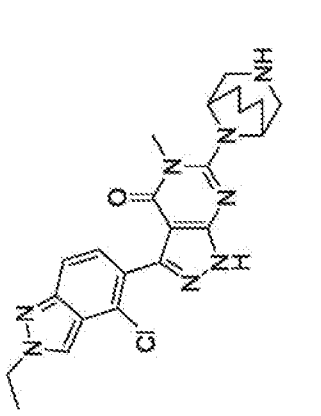
[1653]

105		5-(7-氯苯并[*d*]噻唑-6-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.75 (1H, br s), 9.44 (1H, s), 8.01 (1H, d, J = 8.5 Hz), 7.65 (1H, d, J = 8.5 Hz), 7.04 (1H, d, J = 2.0 Hz), 4.24-4.22 (1H, m), 4.19-4.15 (1H, m), 3.41 (3H, s), 3.16-3.10 (1H, m), 2.24 (4H, br s), 2.10-2.03 (1H, m), 1.92-1.85 (1H, m), 1.72-1.65 (1H, m), 1.48-1.42 (1H, m), 0.95-0.90 (1H, m).	441, 443	2
106		5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, br s), 7.67-7.58 (1H, m), 7.36 (1H, d, J = 9.1 Hz), 7.06-7.00 (1H, m), 4.23-4.19 (1H, m), 4.17-4.13 (1H, m), 4.11 (3H, s), 3.43-3.42 (1H, m), 3.17-3.07 (1H, m), 2.23 (3H, s), 2.11-1.80 (3H, m), 1.73-1.60 (1H, m), 1.51-1.38 (1H, m), 0.99-0.86 (1H, m).	456, 458	2
107		5-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-3-甲基-2-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.73 (1H, br s), 7.82 (1H, d, J = 8.4 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.01 (1H, s), 4.25-4.14 (2H, m), 3.40 (3H, s), 3.17-3.10 (1H, m), 2.82 (3H, s), 2.26-2.16 (1H, m), 2.24 (3H, s), 2.08-1.99 (1H, m), 1.93-1.81 (1H, m), 1.73-1.62 (1H, m), 1.49-1.40 (1H, m), 0.98-0.90 (1H, m).	455, 457	1

[1654]

108		2-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-5-(7-氯苯并[*d*]噻唑-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.70 (1H, s), 9.44 (1H, s), 8.01 (1H, d, *J* = 8.4 Hz), 7.66 (1H, d, *J* = 8.4 Hz), 7.04 (1H, d, *J* = 2.2 Hz), 3.66 (2H, br s), 3.27 (2H, br d, *J* = 11.7 Hz), 2.91 (2H, d, *J* = 11.7 Hz), 2.81-2.63 (1H, m), 2.22-2.04 (2H, m), 1.81-1.66 (2H, m), 1.64-1.49 (1H, m).	441, 443	1
109		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氟-3-(二氟甲基)-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR ($CDCl_3$) δ: 8.43 (1H, br s), 7.90 (1H, t, *J* = 52.8 Hz), 7.67 (1H, d, *J* = 8.8 Hz), 7.47 (1H, d, *J* = 8.8 Hz), 6.90 (1H, d, *J* = 2.2 Hz), 4.70 (2H, q, *J* = 7.3 Hz), 4.21-4.14 (1H, m), 4.06 (1H, br t, *J* = 4.4 Hz), 3.73-3.61 (1H, m), 3.53 (3H, s), 2.53-2.39 (1H, m), 2.19-2.09 (1H, m), 2.08-1.97 (1H, m), 1.91-1.81 (1H, m), 1.63 (3 H, t, *J* = 7.3 Hz), 0.96 (1H, dd, *J* = 12.5, 4.4 Hz).	488, 490	1

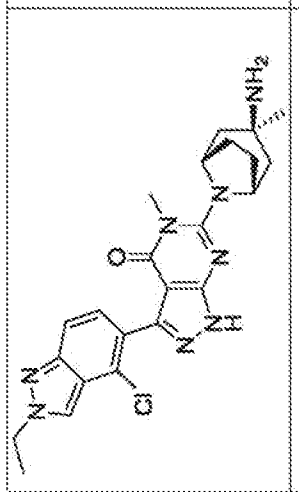
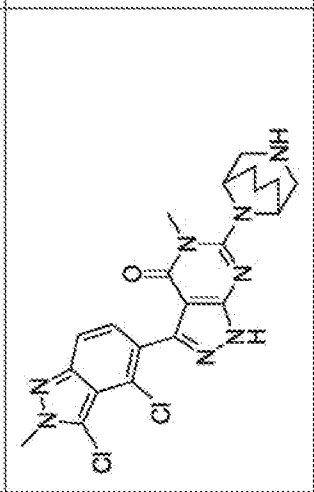
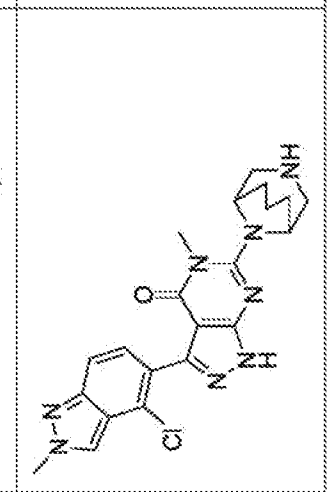
[1655]

110		2-((1*R*,2*R*,4*S*)-2-氟基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氟-2-乙基-3-(羟基甲基)-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, br s), 7.47 (1H, d, J = 8.8 Hz), 7.25 (1H, d, J = 8.8 Hz), 6.89 (1H, br s), 5.42 (1H, br s), 5.12 (2H, s), 4.51 (2H, q, J = 7.2 Hz), 4.14 (1H, br t, J = 4.8 Hz), 4.01 (1H, br t, J = 4.2 Hz), 3.53-3.44 (1H, m), 3.38 (3H, s), 2.33-2.21 (1H, m), 2.20-2.08 (1H, m), 1.98-1.84 (1H, m), 1.79-1.61 (1H, m), 1.57-1.44 (4H, m), 0.90 (1H, dd, J = 11.7, 4.0 Hz).	468, 470	1
111		6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氟-2-乙基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡咯并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.27 (1H, s), 8.54 (1H, s), 7.57 (1H, d, J = 8.8 Hz), 7.29 (1H, d, J = 8.8 Hz), 4.48 (2H, q, J = 7.3 Hz), 3.74-3.71 (2H, m), 3.28 (3H, s), 3.23-3.17 (2H, m), 2.89 (2H, d, J = 12.1 Hz), 2.76-2.65 (1H, m), 2.13-2.01 (2H, m), 1.76-1.69 (2H, m), 1.58-1.52 (1H, m), 1.52 (3H, t, J = 7.3 Hz).	453, 455	2

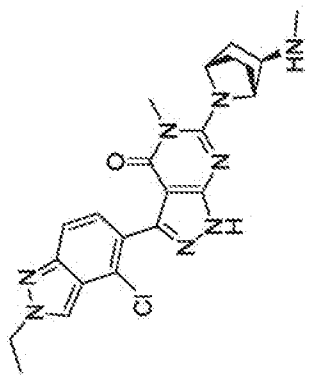
[1656]

112		6-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.36 (1H, s), 8.57 (1H, s), 7.60 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 8.7 Hz), 4.51 (2H, q, J = 7.2 Hz), 4.24-4.19 (1H, m), 4.10-4.05 (1H, m), 3.49-3.43 (1H, m), 3.37 (3H, s), 2.30-2.23 (1H, m), 2.22-2.16 (1H, m), 1.92-1.85 (1H, m), 1.71-1.63 (1H, m), 1.57-1.49 (4H, m), 0.92-0.87 (1H, m).	439, 441	3
113		6-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, d, J = 8.3 Hz), 7.63 (1H, d, J = 8.5 Hz), 4.25-4.22 (1H, m), 4.12-4.10 (1H, m), 3.49-3.48 (2H, m), 3.38 (3H, s), 2.87 (3H, s), 2.29-2.26 (1H, m), 2.19-2.16 (1H, m), 1.90-1.88 (1H, m), 1.71-1.69 (1H, m), 1.55-1.52 (1H, m), 0.95-0.92 (1H, m).	442, 444	3
114		6-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.39 (1H, s), 7.61 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.9 Hz), 4.24-4.20 (1H, m), 4.17 (3H, s), 4.11-4.06 (1H, m), 3.50-3.44 (1H, m), 3.38 (3H, s), 2.31-2.23 (1H, m), 2.21-2.16 (1H, m), 1.93-1.85 (1H, m), 1.73-1.65 (1H, m), 1.55-1.48 (1H, m), 0.93-0.88 (1H, m).	459, 461	3

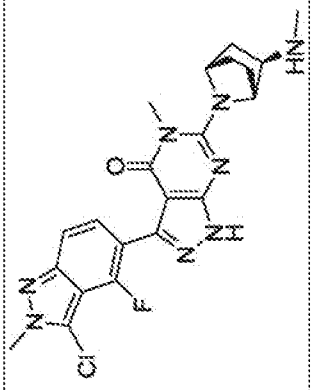
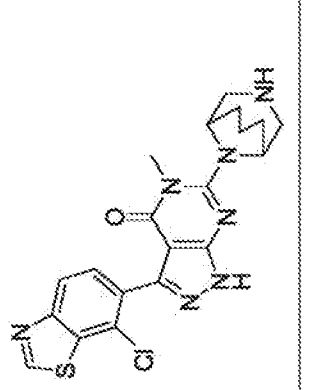
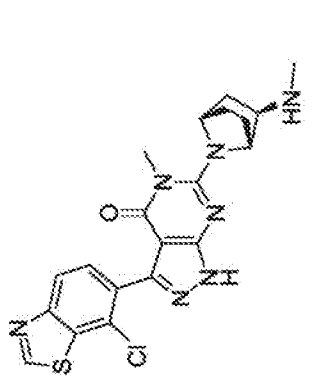
[1657]

115		6-(*endo*-3-氨基-3-甲基-8-氮杂二环[3.2.1]辛烷-8-基)-3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.55 (1H, s), 7.59 (1H, d, J = 8.8 Hz), 7.30 (1H, d, J = 8.8 Hz), 4.54-4.46 (2H, m), 4.18 (2H, br s), 3.38 (3H, s), 2.34-2.26 (2H, m), 1.92-1.83 (4H, m), 1.64-1.50 (5H, m), 1.08 (3H, s).	467, 469	3
116		6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.31 (1H, s), 7.58 (1H, d, J = 8.5 Hz), 7.30 (1H, d, J = 8.5 Hz), 4.14 (3H, s), 3.75-3.72 (2H, m), 3.29 (3H, s), 3.24-3.17 (2H, m), 2.90 (2H, d, J = 11.7 Hz), 2.78-2.64 (1H, m), 2.10-2.04 (2H, m), 1.76-1.69 (2H, m), 1.60-1.51 (1H, m).	473, 475	3
117		6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.27 (1H, s), 8.50 (1H, s), 7.56 (1H, d, J = 9.5 Hz), 7.29 (1H, d, J = 8.8 Hz), 4.19 (3H, s), 3.74-3.72 (2H, m), 3.29 (3H, s), 3.25-3.18 (2H, m), 2.93-2.87 (2H, br m), 2.77-2.68 (1H, m), 2.13-2.01 (2H, m), 1.78-1.69 (2H, m), 1.58-1.53 (1H, m).	439, 441	3

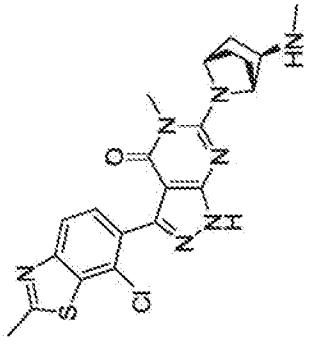
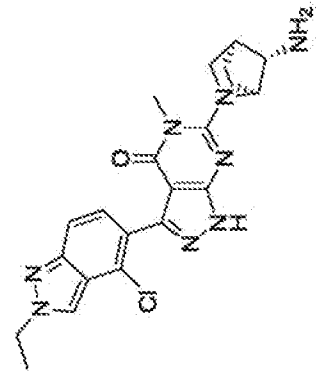
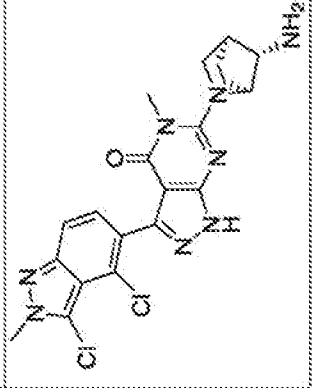
[1658]

118		3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.37 (1H, s), 8.58 (1H, s), 7.60 (1H, d, J = 8.9 Hz), 7.31 (1H, d, J = 8.9 Hz), 4.51 (2H, q, J = 7.2 Hz), 4.33-4.29 (1H, m), 4.27-4.23 (1H, m), 3.39 (3H, s), 3.18-3.13 (1H, m), 2.27-2.19 (4H, m), 2.10-2.04 (1H, m), 1.91-1.84 (1H, m), 1.73-1.65 (1H, m), 1.54 (3H, t, J = 7.2 Hz), 1.51-1.44 (1H, m), 0.98-0.93 (1H, m).	453, 455	3
119		3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.61 (1H, d, J = 8.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 4.33-4.29 (1H, m), 4.28-4.23 (1H, m), 4.17 (3H, s), 3.39 (3H, s), 3.18-3.12 (1H, m), 2.28-2.19 (4H, m), 2.10-2.05 (1H, m), 1.91-1.84 (1H, m), 1.72-1.65 (1H, m), 1.51-1.43 (1H, m), 0.98-0.93 (1H, m).	473, 475	3
120		3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.37 (1H, br s), 8.52 (1H, s), 7.58 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 4.32-4.29 (1H, m), 4.26-4.22 (4H, m), 3.39 (3H, s), 3.17-3.12 (1H, m), 2.25 (4H, br s), 2.11-2.05 (1H, m), 1.91-1.84 (1H, m), 1.72-1.64 (1H, m), 1.51-1.44 (1H, m), 0.97-0.93 (1H, m).	439, 441	3

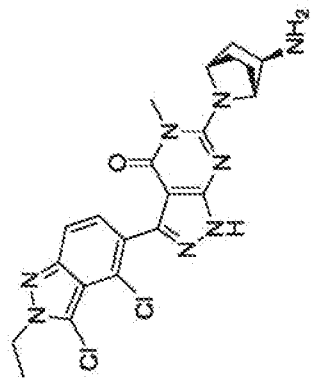
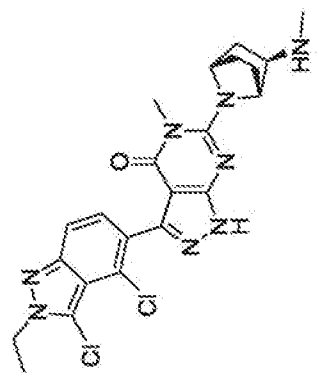
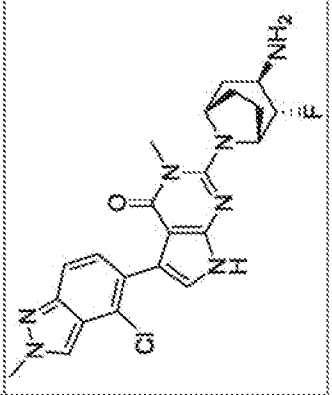
[1659]

121		3-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.55-7.43 (2H, m), 4.32-4.21 (2H, m), 4.14 (3H, s), 3.41 (3H, s), 3.17-3.09 (1H, m), 2.27-2.15 (4H, m), 2.11-2.03 (1H, m), 1.92-1.81 (1H, m), 1.73-1.61 (1H, m), 1.51-1.40 (1H, m), 0.98-0.90 (1H, m).	457, 459	3
122		6-(3,9-二氮杂二环[3.3.1]壬烷-9-基)-3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, br s), 9.53 (1H, s), 8.11 (1H, d, J = 8.5 Hz), 7.70 (1H, d, J = 8.5 Hz), 3.78 (2H, br s), 3.41-3.23 (5H, m), 2.94 (2H, d, J = 11.7 Hz), 2.77-2.63 (1H, m), 2.15-2.03 (2H, m), 1.81-1.71 (2H, m), 1.62-1.53 (1H, m).	442, 444	3
123		3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.51 (1H, s), 9.54 (1H, s), 8.12 (1H, d, J = 8.2 Hz), 7.70 (1H, d, J = 8.2 Hz), 4.34-4.29 (1H, m), 4.28-4.24 (1H, m), 3.40 (3H, s), 3.18-3.11 (1H, m), 2.26-2.18 (4H, m), 2.11-2.05 (1H, m), 1.92-1.84 (1H, m), 1.73-1.65 (1H, m), 1.52-1.44 (1H, m), 0.98-0.93 (1H, m).	442, 444	3

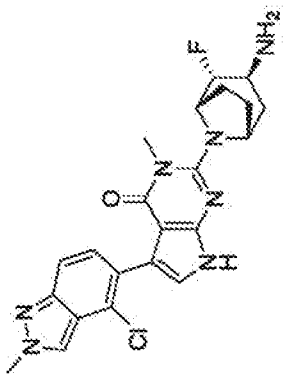
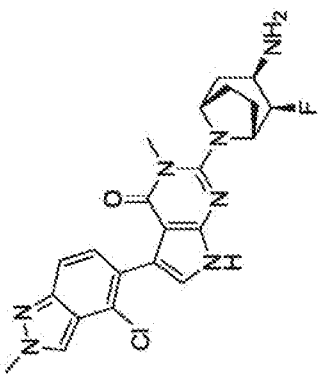
[1660]

124		3-(7-氯-2-甲基苯并[*d*]噻唑-6-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.48 (1H, s), 7.94 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 8.2 Hz), 4.33-4.29 (1H, m), 4.28-4.23 (1H, m), 3.40 (3H, s), 3.17-3.11 (1H, m), 2.87 (3H, s), 2.24-2.18 (4H, m), 2.11-2.05 (1H, m), 1.91-1.83 (1H, m), 1.72-1.64 (1H, m), 1.51-1.44 (1H, m), 0.97-0.92 (1H, m).	456, 458	3
125		*rac*-6-((1*S*,4*S*,7*S*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.55-8.53 (1H, m), 7.58 (2H, d, J = 8.7 Hz), 7.29 (1H, d, J = 8.7 Hz), 4.54-4.45 (2H, m), 3.96-3.91 (1H, m), 3.79-3.72 (1H, m), 3.27 (3H, s), 3.07 (1H, d, J = 9.0 Hz), 2.20-2.12 (1H, m), 2.02-1.81 (4H, m), 1.53 (3H, t, J = 7.4 Hz), 1.40-1.32 (1H, m).	439, 441	3
126		*rac*-6-((1*S*,4*S*,7*S*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.59 (1H, d, J = 9.1 Hz), 7.31 (1H, d, J = 9.0 Hz), 4.15 (3H, s), 3.96-3.93 (1H, m), 3.79-3.73 (1H, m), 3.27 (3H, s), 3.09-3.05 (1H, m), 2.21-2.11 (1H, br m), 2.03-1.82 (4H, m), 1.45-1.30 (1H, m).	459, 461	3

[1661]

127		6-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-(3,4-二氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.40 (1H, s), 7.63 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 8.9 Hz), 4.52 (2H, q, J = 7.3 Hz), 4.24-4.20 (1H, m), 4.10-4.06 (1H, m), 3.49-3.44 (1H, m), 3.38 (3H, s), 2.30-2.24 (1H, m), 2.22-2.16 (1H, m), 1.93-1.86 (1H, m), 1.72-1.64 (1H, m), 1.54-1.47 (4H, m), 0.93-0.87 (1H, m).	473, 475	3
128		3-(3,4-二氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-6-((1*R*,2*R*,4*S*)-2-(甲氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.63 (1H, d, J = 8.9 Hz), 7.33 (1H, d, J = 8.9 Hz), 4.52 (2H, q, J = 7.2 Hz), 4.33-4.29 (1H, m), 4.27-4.23 (1H, m), 3.39 (3H, s), 3.16-3.12 (1H, m), 2.25-2.19 (4H, m), 2.10-2.05 (1H, m), 1.90-1.84 (1H, m), 1.72-1.65 (1H, m), 1.51-1.45 (4H, m), 0.98-0.93 (1H, m).	487, 489	3
129		2-((1*R*,2*S*,3*R*,5*S*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.65 (1H, br s), 8.40 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 6.97 (1H, s), 4.50-4.31 (2H, m), 4.19 (3H, s), 4.15-4.07 (1H, m), 3.45 (3H, s), 3.28-3.17 (1H, m), 2.45-2.28 (1H, m), 2.23-1.69 (4H, m), 1.49-1.37 (1 H, m).	456, 458	5

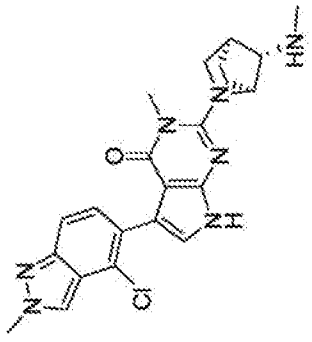
[1662]

130		2-((1*S*,2*R*,3*S*,5*R*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.39 (1H, s), 7.47 (1H, dd, J = 8.8, 0.8 Hz), 7.31 (1H d, J = 8.8 Hz), 6.96 (1H, s), 4.48-4.45 (1H, m), 4.39-4.32 (2H, m), 4.18 (3H, s), 4.13-4.07 (1H, m), 3.44 (3H, s), 3.28-3.19 (1H, m), 2.18-1.75 (4H, m), 1.48-1.41 (1H, m).	456, 458	5
131		2-((1*R*,2*R*,3*R*,5*S*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.66 (1H, br s), 8.39 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.30 (1H, d, J = 8.9 Hz), 6.97 (1H, s), 4.85 (1H, dt, J = 46.5, 5.2 Hz), 4.26-4.19 (1H, m), 4.18 (3H, s), 4.03 (1H, br s), 3.68-3.60 (1H, m), 3.40 (3H, s), 2.55-2.47 (1H, m), 2.21-2.07 (2H, m), 2.00-1.84 (2H, m), 1.75-1.66 (1H, m), 1.62-1.46 (1H, m).	456, 458	5

[1663]

132		2-((1*S*,2*S*,3*S*,5*R*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.68 (1H, s), 8.39 (1H, s), 7.47 (1H, dd, *J* = 8.8, 0.9 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 6.98-6.96 (1H, m), 4.85 (1H, ddd, *J* = 46.4, 5.0, 5.0 Hz), 4.25-4.20 (1H, m), 4.18 (3H, s), 4.06-4.01 (1H, m), 3.66-3.62 (1H, m), 3.40 (3H, s), 2.55-2.44 (1H, m), 2.19-2.09 (2H, m), 1.98-1.86 (2H, m), 1.74-1.67 (1H, m).	456, 458	5
133		*rac*-2-((1*S*,4*S*,7*S*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.49 (1H, br s), 8.42 (1H, s), 7.47 (1H, dd, *J* = 9.0, 0.7 Hz), 7.30 (1H, d, *J* = 9.0 Hz), 6.87 (1H, s), 4.46 (2H, q, *J* = 7.3 Hz), 3.86-3.66 (2H, m), 3.30-3.26 (3H, m), 3.17-3.14 (1H, m), 3.04-2.98 (1H, m), 2.18-2.11 (1H, m), 2.01-1.82 (3H, m), 1.51 (3H, t, *J* = 7.1 Hz), 1.40-1.31 (1H, m).	438, 440	2
134		*rac*-((1*S*,4*S*,7*S*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-3-(7-氯苯并[*d*]噻唑-6-基)-5-甲基-1,5-二氢-4*H*-吡咯并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 9.52 (1H, s), 8.10 (1H, d, *J* = 8.4 Hz), 7.68 (1H, d, *J* = 8.4 Hz), 3.97-3.92 (1H, br), 3.81-3.72 (1H, m), 3.28 (3H, s), 3.16 (1H, d, *J* = 5.2 Hz), 3.08 (1H, d, *J* = 9.0 Hz), 2.21-2.11 (1H, m), 2.04-1.29 (5H, m).	428, 430	3

[1664]

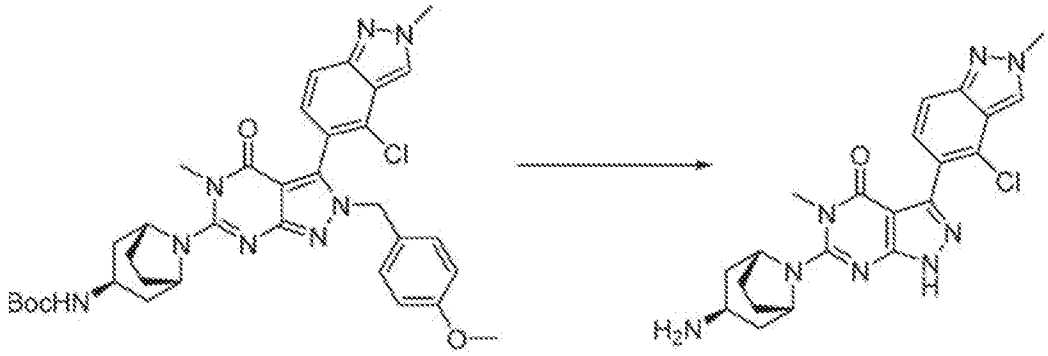
135		*rac*-5-(4-氯-2-甲基-2*H*-吲唑-3-基)-3-甲基-2-((1*S*,4*S*,7*S*)-7-(甲基氨基)-2-氮杂二环[2.2.1]庚烷-2-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, s), 8.39 (1H, s), 7.47 (1H, dd, J = 8.9, 0.8 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.89 (1H, d, J = 2.4 Hz), 4.19 (3H, s), 4.07-4.03 (1H, m), 3.77-3.72 (1H, m), 3.30 (3H, s), 3.05 (1H, d, J = 9.2 Hz), 2.94 (1H, s), 2.36-2.32 (1H, m), 2.30 (3H, s), 1.96-1.78 (3H, m), 1.38-1.33 (1H, m)	438, 440	2

[1665] 将下述方法用于解释说明用于制备下面表11中所列实施例而用的通用方法。

[1666] 方法6:endo-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲

唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

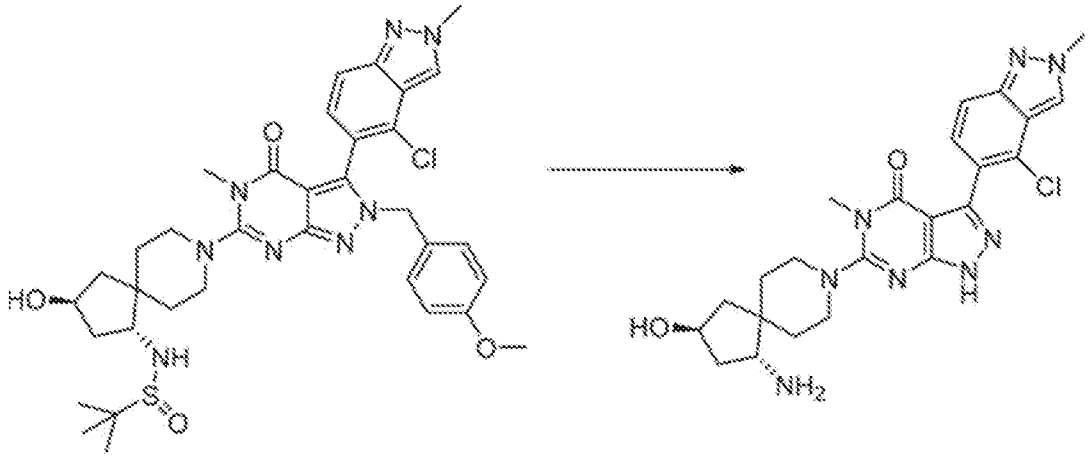
[1667] [化学式161]

[1668] 

[1669] 将三氟甲磺酸(2mL,22.5mmol)滴加至N-[endo-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯(100mg,0.15mmol)的TFA(0.935mL,12.14mmol)和DCM(10mL)溶液中。将得到的紫色混合物在RT搅拌1小时30分钟,然后真空蒸发至红色液体,将其滴加至饱和碳酸钠(50mL)中。将水层用DCM(2x50mL)萃取,并通过Phase Separator回收有机层,并将其真空蒸发。将粗产品经硅胶柱色谱(4g柱,0-10%MeOH/DCM)纯化,得到第一批粗产物(38mg)。将粗产物经制备型HPLC纯化,得到标题化合物(15mg,0.03mmol,产率22%),作为透明无色固体。

[1670] 方法7:6-[(1R,3S)-1-氨基-3-羟基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

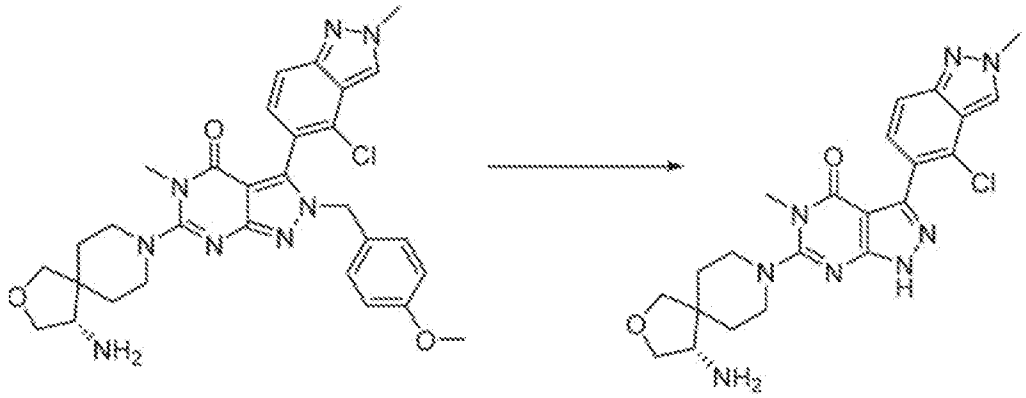
[1671] [化学式162]

[1672] 

[1673] 将N-[(1R,3S)-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-4-氧代-2H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-3-羟基-8-氮杂螺[4.5]癸烷-1-基]-2-甲基丙烷-2-亚磺酰胺(123mg,0.17mmol)溶解于甲醇(0.2mL,4.94mmol)中,然后加入HCl(4M的1,4-二氧六环溶液)(0.435mL,1.74mmol),并将反应物在50℃搅拌1小时。将反应混合物浓缩,得到非常浅的棕色固体。向固体物中加入DCM(2mL)和三氟甲磺酸(0.154mL,1.739mmol),并将得到的紫色溶液在室温搅拌2小时。将混合物装载到SCX(~5g)上,并用DCM、MeOH洗脱,然后用0.7M NH_3的MeOH溶液洗脱。将NH_3的MeOH溶液级分浓缩,得到标题化合物(70mg,0.14mmol,产率81%)。

[1674] 方法8:6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

[1675] [化学式163]

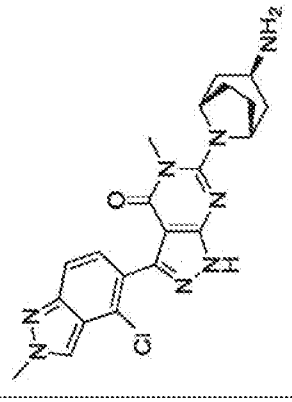
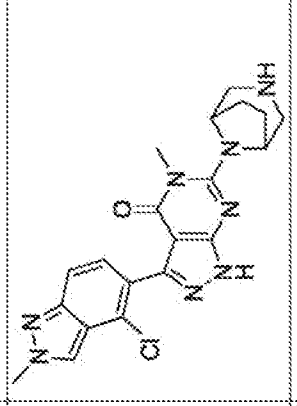
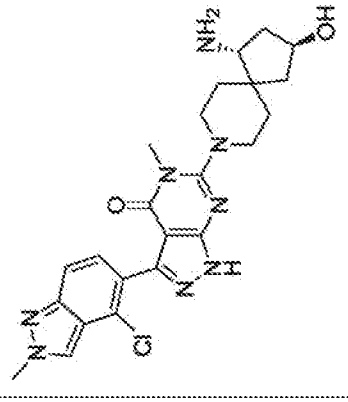
[1676] 

[1677] 将6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-2-[(4-甲氧基苯基)甲基]-5-甲基-2H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮(145mg,0.25mmol)溶解于DCM(2mL)中,并加入三氟甲磺酸(0.22mL,2.46mmol)。将混合物在室温搅拌2小时。将混合物装载到SCX(~5g)上,并用DCM、MeOH洗脱,然后用0.7M NH_3的MeOH溶液洗脱。将NH_3的MeOH溶液级分浓缩,得到标题化合物(83mg,0.18mmol,产率72%)。

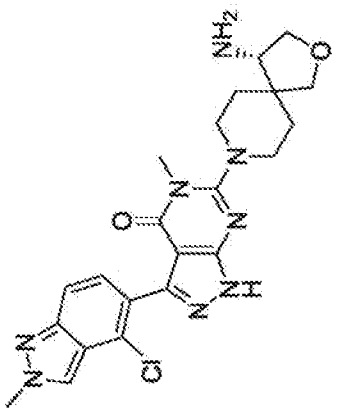
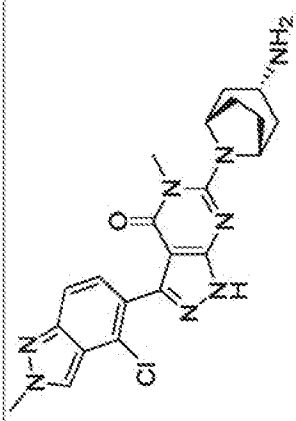
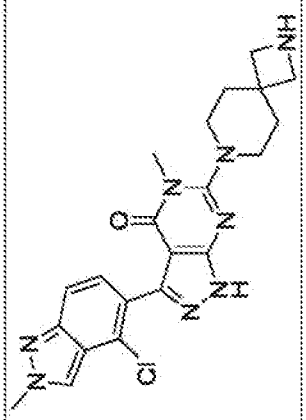
[1678] 通过相似于和/或类似于方法6-8中所述的方法,不需进一步纯化,将表11中的标题化合物作为游离碱或作为适当的盐而直接分离。或者,纯化(例如利用质量导向的制备型HPLC、色谱法、结晶或研制)化合物。在一些情况下,将化合物作为盐酸盐分离;通过用过量HCl(2N HCl的Et_2O溶液)处理最终化合物的溶液(例如MeOH溶液),然后蒸发至干,来分离化合物。

[1679]

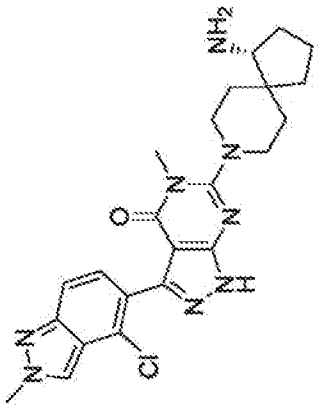
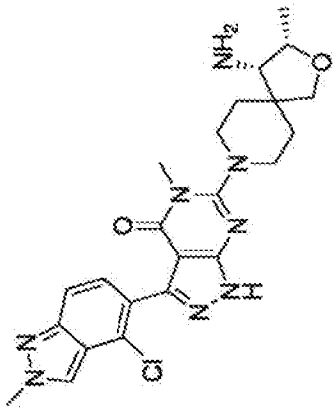
表11

实施例	结构	名称	NMR 数据	$[M+H]^+$ m/z	方法
136		*endo*-6-[3-氯基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.37 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 4.34-4.28 (m, 2H), 4.26 (s, 3H), 3.53 (s, 3H), 3.31-3.25 (m, 1H), 2.47 (app. dt, J = 12.7, 6.1 Hz, 2H), 2.23-2.16 (m, 2H), 2.11-2.03 (m, 2H), 1.67 (app. d, J = 14.4 Hz, 2H).	439	6
137		3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-[3,8-二氮杂二环[3.2.1]辛烷-8-基]-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.39 (s, 1H), 8.53 (s, 1H), 7.60 (dd, J = 8.8, 1.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.23 (s, 3H), 4.12 (br s, 2H), 3.44 (s, 3H), 3.04 (d, J = 11.9 Hz, 2H), 2.73 (d, J = 10.8 Hz, 2H), 2.02-1.83 (m, 4H).	425	6，通过 SCX 色谱分离
138		6-{(1*R*,3*S*)-1-氨基-3-羟基-8-氮杂螺[4.5]癸烷-8-基}-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.54 (s, 1H), 7.60 (dd, J = 8.8, 0.9 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 4.50 (br s, 1H), 4.23 (s, 3H), 4.20-4.13 (m, 1H), 3.48-3.39 (m, 2H), 3.38 (s, 3H), 3.06-2.99 (m, 1H), 2.95-2.84 (m, 2H), 2.09 (dd, J = 13.6, 7.1 Hz, 1H), 1.88-1.74 (m, 2H), 1.74-1.60 (m, 2H), 1.43-1.32 (m, 2H), 1.23 (app. d, J = 12.5 Hz, 1H).	483	7

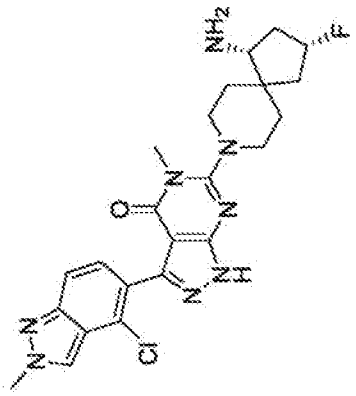
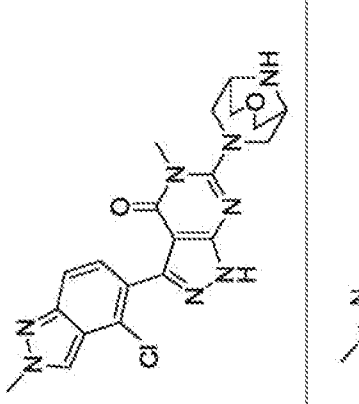
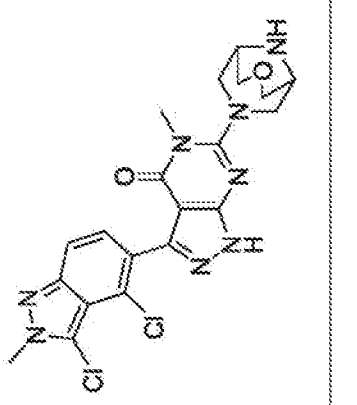
[1680]

139		6-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.48 (br s, 1H), 8.53 (s, 1H), 7.59 (dd, J = 8.8, 0.9 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.22 (s, 3H), 3.96 (dd, J = 8.6, 6.6 Hz, 1H), 3.69 (d, J = 8.4 Hz, 1H), 3.60 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.09 (t, J = 6.0 Hz, 1H), 3.00-2.90 (m, 2H), 1.81 (ddd, J = 13.5, 10.9, 3.5 Hz, 1H), 1.72 (ddd, J = 13.8, 10.8, 3.8 Hz, 1H), 1.55-1.44 (m, 2H).	469	8
140		*exo*-6-[3-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.52 (s, 1H), 7.58 (dd, J = 8.8, 0.9 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 4.24-4.18 (m, 2H), 4.22 (s, 3H), 3.41 (s, 3H), 3.07-2.98 (m, 1H), 2.02-1.92 (m, 2H), 1.84-1.76 (m, 2H), 1.73-1.67 (m, 2H), 1.53 (app. t, J = 11.0 Hz, 2H).	439	8
141		3-(4-氯-2-甲基-2*H*-吲唑-5-基)-6-(2,7-二氮杂螺[3.5]壬烷-7-基)-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 7.59 (dd, J = 8.8, 0.9 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.22 (s, 3H), 3.36 (s, 3H), 3.13-3.04 (m, 4H), 1.90-1.78 (m, 4H).	439	8

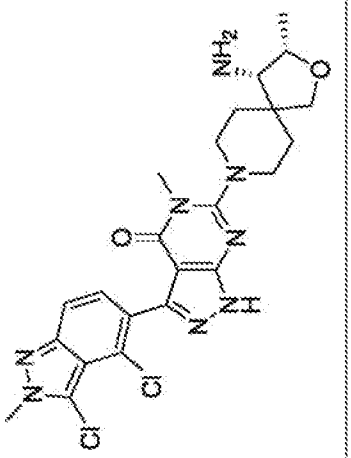
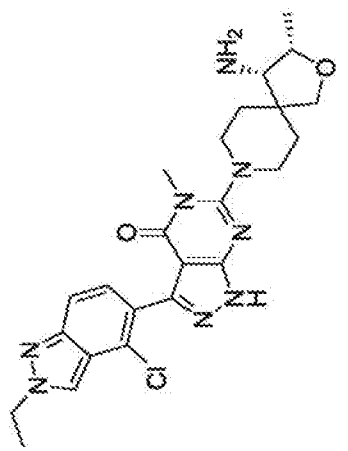
[1681]

142		6-[(1*R*)-1-氨基-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, 甲醇-d_4) δ: 8.38 (s, 1H), 7.59 (dd, J = 8.8, 0.9 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 4.26 (s, 3H), 3.56-3.46 (m, 2 H), 3.50 (s, 3H), 3.06 (dq, J = 12.6, 2.5 Hz, 2H), 2.84 (t, J = 7.4 Hz, 1H), 2.04 (dddd, J = 13.2, 9.1, 7.1, 4.5 Hz, 1H), 1.92-1.81 (m, 2H), 1.84-1.71 (m, 2H), 1.72-1.61 (m, 1 H), 1.61-1.52 (m, 1 H), 1.52-1.42 (m, 2H), 1.41-1.35 (m, 1 H).	467	8
143		6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.47 (br s, 1H), 8.53 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.22 (s, 3H), 4.12-4.03 (m, 1H), 3.69 (d, J = 8.5 Hz, 1H), 3.51 (d, J = 8.5 Hz, 1H), 3.37 (s, 3H), 3.09-3.01 (m, 1H), 3.01-2.91 (m, 2H), 1.92-1.83 (m, 1H), 1.82-1.73 (m, 1H), 1.67-1.60 (m, 1H), 1.60-1.53 (m, 1 H), 1.10 (d, J = 6.3 Hz, 3H).	483	8

[1682]

144		6-[(1*R*,3*R*)-1-氨基-3-氟-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.53 (s, 1H), 8.20 (br s, 3H), 7.60 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 5.32-5.12 (m, 1H), 4.23 (s, 3H), 3.55 (app. d, J = 12.4 Hz, 1H), 3.45 (app. d, J = 12.4 Hz, 1H), 3.39 (s, 3H), 3.31-3.24 (m, 1H), 3.04-2.89 (m, 2H), 2.27 (d, J = 14.8 Hz, 1H), 2.22 (d, J = 14.8 Hz, 1H), 2.10-1.90 (m, 3H), 1.81-1.68 (m, 2H), 1.41 (app. d, J = 12.9 Hz, 1H).	485	8
145		3-(4-氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.44 (br s, 1H), 8.53 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 4.23 (s, 3H), 3.93 (app. d, J = 11.0 Hz, 2H), 3.83 (app. d, J = 11.0 Hz, 2H), 3.62 (app. d, J = 12.0 Hz, 2H), 3.48 (s, 3H), 3.26 (app. d, J = 12.0 Hz, 2H), 2.90 (br. s, 2H).	441	8
146		3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-6-{3-氧杂-7,9-二氮杂二环[3.3.1]壬烷-7-基}-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.59 (br s, 1H), 9.93 (br s, 1H), 9.81 (br s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 4.17 (s, 3H), 4.15 (app. d, J = 12.8 Hz, 2H), 4.08 (app. d, J = 12.8 Hz, 2H), 3.85 (app. d, J = 13.3 Hz, 2H), 3.67 (app. br s, 2H), 3.56 (app. d, J = 13.3 Hz, 2H), 3.48 (s, 3H).	475	8

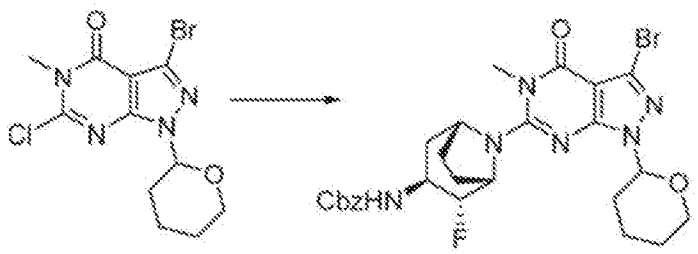
[1683]

147		6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.21 (br s, 3H), 7.62 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 4.25-4.18 (m, 1H), 4.17 (s, 3H), 3.89 (d, J = 9.0 Hz, 1H), 3.65 (d, J = 9.0 Hz, 1H), 3.54-3.46 (m, 1H), 3.46-3.40 (m, 2H), 3.39 (s, 3H), 2.97-2.85 (m, 2H), 2.00-1.89 (m, 2H), 1.79-1.70 (m, 1H), 1.69-1.60 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H).	517	8
148		6-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-3-(4-氯-2-乙基-2*H*-吲唑-5-基)-5-甲基-1*H*,4*H*,5*H*-吡唑并[3,4-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.48 (s, 1H), 8.58 (s, 1H), 8.18 (br s, 3H), 7.61 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 4.52 (q, J = 7.3 Hz, 2H), 4.25-4.18 (m, 1H), 3.89 (d, J = 9.0 Hz, 1H), 3.66 (d, J = 9.0 Hz, 1H), 3.54-3.46 (m, 1H), 3.46-3.40 (m, 2H), 3.39 (s, 3H), 2.91 (app. q, J = 11.6 Hz, 2H), 2.00-1.89 (m, 2H), 1.75 (app. d, J = 13.6 Hz, 1H), 1.65 (app. d, J = 12.8 Hz, 1H), 1.54 (t, J = 7.3 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H).	497	8

[1684] 实施例149:6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

[1685] 步骤1:N-[(1S,2R,3S,5R)-8-[3-溴-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯

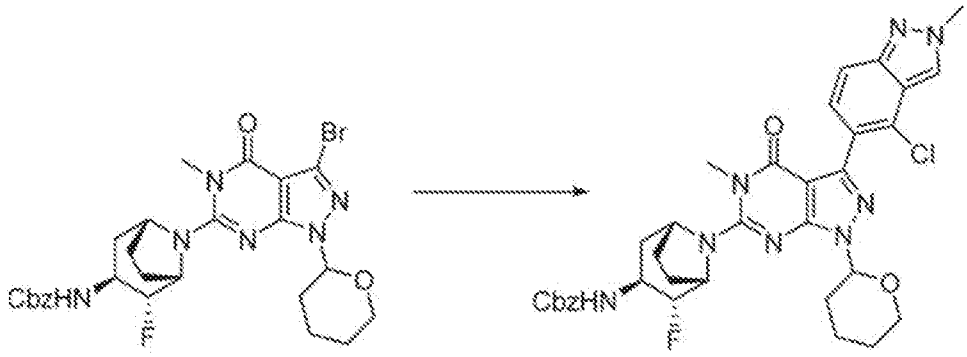
[1686] [化学式164]

[1687] 

[1688] 将3-溴-6-氯-5-甲基-1-(氧杂环己烷-2-基)-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮(0.15g,0.43mmol)、N-[(1S,2S,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(0.144g,0.52mmol)和二异丙基乙胺(0.38mL,2.16mmol)混合物的NMP(10mL)溶液在130℃加热30min。将反应物冷却至环境温度,用TBME/DCM 1:1(20mL)稀释,并用1M LiCl水溶液(2x10mL)洗涤。将水层合并,并用10mL DCM萃取。将合并的有机萃取物用HCl(1M,10mL)洗涤,干燥($MgSO_4$),并减压浓缩,得到N-[(1S,2R,3S,5R)-8-[3-溴-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(310mg,0.40mmol,产率94%),作为灰白色固体。MS:$[M+H]^+$=591.

[1689] 步骤2:N-[(1S,2R,3S,5R)-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯

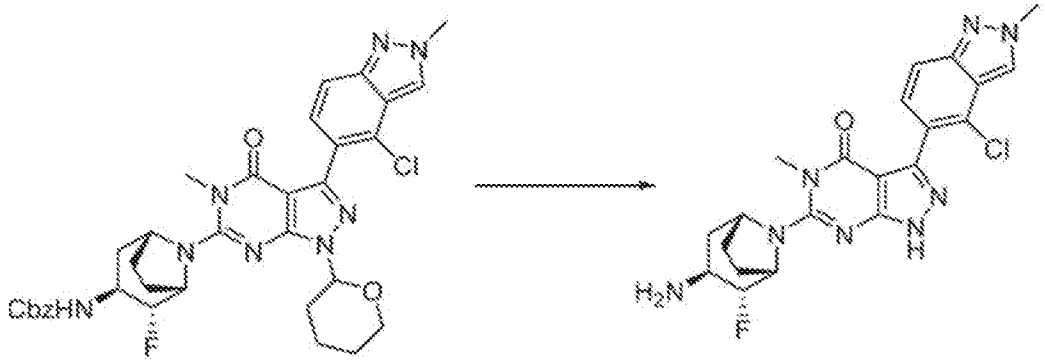
[1690] [化学式165]

[1691] 

[1692] 将N-[(1S,2R,3S,5R)-8-[3-溴-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(0.3g,0.51mmol)、4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(0.18g,0.61mmol)、Na_2CO_3(0.16g,1.53mmol)和$PdCl_2$(dppf).DCM(0.042g,0.05mmol)混合物的1,4-二氧六环(5mL)和水(0.6mL)溶液在N_2气流下脱气。将反应物加热至100℃,保持2h。一旦冷却至环境温度,将反应混合物用2mL水和10mL DCM进行分配,分离有机层,经$MgSO_4$干燥,并减压浓缩。将粗产品经硅胶色谱(12g柱,0-10%MeOH/DCM)纯化,得到产品,作为棕色固体。将粗产品经硅胶色谱(12g金柱,2-4%(0.7M氨/MeOH)/DCM)纯化,得到N-[(1S,2R,3S,5R)-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(0.07g,0.10mmol,产率20%),作为白色粉末。MS:$[M+H]^+$=675.

[1693] 步骤3:6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮

[1694] [化学式166]

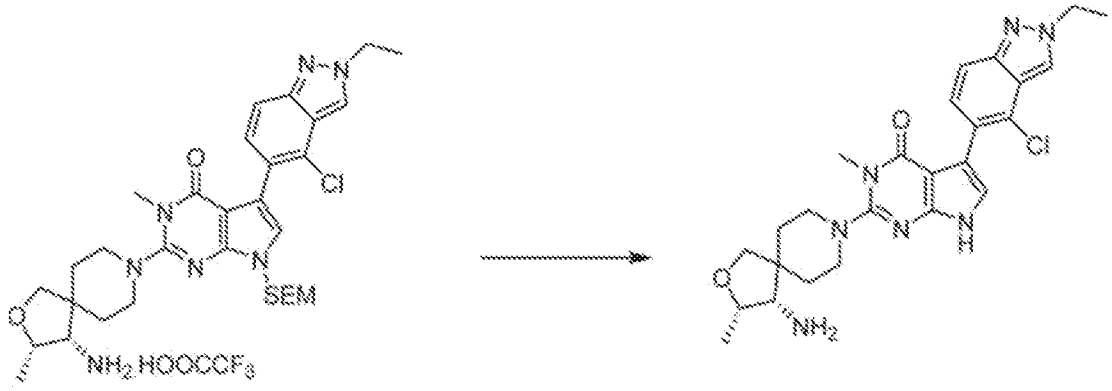
[1695] 

[1696] 将N-[(1S,2R,3S,5R)-8-[3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1-(氧杂环己烷-2-基)-4-氧代-1H,4H,5H-吡唑并[3,4-d]嘧啶-6-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(0.07g,0.10mmol)的TFA溶液(1.04mL,13.5mmol)用三氟甲磺酸(0.11mL,1.24mmol)处理,并在RT搅拌5分钟。通过将其滴加至饱和碳酸钠水溶液(10mL)中而淬灭反应混合物,然后将其用LiCl0.1M(50mL)稀释,并用DCM(3x20mL)萃取。将有机层合并,经$MgSO_4$干燥,过滤并减压浓缩,得到粗品。将粗产物经硅胶色谱(4g金柱,0-10%(0.7M氨/MeOH)/DCM)纯化,得到6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮,作为无色玻璃状物。将产品用5mL 2M HCl的醚溶液处理,超声10min,并过滤,得到6-[(1S,2R,3S,5R)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-3-(4-氯-2-甲基-2H-吲唑-5-基)-5-甲基-1H,4H,5H-吡唑并[3,4-d]嘧啶-4-酮盐酸盐(10mg,0.02mmol,产率19%),作为白色粉末。MS:$[M+H]^+$=457.

[1697] ^1H NMR(500MHz,甲醇-d_4)δ:8.48(s,1H),7.64(dd,J=8.8,0.9Hz,1H),7.47(d,J=8.8Hz,1H),4.75-4.68(m,1H),4.64(dd,J=16.7,7.7Hz,1H),4.49(t,J=7.8Hz,1H),4.30(s,3H),3.75-3.65(m,1H),3.60(s,3H),2.91(q,J=11.5,11.1Hz,1H),2.48(d,J=11.8Hz,1H),2.12(dq,J=12.5,6.4Hz,1H),1.91(dt,J=14.4,8.0Hz,1H),1.68(t,J=10.0Hz,1H),1.44-1.35(m,1H).

[1698] 方法9:2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮

[1699] [化学式167]

[1700] 

[1701] 将TFA(1mL)加到2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮(256mg,1.82mmol)的DCM(1mL)溶液中,并将混合物在RT搅拌18h。将混合物浓缩,并与甲苯共沸两次,向残留物中加入MeOH(2mL)和乙二胺(0.23mL,3.46mmol),并将其在RT搅拌5h。将反应混合物浓缩,悬浮于MeOH中,并经过滤收集固体物,得到标题化合物(24mg,0.048mmol,14%)。

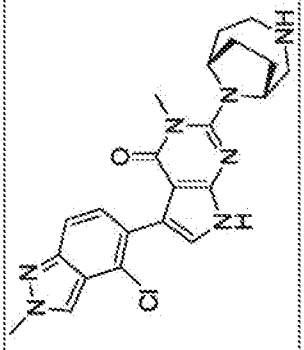
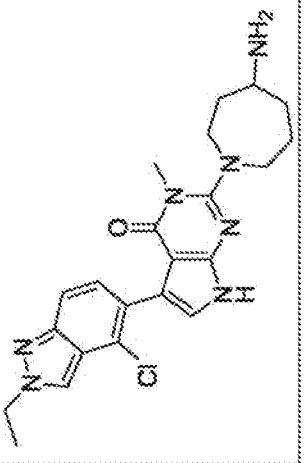
[1702] 利用类似于方法9中所述的方法,制备表12中所示的化合物。可以通过研磨/从溶液中沉淀直接分离化合物,或可以纯化(例如利用质量导向的制备型HPLC、色谱法、结晶)化合物。在一些情况下,将化合物作为盐酸盐分离;通过用过量HCl(2N HCl的Et_2O溶液)处理最终化合物的溶液(例如MeOH溶液),然后蒸发至干,来分离化合物。

[1703]

表12：

实施例	结构	名称	NMR 数据	$[M+H]^+$ m/z	方法
150		2-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.74 (1H, s), 8.45 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.01 (1H, s), 4.49 (2H, q), 4.12–4.03 (1H, m), 3.67 (1H, d), 3.50 (1H, d), 3.40 (3H, s), 3.29-3.16 (2H, m), 3.02-2.84 (3H, m), 1.94-1.82 (1H, m), 1.82-1.71 (1H, m), 1.71-1.57 (2H, m), 1.53 (3H, t), 1.33 (2H, br s), 1.10 (3H, d).	496	9
151		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-(1,4-二氮杂环庚烷-1-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (1H, s), 7.54 (1H, dd), 7.48 (1H, d), 7.06 (1H, s), 4.55 (2H, q), 3.80 (2H, t), 3.65-3.52 (7H, m), 3.46 (2H, t), 2.26-2.17 (2H, m), 1.65 (3H, t).	426	9
152		*rac*-2-[(1*R*,2*R*,5*R*)-2-氨基-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.26-10.98 (1H, m), 8.40 (1H, s), 7.49 (1H, dd), 7.34 (1H, d), 6.96 (1H, s), 4.20 (3H, s), 4.11-4.04 (1H, m), 3.87-3.80 (1H, m), 3.44 (3H, s), 3.05-2.98 (1H, m), 2.04-1.92 (2H, m), 1.89-1.74 (2H, m), 1.71-1.64 (1H, m), 1.57-1.47 (2H, m), 1.28-1.14 (1H, m).	438	9

[1704]

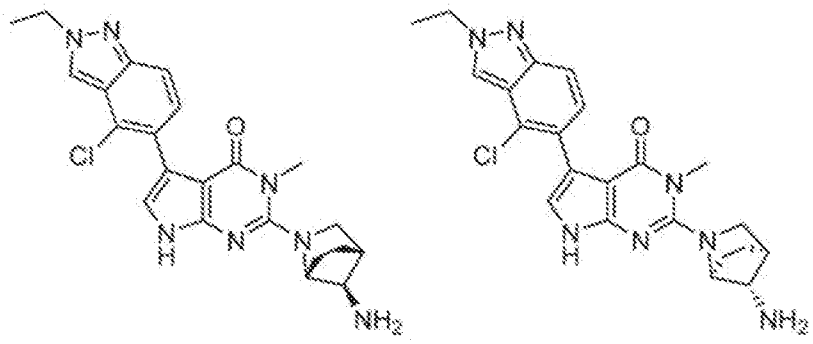
153		*rac*-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(1*R*,6*S*)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.25-10.77 (1H, m), 8.40 (1H, s), 7.49 (1H, dd), 7.33 (1H, d), 6.96 (1H, s), 4.46-4.40 (1H, m), 4.28 (1H, t), 4.20 (3H, s), 3.44 (3H, s), 3.02-2.94 (1H, m), 2.87-2.69 (3H, m), 2.18-1.97 (3H, m), 1.84-1.74 (2H, m), 1.53-1.43 (1H, m).	438	9
154		*rac*-2-(4-氨基氮杂环庚烷-1-基)-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (1H, d), 8.45 (1H, d), 8.02 (3H, br s), 7.51 (1H, dd), 7.32 (1H, d), 6.99 (1H, d), 4.49 (2H, q), 3.56-3.45 (1H, m), 3.45-3.24 (7H, m), 2.22-2.11 (1H, m), 2.10-2.00 (1H, m), 2.00-1.84 (2H, m), 1.84-1.67 (2H, m), 1.53 (3H, t).	440	9

[1705] 实施例155和156

[1706] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-

2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(实施例155)和rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(实施例156)

[1707] [化学式168]

[1708] 

[1709] 将rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮溶解为2.0mg/mL乙醇/DMSO/$CHCl_3$=1/1/3溶液,并在下述条件下完成分离。

[1710] 柱:Daicel CHIRALPAK IG 2x25cm

[1711] 流动相:己烷/2-丙醇=40/60

[1712] 流速:25mL/min

[1713] 各异构体的保留时间:

[1714] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮:8.15分钟

[1715] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮:13.5分钟。

[1716] 手性分析条件:

[1717] 柱子:CHIRALPAK IG 4.6x150mm

[1718] 流动相:己烷/2-丙醇=40/60

[1719] 流速:1.0mL/min

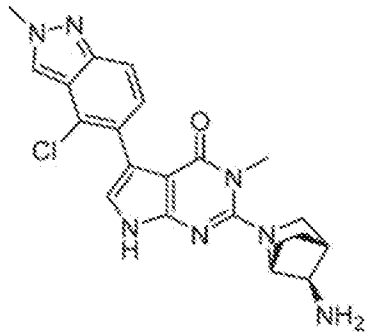
[1720] 各异构体的保留时间:

[1721] rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮:7.406分钟。MS:$[M+H]^+$=438,440.^{1}H-NMR(DMSO-d_6)δ:11.49(1H,br s),8.42(1H,s),7.47(1H,dd,J=9.0,0.7Hz),7.30(1H,d,J=9.0Hz),6.87(1H,s),4.46(2H,q,J=7.3Hz),3.86-3.66(2H,m),3.30-3.26(3H,m),3.17-3.14(1H,m),3.04-2.98(1H,m),2.18-2.11(1H,m),2.01-1.82(3H,m),1.51(3H,t,J=7.1Hz),1.40-1.31(1H,m).

[1722] rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮:11.246分钟。MS:$[M+H]^+$=438,440.^{1}H-NMR(DMSO-d_6)δ:11.49(1H,br s),8.42(1H,s),7.47(1H,dd,J=9.0,0.7Hz),7.30(1H,d,J=9.0Hz),6.87(1H,s),4.46(2H,q,J=7.3Hz),3.86-3.66(2H,m),3.30-3.26(3H,m),3.17-3.14(1H,m),3.04-2.98(1H,m),2.18-2.11(1H,m),2.01-1.82(3H,m),1.51(3H,t,J=7.1Hz),1.40-1.31(1H,m).

[1723] 实施例157:rel-2-((1R,4R,7R)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[1724] [化学式169]

[1725] 

[1726] 步骤1

[1727] 将rac-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(200mg,0.472mmol)溶解于$CHCl_3$/MeOH=4/1(5.0mL)中。在0℃,向其中加入溶解于$CHCl_3$(1.0mL)中的二碳酸二-叔丁酯,随后在RT搅拌3h。蒸馏除去溶剂,并将残留物经NH硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/EtOAc),得到rac-((1S,4S,7S)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯。将rac-((1S,4S,7S)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯溶解为25mg/mL乙醇/$CHCl_3$=1/1溶液,并在下述条件下完成分离。

[1728] 柱:Daicel CHIRALPAK IG 2x25cm

[1729] 流动相:己烷/2-丙醇=45/55

[1730] 流速:25mL/min

[1731] 各异构体的保留时间:

[1732] rel-((1R,4R,7R)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯:7.5分钟

[1733] rel-((1S,4S,7S)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯:12.5分钟。

[1734] 手性分析条件:

[1735] 柱:CHIRALPAK IG 4.6x150mm

[1736] 流动相:己烷/2-丙醇=40/60

[1737] 流速:1.0mL/min

[1738] 各异构体的保留时间:

[1739] rel-((1R,4R,7R)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯:5.668分钟

[1740] rel-((1S,4S,7S)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二

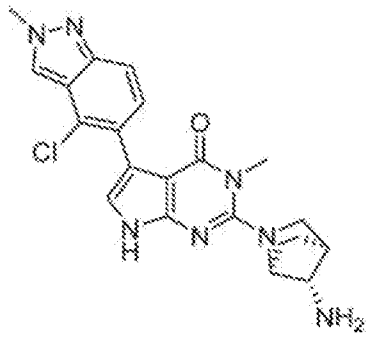
氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯:9.407分钟.

[1741] 步骤2

[1742] 将rel-((1R,4R,7R)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯(81.5mg,0.155mmol)和TFA(1.0mL)溶解于甲醇(1.0mL)中。将混合物在RT搅拌30分钟。将溶剂蒸馏除去,并将残留物经NH硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/EtOAc),得到标题化合物。MS:$[M+H]^+$=424,426.^{1}H-NMR(DMSO-d_6)δ:11.49(1H,brs),8.37(1H,s),7.46(1H,d,J=8.9Hz),7.31(1H,d,J=8.9Hz),6.88(1H,s),4.18(3H,s),3.84(1H,s),3.73-3.65(1H,m),3.28-3.23(4H,m),3.02(1H,d,J=8.8Hz),2.15(1H,s),2.01-1.83(3H,m),1.74-1.49(2H,m),1.42-1.31(1H,m).

[1743] 实施例158:rel-2-((1S,4S,7S)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

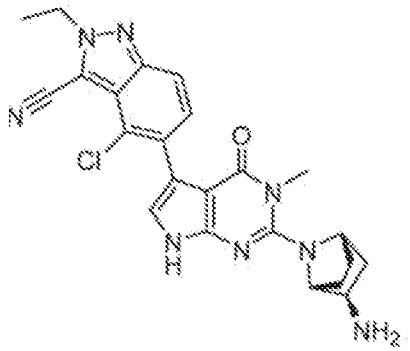
[1744] [化学式170]

[1745] 

[1746] 根据实施例157的步骤2,除了将实施例157步骤1中得到的rel-((1S,4S,7S)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯用于代替rel-((1R,4R,7R)-2-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯,得到标题化合物。MS:$[M+H]^+$=424,426.^{1}H-NMR(DMSO-d_6)δ:11.49(1H,br s),8.37(1H,s),7.46(1H,d,J=8.9Hz),7.31(1H,d,J=8.9Hz),6.88(1H,s),4.18(3H,s),3.84(1H,s),3.73-3.65(1H,m),3.28-3.23(4H,m),3.02(1H,d,J=8.8Hz),2.15(1H,s),2.01-1.83(3H,m),1.74-1.49(2H,m),1.42-1.31(1H,m).

[1747] 实施例159:5-(2-((1R,2R,4S)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-4-氧代-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-5-基)-4-氯-2-乙基-2H-吲唑-3-甲腈

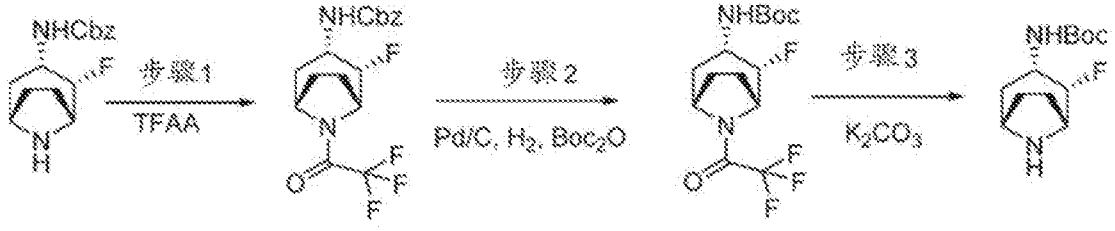
[1748] [化学式171]

[1749] 

[1750] 将((1R,2R,4S)-7-(5-(4-氯-3-氰基-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(50mg,0.072mmol)溶解于N,N-二甲基甲酰胺(0.5mL)中。向所述溶液中,加入四丁基氟化铵(1M的THF溶液,0.22mL,0.22mmol),并在80℃搅拌1d。向混合物中,加入5M NaOH aq.(0.072mL,0.36mmol,5mol/L),并在RT搅拌1h。将混合物真空浓缩,并将残留物经r-HPLC纯化。将得到的级分真空浓缩,并将残留物溶解于乙腈(1.0mL)中。向溶液中,加入碘化钠(5.8mg,0.039mmol)和氯化三甲基硅烷(0.0031mL,0.024mmol),并将混合物在RT搅拌2h。将混合物真空浓缩,并将残留物经NH硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/$CHCl_3$),得到标题化合物(4.9mg)。MS:$[M+H]^+$=463,465.^{1}H-NMR(DMSO-d_6)δ:11.78(1H,br s),7.79(1H,d,J=8.8Hz),7.53(1H,d,J=8.8Hz),7.07(1H,s),4.68(2H,q,J=7.2Hz),4.15(1H,br t,J=4.8Hz),4.02(1H,br t,J=4.4Hz),3.53-3.45(1H,m),3.40(3H,s),2.36-2.21(1H,m),2.20-2.09(1H,m),1.96-1.84(1H,m),1.75-1.64(1H,m),1.58(3H,t,J=7.2Hz),1.54-1.44(1H,m),0.97-0.87(1H,m).

[1751] 制备117:N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯

[1752] [化学式172]

[1753] 

[1754] 步骤1:N-[(1R,2S,3S,5S)-2-氟-8-(2,2,2-三氟乙酰基)-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯

[1755] 向N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(1.0g,3.6mmol)和Et_3N(1.0mL,7.2mmol)的DCM(15mL)溶液中,加入三氟乙酸酐(0.53mL,3.78mmol),然后将反应混合物在RT搅拌1h。将反应物用DCM稀释,并加入饱和$NaHCO_3$水溶液。用DCM萃取水层,将水相干燥($MgSO_4$),过滤并浓缩。将粗产品经硅胶柱色谱(梯度洗脱,0-60%,EtOAc/Petrol)纯化,得到标题化合物(1.32g)。^{1}H NMR(400MHz,DMSO-d_6)δ:7.47(1H,d),7.42-7.25(5H,m),5.05(2H,s),4.88-4.60(2H,m),4.59-4.33(1H,m),4.01-3.85(1H,m),3.35(1H,s),2.13-2.01(1H,m),1.99-1.68(5H,m).

[1756] 步骤2:N-[(1R,2S,3S,5S)-2-氟-8-(2,2,2-三氟乙酰基)-8-氮杂二环[3.2.1]辛

烷-3-基]氨基甲酸叔丁酯

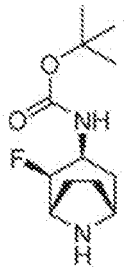
[1757] 向N-[(1R,2S,3S,5S)-2-氟-8-(2,2,2-三氟乙酰基)-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯(1.32g,3.53mmol)的乙醇(15mL)溶液中,加入二碳酸二-叔丁酯(1.0g,4.58mmol)和Pd/C(10%,0.13g),将混合物氢化6h。将反应物过滤,并蒸发滤液。将残留物经硅胶柱色谱纯化(梯度洗脱,0-40%,EtOAc/Petrol),得到标题化合物(1.04g)。^{1}H NMR(400MHz,DMSO-d_6)δ:6.98(1H,d),4.89-4.21(3H,m),3.86(1H,d),2.19-1.53(6H,m),1.39(9H,s).

[1758] 步骤3:N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯

[1759] 向N-[(1R,2S,3S,5S)-2-氟-8-(2,2,2-三氟乙酰基)-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯(1.04g,3.07mmol)的MeOH(15mL)和H_2O(3mL)溶液中,加入K_2CO_3(2.11g,15.35mmol),并将混合物搅拌过夜。将MeOH蒸发,加入H_2O,并将产物用DCM萃取。将有机相干燥($MgSO_4$)、过滤并蒸发,得到标题化合物(0.733g)。^{1}H NMR(400MHz,DMSO-d_6)δ:6.75(1H,d),4.34(1H,d),3.72-3.52(1H,m),3.46(1H,s),3.35(1H,s),2.14(1H,s),1.69(2H,d),1.60-1.25(13H,m).

[1760] 制备118:N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸叔丁酯

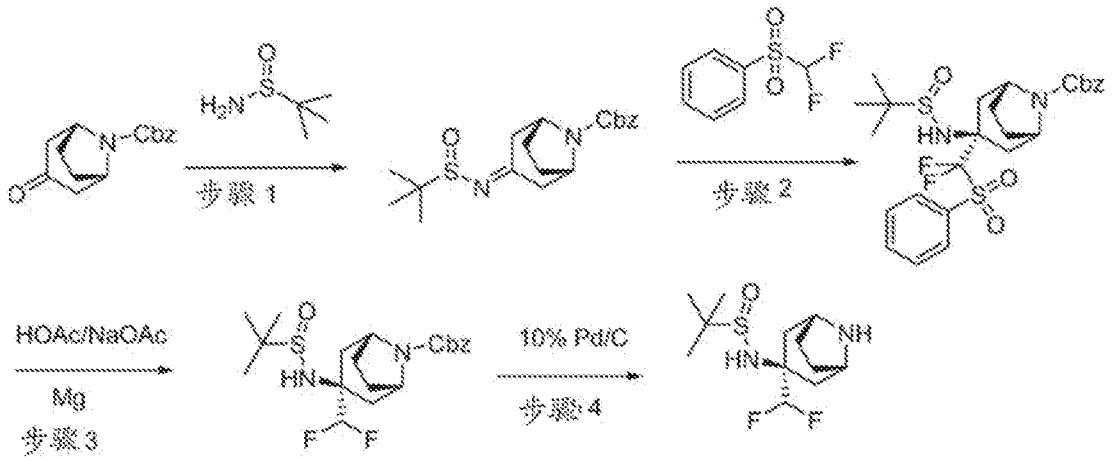
[1761] [化学式173]

[1762] 

[1763] 利用与制备117中类似的方法,用N-[(1S,2R,3S,5R)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯代替N-[(1R,2R,3S,5S)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯,制备标题化合物,得到标题化合物,^{1}H NMR(400MHz,DMSO-d_6)δ:6.02(1H,s),4.96-4.44(1H,m),4.11-3.85(1H,m),3.40(1H,q),3.27(1H,d),2.35(1H,s),2.18-1.97(1H,m),1.97-1.83(1H,m),1.83-1.68(1H,m),1.68-1.48(3H,m),1.39(9H,s)。

[1764] 制备119:N-[(endo)-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-3-基]-2-甲基丙烷-2-亚磺酰胺

[1765] [化学式174]

[1766] 

[1767] 步骤1. 3-[(2-甲基丙烷-2-亚磺酰基)亚氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯

[1768] 向搅拌的3-氧代-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(75.0g,289.2mmol,1.0eq)的THF(1.5L)溶液中,加入2-甲基-2-丙烷亚磺酰胺(43.0g,354.8mmol,1.2eq)和Ti(OEt)$_4$(200.0g,876.8mmol,3.0eq)。将反应物加热回流3小时,并冷却至rt。通过缓慢加入H_2O(550mL)淬灭混合物,并搅拌1h。过滤除去固体,并将滤液用EtOAc稀释,并用饱和盐水洗涤,并干燥(Na_2SO_4)。减压除去溶剂,得到粗产物(103g),作为黄色粉末。将其从石油醚/EtOAc=4:1中重结晶,得到纯产物(36g,34%),作为白色固体。LC-MS:$[M+H]^+$=363.

[1769] 步骤2.(endo)-3-[(苯磺酰基)二氟甲基]-3-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯

[1770] 在N_2气氛下,于-78℃,向3-[(2-甲基丙烷-2-亚磺酰基)亚氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(75.1g,207.0mmol,1.0eq)和二氟甲烷磺酰基苯(47.8g,248.0mmol,1.2eq)混合物的甲苯(750mL)溶液中,加入KHMDS(269ml,269.0mmol,1.3eq)。加完后,将反应物在相同温度下再搅拌2小时,然后通过加入H_2O(280mL)淬灭。分离有机层,并将其经Na_2SO_4干燥。真空除去溶剂,并将残留物经硅胶柱纯化(0-30%EtOAc的石油醚溶液,v/v),得到产物(30.0g,产率26%),作为黄色固体。LC-MS:$[M+H]^+$=555.

[1771] 步骤3.(endo)-3-(二氟甲基)-3-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯

[1772] 在r.t.下,向(endo)-3-[(苯磺酰基)二氟甲基]-3-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(56.6g,102mmol,1.0eq)的DMF(1050mL)和HOAc/NaOAc(8mol/L)(1:1,1050mL)溶液中,分批加入Mg(50.9g,2.09mol,20.5eq)。加完后,将反应物在r.t.再搅拌4小时。LC-MS显示反应完全。将反应混合物用水稀释,并用EtOAc(1000mL×2)萃取。将合并的萃取物用水洗涤,经Na_2SO_4干燥,并真空浓缩,得到粗产物,将其用反相柱(洗脱剂:MeOH的H_2O/TFA溶液)纯化,得到纯产物(24.5g,产率58%),作为白色固体。LC-MS:$[M+H]^+$=415.

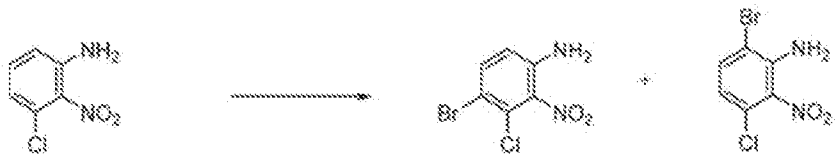
[1773] 步骤4.N-[(endo)-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-3-基]-2-甲基丙烷-2-亚磺酰胺

[1774] H_2气氛下,将(endo)-3-(二氟甲基)-3-[(2-甲基丙烷-2-亚磺酰基)氨基]-8-氮杂二环[3.2.1]辛烷-8-甲酸苄酯(24.5g,59.0mmol,1.0eq)和Pd/C(10%,3.0g)混合物的MeOH

溶液(100mL)在50℃搅拌大约20h。经过滤除去Pd/C,并将滤液真空浓缩,得到粗产物,将其经硅胶柱(MeOH在DCM中0-10%NH_4OH)纯化,得到标题化合物(10.8g,产率65%),作为无色油状物。LC-MS:$[M+H]^+$=281.^1H NMR($CDCl_3$)δ:5.79(1H,t),3.65(3H,br s),2.22(2H,m),1.94(2H,m),1.83(3H,m),1.54(1H,d),1.28(9H,s).

[1775] 制备120:4-溴-3-氯-2-硝基苯胺和6-溴-3-氯-2-硝基苯胺

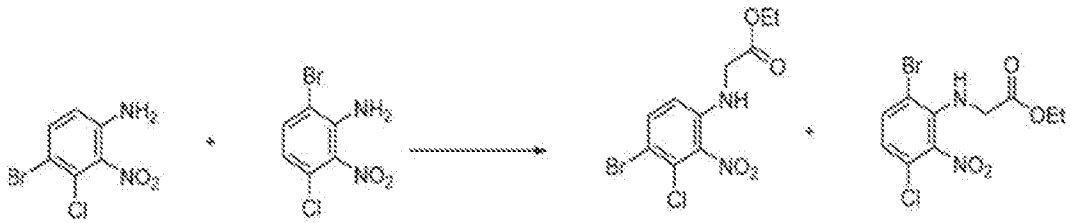
[1776] [化学式175]

[1777] 

[1778] 将3-氯-2-硝基苯胺(25g,145mmol)和N-溴琥珀酰亚胺(25.5g,143mmol)的AcOH(600mL)溶液回流45min。冷却至RT后,将反应混合物倒入冰冷的水(2L)中。经过滤收集沉淀,用冰冷的水(2x200mL)洗涤,并在真空干燥箱中干燥过夜,得到标题化合物(36g),作为异构体的混合物(4-溴/6-溴,以9:1比率)。^1H NMR(500MHz,DMSO-d_6)δ:7.56(1H,d),6.84(1H,d),6.40(2H,s).

[1779] 制备121:2-[(4-溴-3-氯-2-硝基苯基)氨基]乙酸乙酯和2-[(6-溴-3-氯-2-硝基苯基)氨基]乙酸乙酯

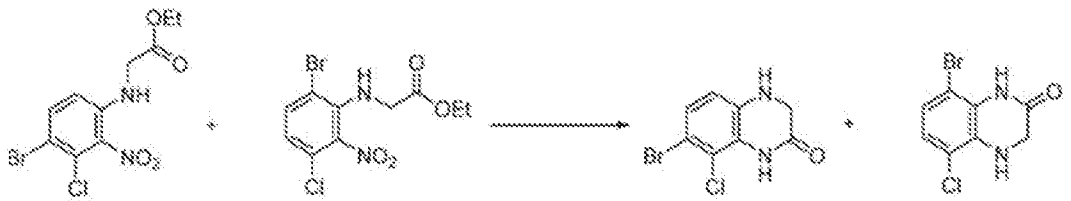
[1780] [化学式176]

[1781] 

[1782] 将4-溴-3-氯-2-硝基苯胺和6-溴-3-氯-2-硝基苯胺(以9:1比率)(30g,119mmol)、溴乙酸乙酯(133mL,119mmol)和K_2CO_3(26.4g,191mmol)的混合物在140℃于氮气气氛下加热30h。将混合物冷却至RT,然后历经10min加入1M NaOH水溶液(250mL)。将混合物再搅拌10min,然后用DCM(3x30mL)萃取。将合并的有机层经$MgSO_4$干燥,过滤,并真空浓缩。将粗产物经硅胶柱色谱(梯度洗脱,5-30%,EtOAc/异己烷)纯化。将纯化的混合物从沸腾的IPA(70mL)中重结晶。将固体物过滤,用环己烷(2x50mL)洗涤,并在真空干燥箱中干燥过夜,得到标题化合物(4g),作为异构体(4-溴/6-溴,以9:1比率)的混合物。MS:$[M+H]^+$=337.

[1783] 制备122:7-溴-8-氯-1,2,3,4-四氢喹喔啉-2-酮和8-溴-5-氯-1,2,3,4-四氢喹喔啉-2-酮

[1784] [化学式177]

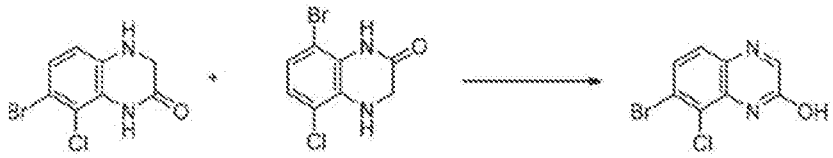
[1785] 

[1786] 将2-[(4-溴-3-氯-2-硝基苯基)氨基]乙酸乙酯和2-[(6-溴-3-氯-2-硝基苯基)氨基]乙酸乙酯(以9:1比率)(3.5g,10.4mmol)、铁(3.5g,62.7mmol)和NH_4Cl(0.555g,

10.4mmol)混合物的EtOH(75mL)溶液回流30min。加入AcOH(30mL),并继续加热30min。将反应混合物用水(300mL)稀释,并用DCM(3x100mL)萃取。将合并的有机层经$MgSO_4$干燥,过滤,并真空浓缩,得到标题化合物(2.8g),作为异构体的混合物(7-溴/8-溴,以9:1比率)。MS:$[M+H]^+$=261.

[1787] 制备123:7-溴-8-氯喹喔啉-2-醇

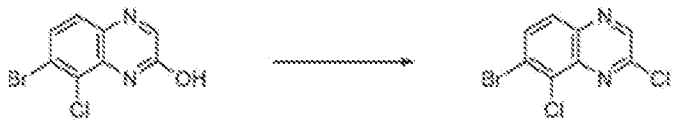
[1788] [化学式178]

[1789] 

[1790] 将7-溴-8-氯-1,2,3,4-四氢喹喔啉-2-酮和8-溴-5-氯-1,2,3,4-四氢喹喔啉-2-酮(以9:1比率)(3.2g,12.2mmol)悬浮于50wt%NaOH水溶液(1.5mL,29.3mmol)和3wt%H_2O_2水溶液(32mL,28.1mmol)中。将反应混合物回流3h。将混合物冷却至RT,使产物沉淀。加入AcOH(1.6mL)。通过过滤收集沉淀物,用水(2x5mL)洗涤。将固体与乙腈(2x20mL)共沸,得到标题化合物(2.8g)。MS:$[M+H]^+$=259.

[1791] 制备124:7-溴-2,8-二氯喹喔啉

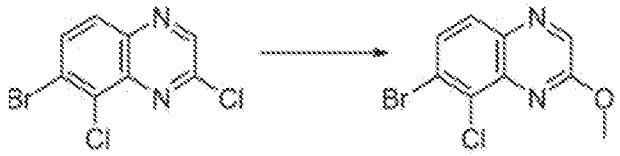
[1792] [化学式179]

[1793] 

[1794] 向7-溴-8-氯喹喔啉-2-醇(3g,11.6mmol)的甲苯(23mL)溶液中,加入氧氯化磷(V)(4.85mL,52.0mmol),并将反应混合物在70℃下搅拌过夜。通过滴加至冰冷的饱和$NaHCO_3$水溶液(200mL)中而淬灭反应混合物,并在RT搅拌2h。然后将混合物用DCM(3x80mL)萃取,并将合并的有机层经$MgSO_4$干燥,过滤并减压浓缩,得到标题化合物(2.5g)。^1H NMR(500MHz,DMSO-d_6):δ:9.13(1H,s),8.22(1H,d),8.07(1H,d).

[1795] 制备125:7-溴-8-氯-2-甲氧基喹喔啉

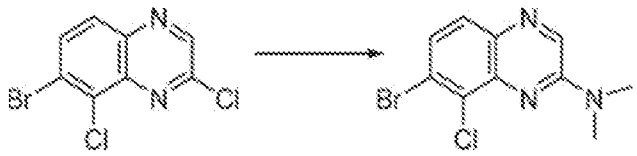
[1796] [化学式180]

[1797] 

[1798] 将7-溴-2,8-二氯喹喔啉(2g,7.12mmol)和碳酸钾(3.94g,28.5mmol)合并于100mL三颈瓶里的MeOH(40mL)中。将得到的无色混悬液在65℃(内部温度)下加热18h。将反应混合物冷却至RT。加入水(150mL),并将沉淀物过滤,得到7-溴-8-氯-2-甲氧基喹喔啉(1.79g,6.48mmol,产率91%),为浅无色固体。MS:$[M+H]^+$=275.^1H NMR(DMSO-d_6)δ:8.69(1H,s),8.00-7.89(2H,m),4.10(3H,s).

[1799] 制备126:7-溴-8-氯-N,N-二甲基喹喔啉-2-胺

[1800] [化学式181]

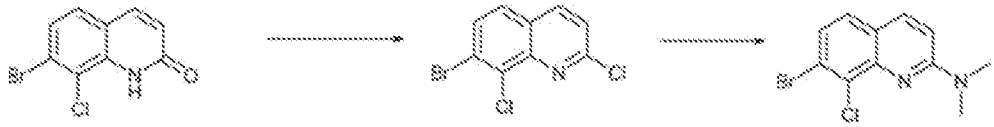
[1801] 

[1802] 在100mL三颈瓶中，将二甲基胺的2M THF溶液(22mL，44.0mmol)在0℃(内部温度，冰浴)用7-溴-2,8-二氯喹喔啉(2.01g，7.16mmol)处理。将得到的黄色溶液加热至RT，并搅拌3h。将反应混合物真空浓缩，并在EtOAc(50mL)和饱和$NaHCO_3$水溶液(50mL)之间分配。分离各层，并将水相用EtOAc(2x50mL)萃取。将有机萃取物合并，并用饱和盐水(1x50mL)洗涤，然后经$MgSO_4$干燥，过滤并真空浓缩，得到7-溴-8-氯-N,N-二甲基喹喔啉-2-胺(1.98g，6.77mmol，产率95%)，作为浅黄色固体。MS:$[M+H]^+$=288.

[1803] ^1H NMR(500MHz，DMSO-d_6) δ:8.76(s，1H)，7.72(d，J=8.8Hz，1H)，7.63(d，J=8.8Hz，1H)，3.29(s，6H).

[1804] 制备127:7-溴-8-氯-N,N-二甲基喹啉-2-胺

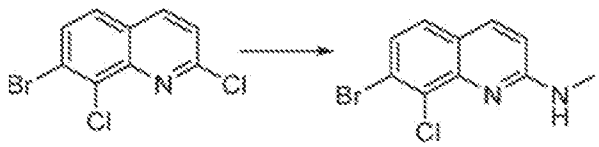
[1805] [化学式182]

[1806] 

[1807] 将7-溴-8-氯-1,2-二氢喹啉-2-酮(1.0g，3.87mmol)的$POCl_3$溶液加热回流1h。冷却后，将大部分$POCl_3$蒸发，加入冰和NH_4OH，并将产物用EtOAc萃取。将有机相干燥($MgSO_4$)，过滤并蒸发，得到7-溴-2,8-二氯喹啉(0.79g)，MS:$[M+H]^+$=278。将7-溴-2,8-二氯喹啉(250mg，0.9mmol)溶解于吡啶(1.5mL)中，加入二甲胺(40%的水溶液，1.5mL)，并将反应混合物在密封管中加热3h。冷却后，加入水(10ml)，并将产物用EtOAc(2x15mL)萃取。将有机相干燥($MgSO_4$)，过滤并蒸发。将残留物经硅胶柱色谱纯化(梯度洗脱，0-50%，EtOAc/Petrol)，得到标题化合物(220mg)，MS:$[M+H]^+$=287.

[1808] 制备128:7-溴-8-氯-N-甲基喹啉-2-胺

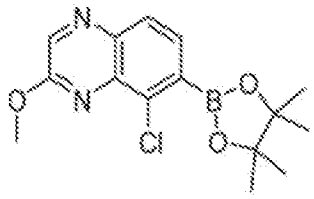
[1809] [化学式183]

[1810] 

[1811] 将7-溴-2,8-二氯喹啉(500mg，1.8mmol)溶解于吡啶(3.0mL)中，加入甲胺(40%的水溶液，3.0mL)，并将反应混合物在密封管中加热3h。冷却后，加入水(20ml)，并将产物用EtOAc(2x20mL)萃取。将有机相干燥($MgSO_4$)，过滤并蒸发。将残留物经硅胶柱色谱纯化(梯度洗脱，0-50%，EtOAc/Petrol)，得到标题化合物(360mg)，MS:$[M+H]^+$=271.

[1812] 制备129:8-氯-2-甲氧基-7-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)喹喔啉

[1813] [化学式184]

[1814] 

[1815] 根据上文制备82，利用7-溴-8-氯-2-甲氧基喹喔啉，制备8-氯-2-甲氧基-7-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)喹喔啉。MS:$[M+H]^+$=321,323.

[1816] 制备130:3-溴-2-氯-5,6-二氟苯甲醛

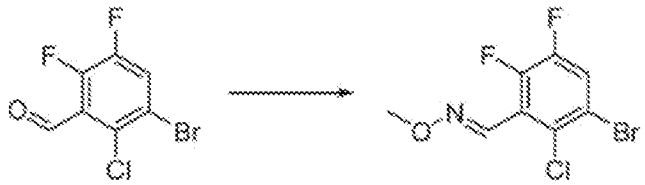
[1817] [化学式185]

[1818] 

[1819] 在60℃，向2-氯-5,6-二氟苯甲醛(5.3g,30mmol)和硫酸(15mL)的混合物中，加入N-溴琥珀酰亚胺(6.6g,37mmol)。将得到的混合物在相同温度下搅拌5h。将混合物倒入碎冰中，然后用EtOAc萃取。将有机相用盐水洗涤，并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-20%，EtOAc/己烷)，得到标题化合物(6.5g)，^{1}H-NMR(400MHz,$CDCl_3$)δ:10.37(1H,s),7.72(1H,dd).

[1820] 制备131:3-溴-2-氯-5,6-二氟苯甲醛O-甲基肟

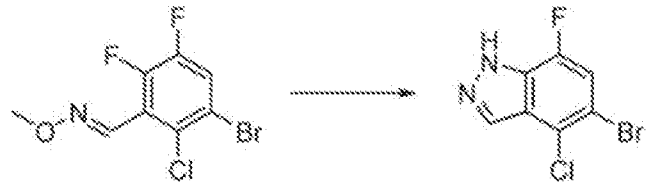
[1821] [化学式186]

[1822] 

[1823] 将3-溴-2-氯-5,6-二氟苯甲醛(6.5g,26mmol)、O-甲基羟基胺盐酸盐(2.4g,29mmol)、碳酸钾(4.6g,33mmol)和1,2-二甲氧基乙烷(26mL)的混合物在60℃搅拌过夜。将混合物过滤并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱，0-20%，EtOAc/己烷)，得到标题化合物(7.2g)，MS:$[M+H]^+$=284.

[1824] 制备132:5-溴-4-氯-7-氟-1H-吲唑

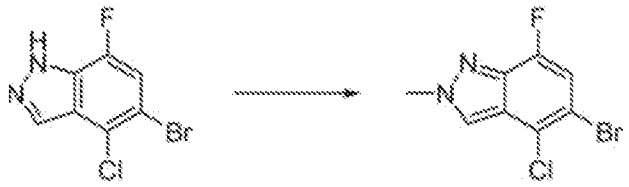
[1825] [化学式187]

[1826] 

[1827] 将3-溴-2-氯-5,6-二氟苯甲醛O-甲基肟(7.1g,25mmol)、四氢呋喃(25mL)和肼一水合物(25mL)的混合物搅拌回流30h。向冷却的混合物中，加入EtOAc(120mL)和水(50mL)。将分离的有机层真空浓缩。将残留物悬浮于EtOAc和己烷中。收集沉淀，并在50℃减压干燥，得到标题化合物(4.4g)，MS:$[M+H]^+$=249.

[1828] 制备133:5-溴-4-氯-7-氟-2-甲基-2H-吲唑

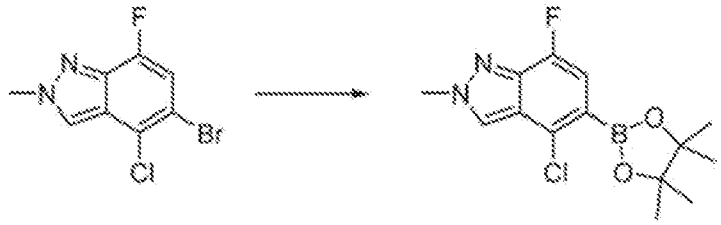
[1829] [化学式188]

[1830] 

[1831] 向5-溴-4-氯-7-氟-1H-吲唑(1.8g,7.4mmol)的EtOAc(40mL)溶液中,加入三甲基氧鎓四氟硼酸盐(1.7g,12mmol),并将得到的混合物在RT搅拌过夜。将反应混合物用EtOAc稀释,用饱和$NaHCO_3$水溶液淬灭,并分离各相。将有机相用盐水洗涤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-60%,EtOAc/己烷),得到标题化合物(0.76g),MS:$[M+H]^+$=263.

[1832] 制备134:4-氯-7-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

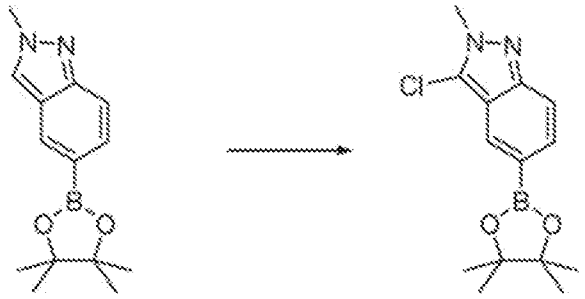
[1833] [化学式189]

[1834] 

[1835] 根据制备82制备,除了利用5-溴-4-氯-7-氟-2-甲基-2H-吲唑,得到标题化合物。MS:$[M+H]^+$=311.

[1836] 制备135:3-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

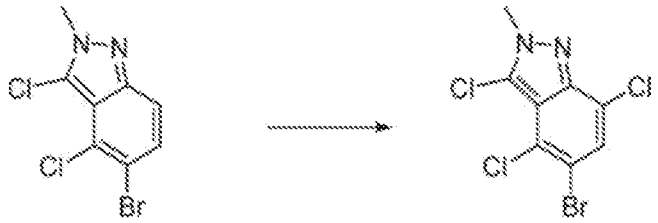
[1837] [化学式190]

[1838] 

[1839] 将2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(190.8mg,0.7392mmol)溶解于THF(10mL)中。在RT下,于搅拌下向溶液中加入N-氯琥珀酰亚胺(109.2mg,0.8178mmol)。在RT搅拌2小时后,加入DMF(5mL)。并将混合物在搅拌下加热至60℃。再搅拌1小时后,将混合物冷却至RT。将混合物倒入5%$NaHCO_3$水溶液中,并用EtOAc萃取。将萃取物用水洗涤,经Na_2SO_4干燥,并浓缩。将残留物用硅胶柱色谱纯化(Biotage SNAP Ultra HP-Sphere,25g),用己烷/EtOAc洗脱,得到标题化合物(142.9mg),作为灰白色蜡状。MS:$[M+H]^+$=292.

[1840] 制备136:5-溴-3,4,7-三氯-2-甲基-2H-吲唑

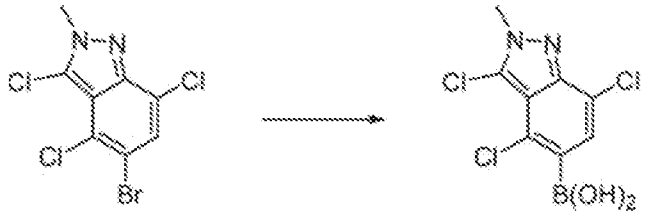
[1841] [化学式191]

[1842] 

[1843] 将5-溴-3,4-二氯-2-甲基-2H-吲唑(5.001g,17.863mmol)悬浮于DMF(50mL)中。将混悬液在搅拌下加热至65℃,得到溶液。向热溶液中,分批加入N-氯琥珀酰亚胺(3.578g,26.80mmol)。在65℃搅拌1.5小时后,将混合物冷却至RT。将混合物倒入9%$NaHCO_3$水溶液中,并用EtOAc提取。将萃取物用水洗涤,经Na_2SO_4干燥,并浓缩。将残留物用硅胶柱色谱(Biotage SNAP Ultra HP-Sphere,100g)纯化,用己烷/EtOA洗脱,得到标题化合物(2.037g),作为无色固体。MS:$[M+H]^+$=313.

[1844] 制备137:(3,4,7-三氯-2-甲基-2H-吲唑-5-基)硼酸

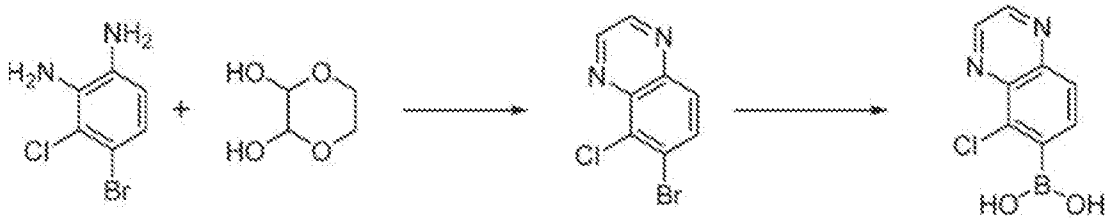
[1845] [化学式192

[1846] 

[1847] 将5-溴-3,4,7-三氯-2-甲基-2H-吲唑(2.037g,6.479mmol)溶解于THF(40mL)中。将溶液减压脱气,通入N_2气,并在搅拌下冷却至0℃。在0℃、搅拌下,向冷却的溶液中滴加i-PrMgCl·LiCl络合物的THF溶液(2.0M,7.75mL,15.5mmol)。搅拌1小时后,在0℃下加入三异丙基硼酸酯(7.50ml,32.7mmol)。并在搅拌下将混合物升至RT。搅拌1.5小时后,加入乙酸(5.60mL,97.80mmol),以淬灭反应。将得到的混合物用2-甲基四氢呋喃稀释。然后,将标题化合物萃取至3M NaOH水溶液(300mL)中。将水层的pH值调节至大约2-3。通过过滤收集沉淀物,用H_2O洗涤,并在70℃下真空干燥,得到标题化合物(1.340g,74%),作为无色固体。MS:$[M+H]^+$=279.

[1848] 制备138:(5-氯喹喔啉-6-基)硼酸

[1849] [化学式193]

[1850] 

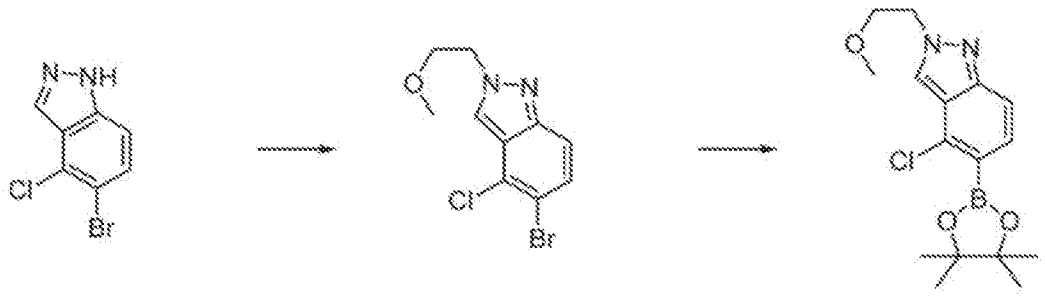
[1851] 在r.t.下,向4-溴-3-氯-苯-1,2-二胺(500mg,2.26mmol)的EtOH溶液(20.0mL)中,加入1,4-二氧六环-2,3-二醇(380mg,3.16mmol)。将混合物在r.t.搅拌18h。然后,将反应混合物真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,20-40%EtOAc/己烷),得到6-溴-5-氯喹喔啉(269mg)。MS:$[M+H]^+$=243,245.

[1852] 在r.t.下,向6-溴-5-氯喹喔啉(200mg,0.823mmol)的1,4-二氧六环(2.00mL)溶液中,加入双(频哪醇合)二硼(313mg,1.23mmol)、KOAc(161mg,1.64mmol)和双(二苯基膦基)

二茂铁]二氯合钯(II)与二氯甲烷的络合物(53.7mg,0.0657mmol)。将混合物在100℃搅拌18h,用MTBE稀释,并加入2M NaOH。向水层加入6M HCl,并用$CHCl_3$萃取3次。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩,得到标题化合物(108mg)。MS:$[M+H]^+$=209.

[1853] 制备139:4-氯-2-(2-甲氧基乙基)-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

[1854] [化学式194]

[1855] 

[1856] 步骤1. 5-溴-4-氯-2-(2-甲氧基乙基)-2H-吲唑

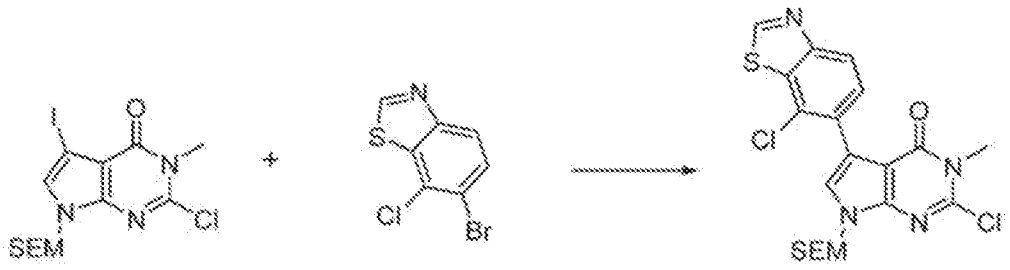
[1857] 在室温,向5-溴-4-氯-1H-吲唑(1.0g,4.7mmol)和碳酸钾(1.79g,13mmol)的DMSO(5ml)混悬液中,加入1-溴-2-甲氧基-乙烷(0.83ml,8.6401mmol)。在相同温度下搅拌过周末,将混合物用EtOAc稀释,并用水洗涤。将有机相用盐水洗涤,经Na_2SO_4干燥,过滤,并真空浓缩。柱色谱(SNAP Ultra 50g,梯度洗脱,0-100%EtOAc的己烷溶液)得到标题化合物(0.45g,1.5mmol,36%),作为棕色固体。MS:$[M+H]^+$=289,291,293.

[1858] 步骤2. 4-氯-2-(2-甲氧基乙基)-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑

[1859] 在室温下,向5-溴-4-氯-2-(2-甲氧基乙基)-2H-吲唑(0.45g,1.5mmol)的1,4-二氧六环混悬液(10mL)中,加入乙酸钾(0.30g,3.13mmol)、4,4,4′,4′,5,5,5′,5′-八甲基-2,2′-二(1,3,2-二氧硼杂环戊烷)(0.59g,2.3mmol)和1,1'-双(二苯基膦基)二茂铁-二氯合钯(II)二氯甲烷络合物(0.12g,0.15mmol)。在120℃搅拌4h后,将混合物用EtOAc稀释,并经Hyflo Super-Cel垫过滤。将滤液真空浓缩。柱色谱(SNAP Ultra 25g,梯度洗脱,0-100%EtOAc的己烷溶液)得到标题化合物(0.68g),作为浅棕色油状物。物质不是纯的,但不纯化即可使用。MS:$[M+H]^+$=337,339.

[1860] 制备140:2-氯-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

[1861] [化学式195]

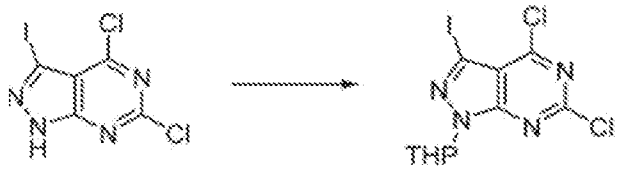
[1862] 

[1863] 将6-溴-7-氯-1,3-苯并噻唑(300mg,1.21mmol)、双(频哪醇合)二硼(460mg,1.81mmol)、Pd(dppf)Cl_2(177mg,0.24mmol)和乙酸钾(592mg,6.04mmol)混合物的1,4-二氧六环(6mL)溶液在100℃搅拌2h,然后冷却。向混合物中,加入2-氯-5-碘-3-甲基-7-((2-(三

甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(350mg,0.8mmol)、Pd(dppf)Cl_2(114mg,0.16mmol)、K_2CO_3(667mg,4.83mmol)和水(3mL)。然后,将混合物在70℃再加热2h。将混合物冷却,然后在EtOAc和水之间分配。将有机层用盐水洗涤,干燥($MgSO_4$),然后真空蒸发。将残留物经SiO_2色谱(用0-40%丙酮/石油醚洗脱)纯化,得到产物(220mg)。MS:$[M+H]^+$=481.

[1864] 制备141:4,6-二氯-3-碘-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[3,4-d]嘧啶

[1865] [化学式196]

[1866] 

[1867] 将4,6-二氯-3-碘-1H-吡唑并[3,4-d]嘧啶(4.0g,13mmol)、3,4-二氢-2H-吡喃(3.5mL,38mmol)和p-甲苯磺酸一水合物(0.48g,2.5mmol)溶解于THF(60mL)中,并在70℃加热1.5h。真空除去溶剂,并将残留物经硅胶柱色谱(梯度洗脱,0-100%,EtOAc/己烷)纯化,得到标题化合物(3.47g)。MS:$[M+H]^+$=399.

[1868] 制备142:6-氯-3-碘-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

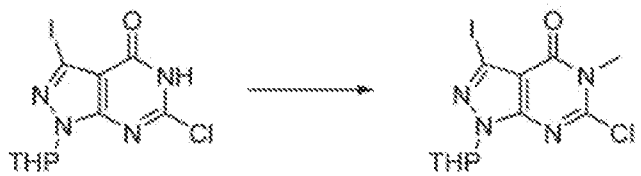
[1869] [化学式197]

[1870] 

[1871] 在r.t.下,向4,6-二氯-3-碘-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[3,4-d]嘧啶(2.0g,5.0mmol)的THF(20mL)溶液中,加入5M NaOH(9.0mL)。将混合物在相同温度下搅拌5小时,然后向混合物中加入THF(10ml)。将混合物在RT搅拌过夜。将混合物用6M HCl酸化,用EtOAc萃取。将有机层用盐水洗涤,经Na_2SO_4干燥,过滤,并真空浓缩,得到标题化合物(1.87g)。MS:$[M+H]^+$=381.

[1872] 制备143:6-氯-3-碘-5-甲基-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

[1873] [化学式198]

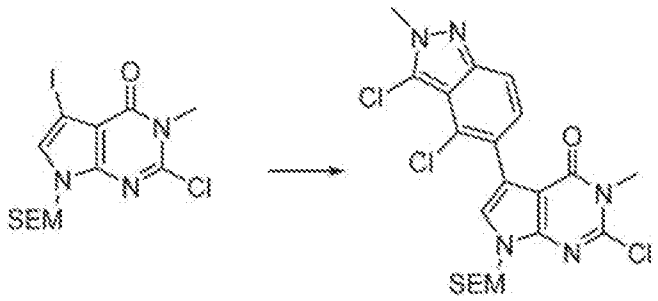
[1874] 

[1875] 在RT,向6-氯-3-碘-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(28.5g,74.9mmol)和K_2CO_3(12.4g,90.0mmol)混合物的DMF(270mL)溶液中,加入碘甲烷(11.7g,82.4mmol)的DMF(15ml)溶液。将混合物在RT搅拌4h,然后用水稀释。搅拌4h后,经过滤收集沉淀,并真空干燥,得到标题化合物(27.8g)。MS:$[M+H]^+$=395.

[1876] 制备144:2-氯-5-(3,4-二氯-2-甲基-吲唑-5-基)-3-甲基-7-(2-三甲基硅烷基乙

氧基甲基)吡咯并[2,3-d]嘧啶-4-酮

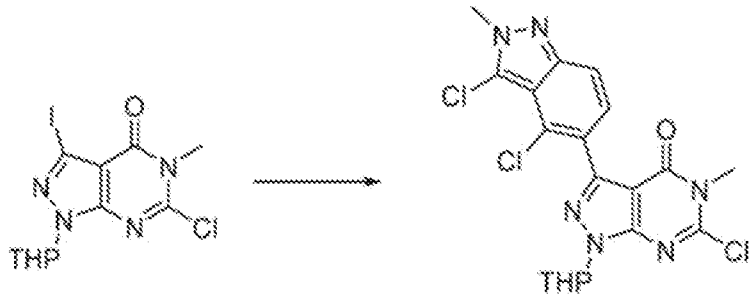
[1877] [化学式199]

[1878] 

[1879] 将2-氯-5-碘-3-甲基-7-(2-三甲基硅烷基乙氧基甲基)吡咯并[2,3-d]嘧啶-4-酮(107mg,0.244mmol)、3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)吲唑(107mg,0.326mmol)、K_3PO_4(108mg,0.506mmol)、双(二-叔丁基(4-二甲基氨基苯基)膦)二氯合钯(II)(18mg,0.026mmol)、1,4-二氧六环(1.2mL)和水(0.24mL)的混合物在70℃搅拌5h,并冷却至RT。将混合物经硅胶柱色谱(梯度洗脱,0-60%EtOAc/己烷)纯化,得到标题化合物(113mg)。MS:$[M+H]^+$=514,516.

[1880] 制备145:6-氯-3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

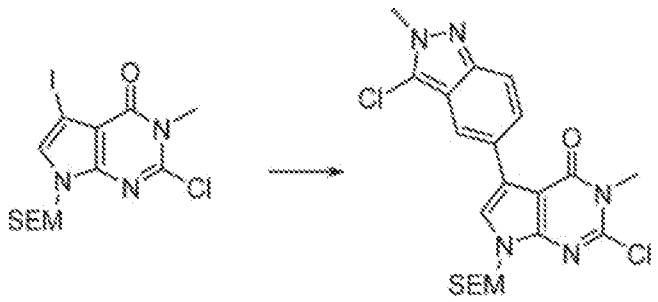
[1881] [化学式200]

[1882] 

[1883] 将6-氯-3-碘-5-甲基-1-(四氢-2H-吡喃-2-基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(500mg,1.27mmol)、3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(497mg,1.52mmol)、K_3PO_4(806mg,3.80mmol)、[1,1'-双(二苯基膦基)二茂铁]二氯合钯(II)与二氯甲烷的络合物(103mg,0.127mmol)、1,4-二氧六环(5.0mL)和水(1.25mL)的混合物在90℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(413mg)。MS:$[M+H]^+$=467,469.

[1884] 制备146:2-氯-5-(3-氯-2-甲基-2H-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

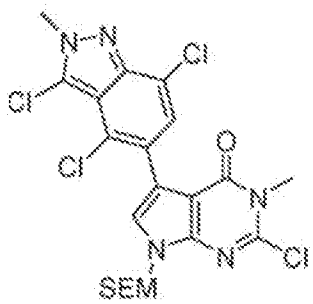
[1885] [化学式201]

[1886] 

[1887] 将2-氯-5-碘-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮(362.7mg,0.8248mmol)、3-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑(289.1mg,0.9881mmol)、Pd(Amphos)$_2$Cl$_2$(34.7mg,0.0490mmol)和K_3PO_4(263.3mg,1.240mmol)在管中混合。向混合物中,加入THF(10mL)和水(1mL)。将混合物减压脱气,并通入N_2气。在75℃搅拌5小时后,将混合物冷却至RT。将混合物倒入水中,并用EtOAc萃取。将萃取物用9%$NaHCO_3$水溶液洗涤。向萃取物中,加入Na_2SO_4和SH-硅胶(Fuji Silysia)。在RT搅拌1小时后,经过滤除去固体,并将滤液浓缩。将残留物用硅胶柱色谱纯化(Biotage SNAP Ultra HP-Sphere,25g),用已烷/EtOAc洗脱,得到标题化合物(279.8mg),作为灰白色固体。MS:$[M+H]^+$=478.

[1888] 制备147:2-氯-3-甲基-5-(3,4,7-三氯-2-甲基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮

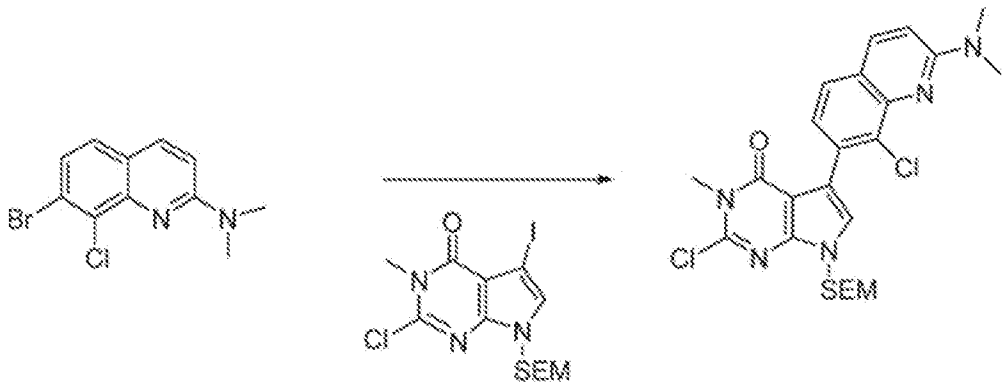
[1889] [化学式202]

[1890] 

[1891] 用与制备146类似的方式,除了用(3,4,7-三氯-2-甲基-2H-吲唑-5-基)硼酸代替3-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑,制备2-氯-3-甲基-5-(3,4,7-三氯-2-甲基-2H-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮。MS:$[M+H]^+$=546.

[1892] 制备148:2-氯-5-[8-氯-2-(二甲基氨基)喹啉-7-基]-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮

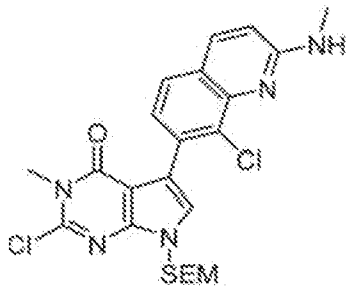
[1893] [化学式203]

[1894] 

[1895] 将7-溴-8-氯-N,N-二甲基喹啉-2-胺(390mg,1.36mmol)、双(频哪醇合)二硼(520mg,2.04mmol)、[1,1'-双(二苯基膦基)二茂铁]二氯合钯(II)(150mg,0.2mmol)和乙酸钾(650mg,6.8mmol)合并于30mL微波管中,密封,抽真空,并填充氮气(x2)。加入1,4-二氧六环(8mL),并将管子再填充氮气(x2)后,加热至90℃,保持2h。冷却后,加入2-氯-5-碘-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮(590mg,1.36mmol)、双(二苯基膦基)二茂铁]二氯合钯(II)(150mg,0.2mmol)、碳酸钾(1.12g,8.16mmol)和水(2mL)。将反应物再密封,填充氮气(x2),并加热至70℃,保持2h。冷却后,将反应物用水稀释,并用EtOAc(3x)提取。将合并的有机物经无水$MgSO_4$干燥,过滤,并蒸发。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%,EtOAc/Petrol),得到标题化合物(426mg)。MS:$[M+H]^+$=518.

[1896] 制备149:2-氯-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮

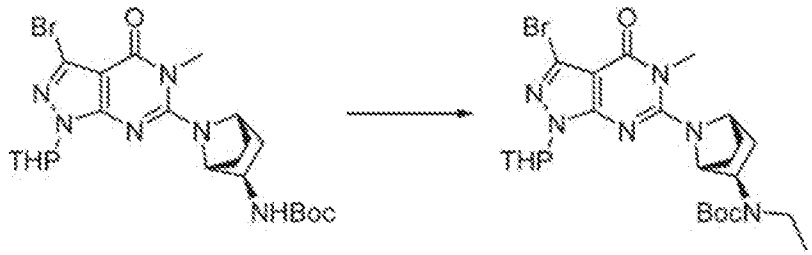
[1897] [化学式204]

[1898] 

[1899] 利用与对2-氯-5-[8-氯-2-(二甲基氨基)喹啉-7-基]-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮所述的类似方法,用7-溴-8-氯-N-甲基喹啉-2-胺开始,制备标题化合物。MS:$[M+H]^+$=504.

[1900] 制备150:((1R,2R,4S)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(乙基)氨基甲酸叔丁酯

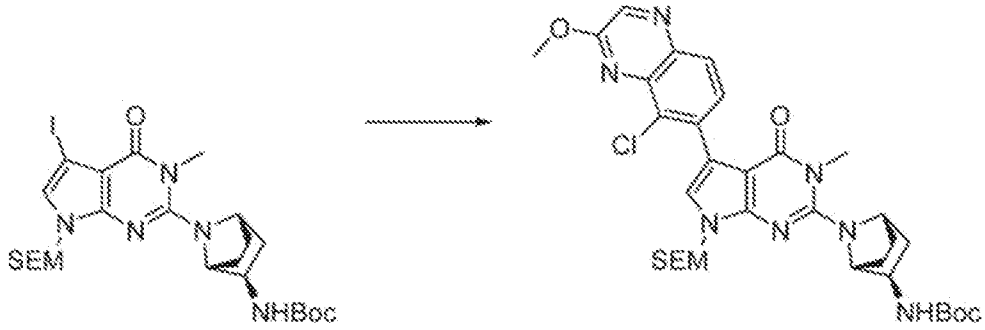
[1901] [化学式205]

[1902] 

[1903] 在0℃,向((1R,2R,4S)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(500mg,0.955mmol)的THF(5.00mL)溶液中,加入NaH(60%,在矿物油中,76.4mg,1.91mmol)。将混合物在0℃搅拌15min。在0℃,向混合物中加入碘乙烷(0.153mL,1.91mmol)。将混合物在r.t.搅拌过夜。在0℃,向混合物中,加入NaH(60%,在矿物油中,57.3mg,1.43mmol)和碘乙烷(0.115mL,1.43mmol)。将混合物在r.t.搅拌6h。将混合物倒入饱和NH_4Cl中,并用EtOAc萃取。将有机层用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,10-40%EtOAc/己烷),得到标题化合物(335mg)。MS:$[M+H]^+$=551,553.

[1904] 通用方法6:((1R,2R,4S)-7-(5-(5-氯-3-甲氧基喹喔啉-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

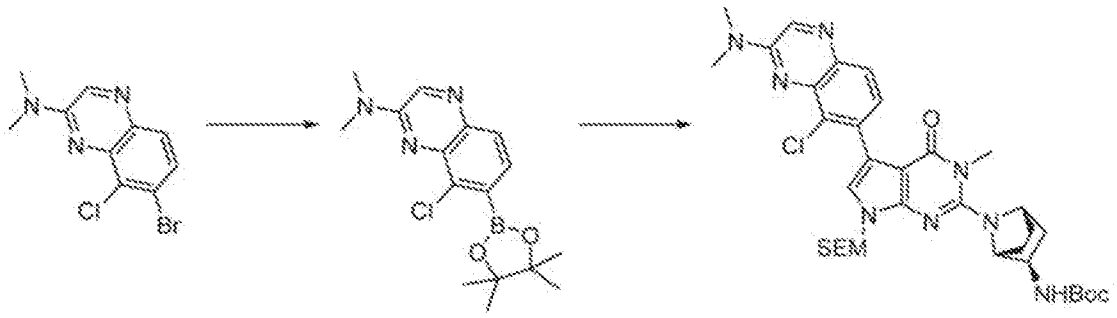
[1905] [化学式206]

[1906] 

[1907] 将((1R,2R,4S)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(75.0mg,0.122mmol)、8-氯-2-甲氧基-7-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)喹喔啉(46.9mg,0.146mmol)、K_3PO_4(38.8mg,0.183mmol)、双(二-叔丁基(4-二甲基氨基苯基)膦)二氯合钯(II)(64.8mg,0.0794mmol)、1,4-二氧六环(1.5mL)和水(0.15mL)的混合物在80℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱(梯度洗脱,0-100%EtOAc/己烷)纯化,得到标题化合物(58.0mg)。MS:$[M+H]^+$=682,684.

[1908] 通用方法7:((1R,2R,4S)-7-(5-(5-氯-3-(二甲基氨基)喹喔啉-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯

[1909] [化学式207]

[1910] 

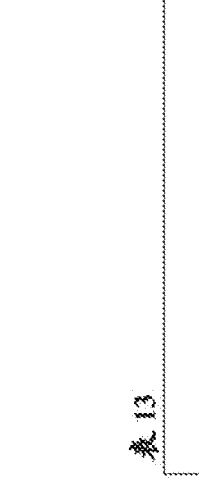
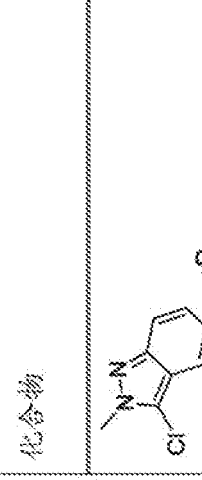
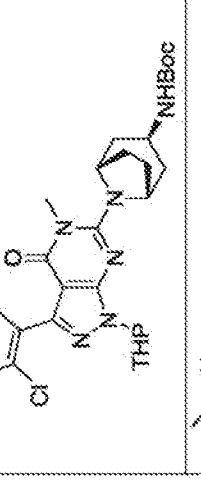
[1911] 将7-溴-8-氯-N,N-二甲基喹喔啉-2-胺(200mg,0.698mmol)、双(频哪醇合)二硼(354mg,1.40mmol)、[1,1'-双(二苯基膦基)二茂铁]二氯合钯(II)与二氯甲烷的络合物(57.0mg,0.0698mmol)和乙酸钾(137mg,1.40mmol)混合物的1,4-二氧六环(2.0mL)溶液脱气,填充氮气,并在100℃搅拌6h。将反应物冷却至RT,通过硅藻土垫过滤,并用EtOAc洗涤。将滤液真空浓缩。将粗残留物用于下一步骤。MS:$[M+H]^+$=334,336.

[1912] 将((1R,2R,4S)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(75.0mg,0.122mmol)、8-氯-N,N-二甲基-7-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)喹喔啉-2-胺(48.8mg,0.146mmol)、K_3PO_4(38.8mg,0.183mmol)、双(二-叔丁基(4-二甲基氨基苯基)膦)二氯合钯(II)(64.8mg,0.0794mmol)、1,4-二氧六环(1.5mL)和水(0.15mL)的混合物在80℃搅拌2h,冷却至RT,倒入水中,并用EtOAc萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤,并真空浓缩。将残留物经硅胶柱色谱纯化(梯度洗脱,0-100%EtOAc/己烷),得到标题化合物(60.3mg)。MS:$[M+H]^+$=695,697.

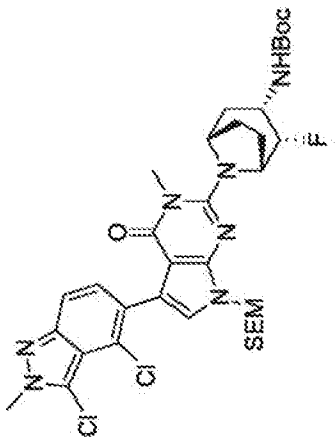
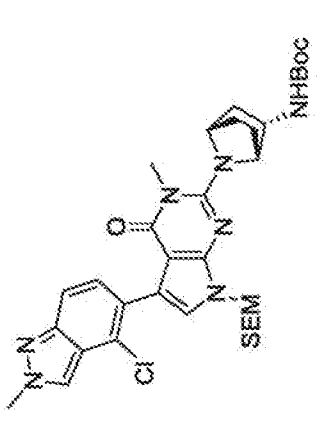
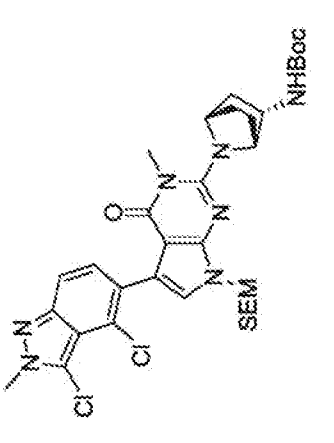
[1913] 利用与通用方法1所述的类似方法,从适当取代、保护的吡咯并嘧啶酮或吡唑并嘧啶酮和不同的胺开始,制备下面表13的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1914]

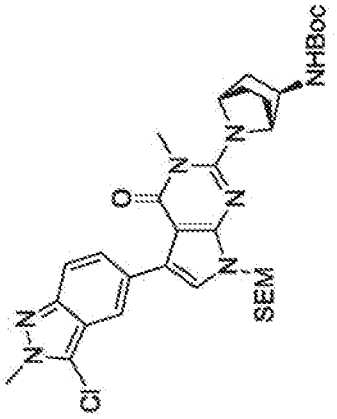
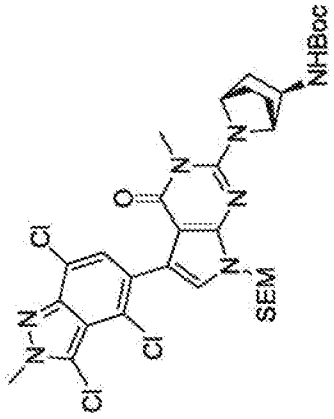
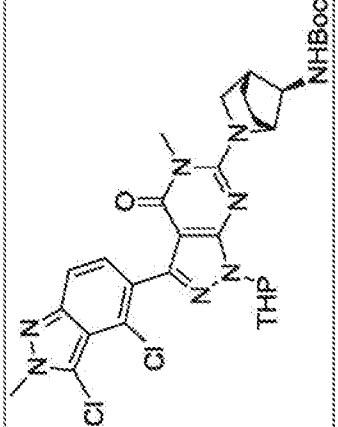
表 13

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	(*endo*-8-{3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基}-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	657, 659	根据上述通用方法 1，利用 6-氯-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和(*endo*-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	(*endo*-8-{3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基}-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	671, 673	根据上述通用方法 1，利用 6-氯-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 *N*-(*endo*-3-甲基-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	((3*R*,4*S*)-1-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-3-氟吡啶-4-基)氨基甲酸叔丁酯	649, 651	根据上述通用方法 1，利用 6-氯-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和 *N*-((3*R*,4*S*)-3-氟吡啶-4-基)氨基甲酸叔丁酯制备

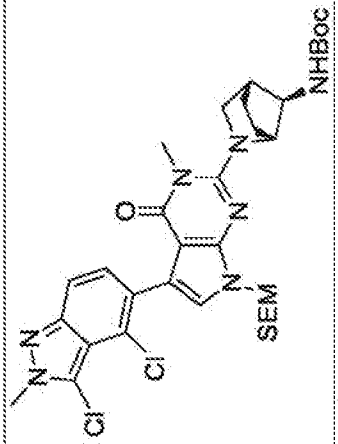
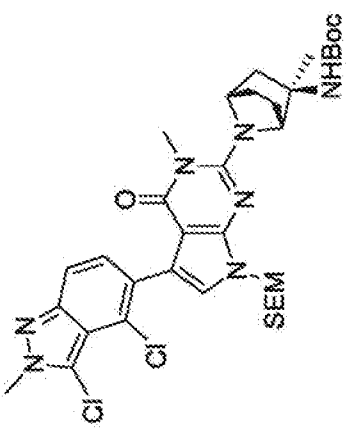
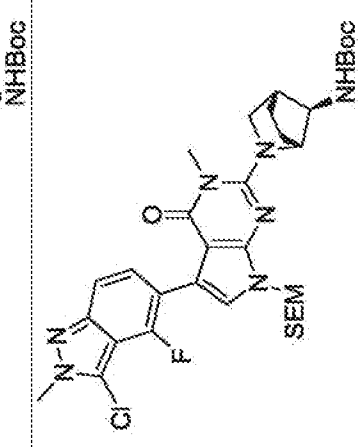
[1915]

	((1*R*,2*S*,3*S*,5*S*)-8-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯	720, 722	根据上述通用方法 1，利用 2-氯-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *N*-((1*S*,2*R*,3*S*,5*R*)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯制备
	(*rac*-(1*R*,2*S*,4*S*)-7-(5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	654, 656	根据上述通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *rac*-(1*S*,2*R*,4*R*)-7-氮杂二环[2.2.1]庚-2-基氨基甲酸叔丁酯盐酸盐制备
	(*rac*-7-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	688, 690	根据上述通用方法 1，利用 2-氯-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *rac*-(1*S*,2*R*,4*R*)-7-氮杂二环[2.2.1]庚-2-基氨基甲酸叔丁酯盐酸盐制备

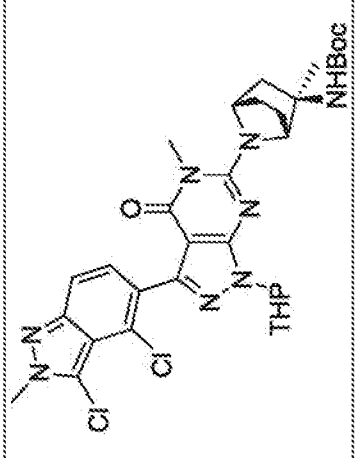
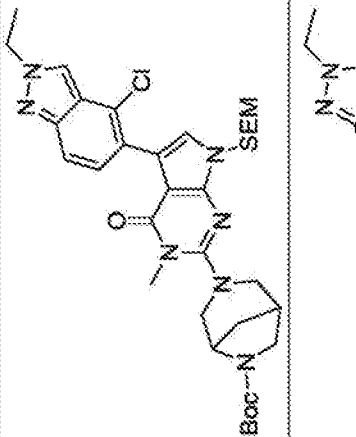
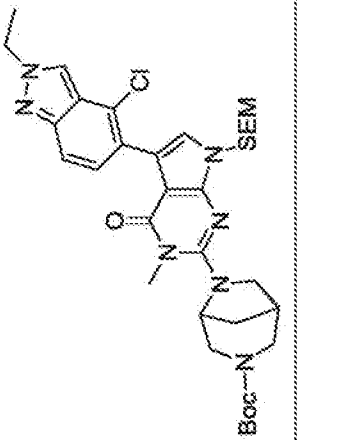
[1916]

	(((1*R*,2*R*,4*S*)-7-(5-(3-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	654	根据上述通用方法 1，利用 2-氯-5-(3-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	(((1*R*,2*R*,4*S*)-7-(3-甲基-4-氧代-5-(3,4,7-三氯-2-甲基-2*H*-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	722, 724	根据上述通用方法 1，利用 2-氯-3-甲基-5-(3,4,7-三氯-2-甲基-2*H*-吲唑-5-基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯制备
	(((1*R*,4*R*,7*R*)-2-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-4,5-二氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	643, 645	根据上述通用方法 1，利用 6-氯-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和((1*R*,4*R*,7*R*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备

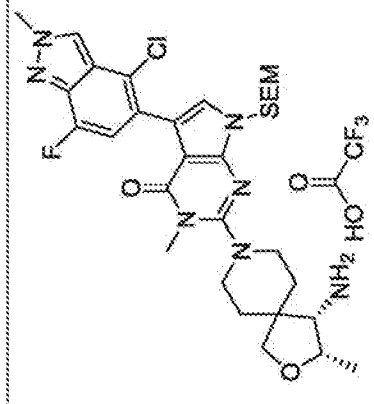
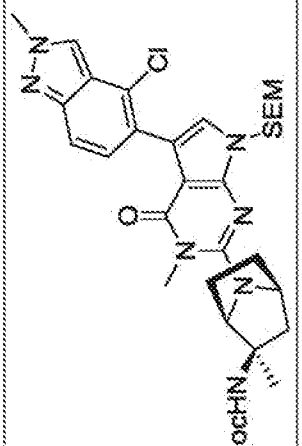
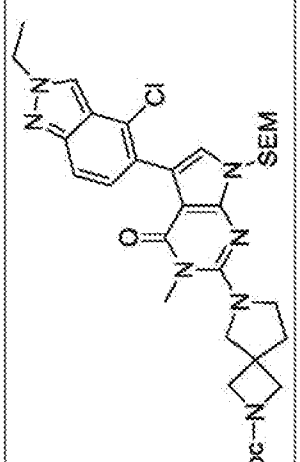
[1917]

	((1*R*,4*R*,7*R*)-2-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	688, 690	根据上述通用方法 1，利用 2-氯-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,4*R*,7*R*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备
	*rac*-((1*R*,2*R*,4*S*)-7-(5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-甲基-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	702, 704	根据上述通用方法 1，利用 2-氯-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *rac*-((1*R*,2*R*,4*S*)-2-甲基-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯苯甲酸盐制备
	((1*R*,4*R*,7*R*)-2-(5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯	672, 674	根据上述通用方法 1，利用 2-氯-5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和((1*R*,4*R*,7*R*)-2-氮杂二环[2.2.1]庚烷-7-基)氨基甲酸叔丁酯制备

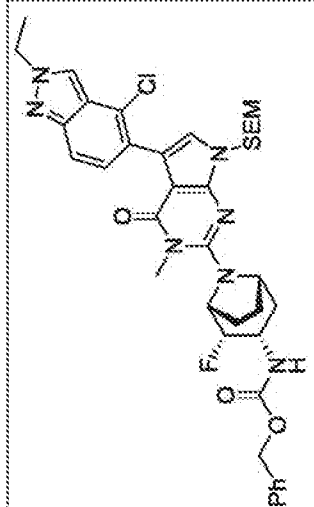
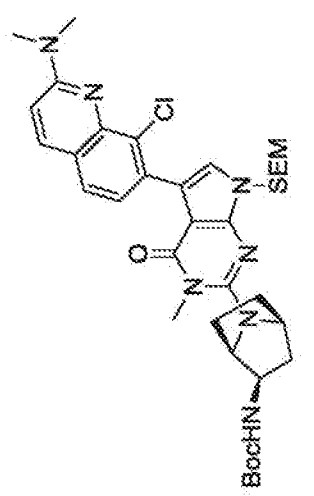
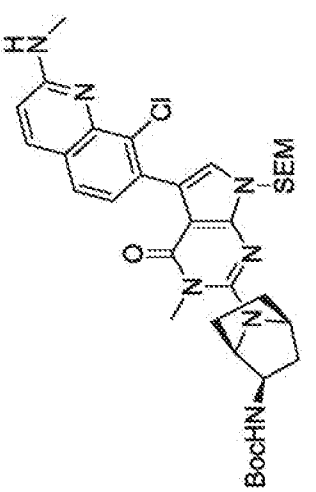
[1918]

	*rac*-((1*R*,2*R*,4*S*)-7-(3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2*H*-吡喃-2-基)-1,4,5-三氢-1*H*-吡唑并[3,4-*d*]嘧啶-6-基)-2-甲基-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	657, 659	根据上述通用方法1，利用6-氯-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1-(四氢-2*H*-吡喃-2-基)-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮和*rac*-((1*R*,2*R*,4*S*)-2-甲基-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯草酸盐制备
	*rac*-3-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-3*H*,4*H*,7*H*-吡喃并[2,3-*d*]嘧啶-2-基)-3,6-二氮杂二环[3.2.1]辛烷-6-甲酸叔丁酯	668	利用通用方法1，用2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡喃并[2,3-*d*]嘧啶-4-酮和*rac*-3,6-二氮杂二环[3.2.1]辛烷-6-甲酸叔丁酯制备，通过正相硅胶色谱纯化。
	*rac*-6-(5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-3*H*,4*H*,7*H*-吡喃并[2,3-*d*]嘧啶-2-基)-3,6-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯	669	利用通用方法1，用2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4*H*-吡喃并[2,3-*d*]嘧啶-4-酮和*rac*-3,6-二氮杂二环[3.2.1]辛烷-3-甲酸叔丁酯制备，通过正相硅胶色谱纯化。

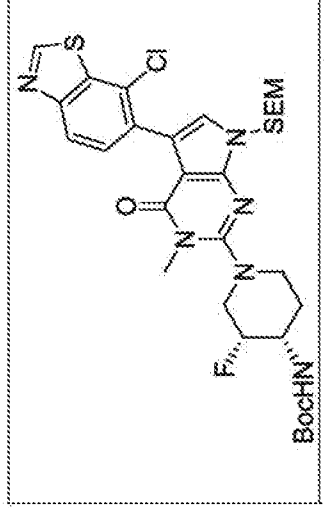
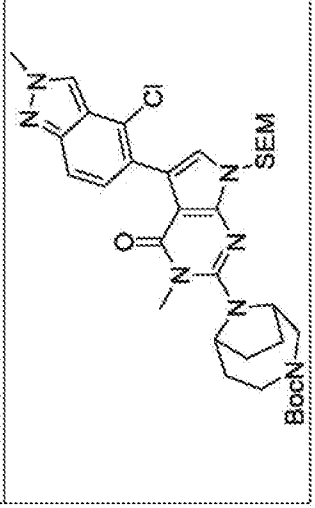
[1919]

	2-[(3S,4S)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-7-氟-2-甲基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮；三氟乙酸盐	630	利用与实施例 72 所述的类似方法，从 4-氯-7-氟-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑开始，制备标题化合物。经反相 C18 硅胶色谱纯化。
	rac-N-[endo-7-[5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-2-基]-7-甲基-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯	668	根据通用方法 1，利用 2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮和 rac-N-[endo-2-甲基-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯(ChemExpress HY-23145)制备。经正相 NH 硅胶色谱纯化。
	rac-6-[5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-4-氧代-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3H,4H,7H-吡咯并[2,3-d]嘧啶-2-基]-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯	668.7	利用通用方法 1，用 2-氯-5-(4-氯-2-乙基-2H-吲唑-5-基)-3-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮和 rac-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯制备，通过正相硅胶色谱纯化。

[1920]

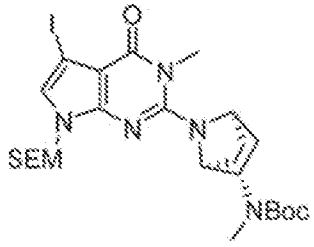
	*N*-[(1*R*,2*S*,3*S*,5*S*)-8-[5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基]-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯	734	利用通用方法 1，用 2-氯-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *N*-[(1*R*,2*R*,3*S*,5*S*)-2-氟-8-氮杂二环[3.2.1]辛烷-3-基]氨基甲酸苄酯盐酸盐制备，通过正相硅胶色谱纯化。
	*N*-[(1*R*,2*R*,4*S*)-7-(5-[8-氯-2-(二甲氨基)喹啉-7-基]-3-甲基-4-氧代-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯	694	根据通用方法 1，在 120°C 加热 7h，用 2-氯-5-[8-氯-2-(二甲氨基)喹啉-7-基]-3-甲基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *N*-[(1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯制备，在 KP-NH 柱上纯化。
	*N*-[(1*R*,2*R*,4*S*)-7-(5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-4-氧代-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯	694	根据通用方法 1，在 120°C 加热 7h，用 2-氯-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮和 *N*-[(1*R*,2*R*,4*S*)-7-氮杂二环[2.2.1]庚烷-2-基]氨基甲酸叔丁酯制备，在 KP-NH 柱上纯化。

[1921]

	2-((3R,4S)-4-氟基-3-氟吡啶-1-基)-5-(7-氯苯并[d]噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮	663	利用通用方法1，用2-氯-5-(7-氯-1,3-苯并噻唑-6-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮和 N-((3R,4S)-3-氟哌啶-4-基)氨基甲酸叔丁酯制备
	rac-9-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,4,7H-吡咯并[2,3-d]嘧啶-2-基)-3,9-二氮杂二环[4.2.1]壬烷-3-甲酸叔丁酯	668	利用通用方法1，用2-氯-5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-7-((2-(三甲基硅烷基)乙氧基)甲基)-3,7-二氢-4H-吡咯并[2,3-d]嘧啶-4-酮和 rac-3,9-二氮杂二环[4.2.1]壬烷-3-甲酸叔丁酯制备

[1922] 制备151：((1S,2S,4R)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯

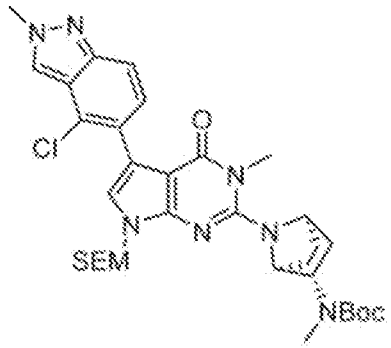
[1923] [化学式208]

[1924] 

[1925] 用与制备93和94类似的方式,除了用((1S,2S,4R)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯代替((1R,2R,4S)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯,制备((1S,2S,4R)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯。MS:$[M+H]^+$=630.

[1926] 制备152:((1S,2S,4R)-7-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯

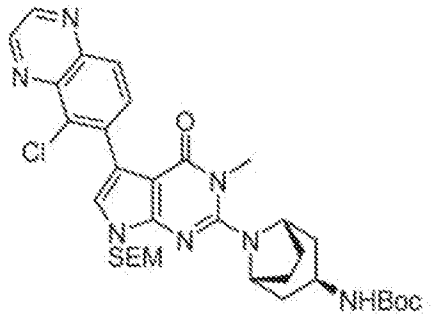
[1927] [化学式209]

[1928] 

[1929] 除了利用((1S,2S,4R)-7-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯和4-氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑,用与通用方法2类似的方式,制备((1S,2S,4R)-7-(5-(4-氯-2-甲基-2H-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)(甲基)氨基甲酸叔丁酯,MS:$[M+H]^+$=668,670.

[1930] 制备153:(endo-8-(5-(5-氯喹喔啉-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯

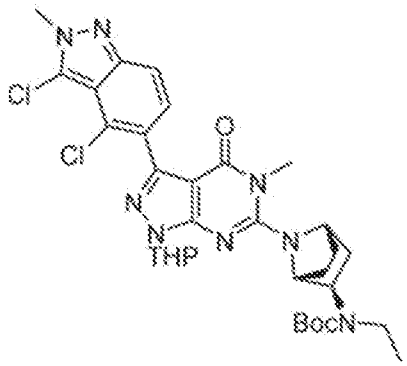
[1931] [化学式210]

[1932] 

[1933] 除了利用(endo-8-(5-碘-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯和(5-氯喹喔啉-6-基)硼酸,用与通用方法2类似的方式,制备(endo-8-(5-(5-氯喹喔啉-6-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3H-吡咯并[2,3-d]嘧啶-2-基)-8-氮杂二环[3.2.1]辛烷-3-基)氨基甲酸叔丁酯。MS:$[M+H]^+$=666,668.

[1934] 制备154:((1R,2R,4S)-7-(3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(乙基)氨基甲酸叔丁酯

[1935] [化学式211]

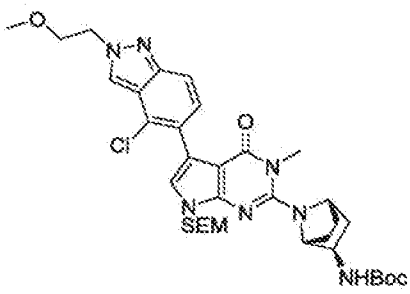
[1936] 

[1937] 除了利用((1R,2R,4S)-7-(3-溴-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(乙基)氨基甲酸叔丁酯和3,4-二氯-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2H-吲唑,用与通用方法3类似的方式,制备((1R,2R,4S)-7-(3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-5-甲基-4-氧代-1-(四氢-2H-吡喃-2-基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-6-基)-7-氮杂二环[2.2.1]庚烷-2-基)(乙基)氨基甲酸叔丁酯。MS:$[M+H]^+$=671,673.

[1938] 利用通用方法2中所述的类似方法,从适当取代、保护的吡咯并嘧啶酮和不同的硼酸酯或硼酸开始,制备下面表14的化合物(如上所述合成,具有下文所示的任何显著变化)。

[1939] 表14

[1940]

化合物	化合物名称	MS: $[M+H]^+$ m/z	方法
	((1*R*,2*R*,4*S*)-7-(5-(4-氯-2-(2-甲氧基乙基)-2*H*-吲唑-5-基)-3-甲基-4-氧代-7-((2-(三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯	698, 700	根据上述通用方法 2，利用((1*R*,2*R*,4*S*)-7-(5-碘-3-甲基-4-氧代-7-((2-三甲基硅烷基)乙氧基)甲基)-4,7-二氢-3*H*-吡咯并[2,3-*d*]嘧啶-2-基)-7-氮杂二环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯和 4-氯-2-(2-甲氧基乙基)-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊-2-基)-2*H*-吲唑制备

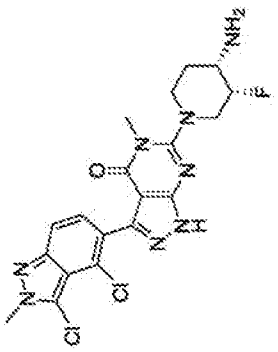
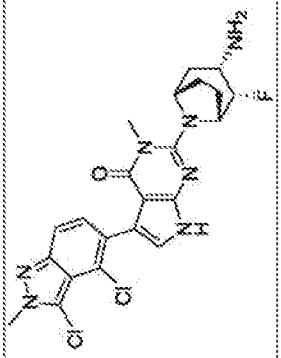
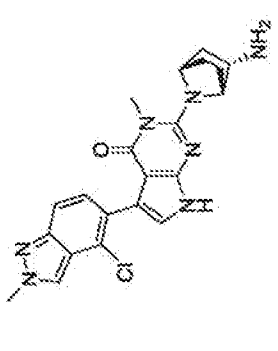
[1941]

表 15：实施例 160-178

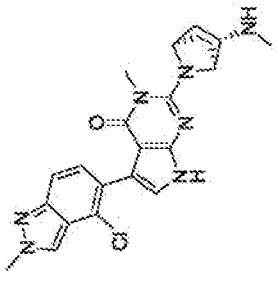
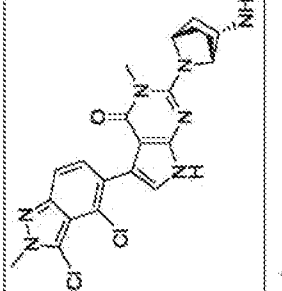
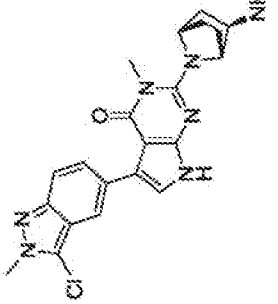
根据与制备式(I)化合物的通用方法(方法 1-3)所述的相似和/或类似的方法，制备表 15 中列出的化合物，并具有指出的任何显著变化。可将标题化合物作为游离碱或作为适当的盐直接分离而无需进一步纯化、或者利用质量导向的制备型 HPLC、色谱、结晶或研制纯化化合物，并转化为适当的盐。

实施例	结构	名称	NMR 数据	MS: $[M+H]^+$ m/z	方法
160	HCl	6-(*endo*-3-氨基-8-氮杂二环 [3.2.1] 辛烷 -8-基)-3-(3,4- 二氯 -2- 甲基 -2*H*- 吲唑 -5- 基)-5- 甲基 -1,5- 二氢 -4*H*- 吡唑并 [3,4-*d*]嘧啶 -4- 酮，盐酸盐	^{1}H-NMR (DMSO-d_6) δ: 13.40 (1H, s), 7.95 (3H, s), 7.59 (1H, *J* = 9.2 Hz, d), 7.29 (1H, *J* = 9.2 Hz, d), 4.28 (2H, s), 4.14 (3H, s), 3.48-3.40 (1H, m), 3.37 (3H, s), 2.53-2.48 (2H, m), 2.12-2.06 (2H, m), 1.84-1.78 (2H, m), 1.72-1.65 (2H, m).	473, 475	3 (不需纯化而提供)
161		6-(*endo*-3-氨基-3- 甲基 -8-氮杂二环 [3.2.1] 辛烷 -8-基)-3-(3,4- 二氯 -2- 甲基 -2*H*- 吲唑 -5- 基)-5- 甲基 -1,5- 二氢 -4*H*- 吡唑并 [3,4-*d*]嘧啶 -4- 酮	^{1}H-NMR (DMSO-d_6) δ: 7.58 (1H, *J* = 8.8 Hz, d), 7.29 (1H, *J* = 8.8 Hz, d), 4.18-4.13 (2H, m), 4.14 (3H, s), 3.36 (3H, s), 2.31-2.25 (2H, m), 1.89-1.82 (4H, m), 1.62-1.55 (2H, m), 1.06 (3H, s).	487, 489	3

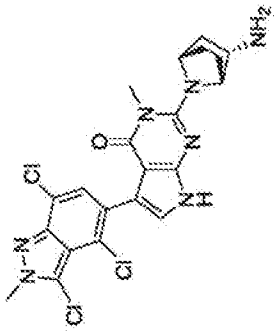
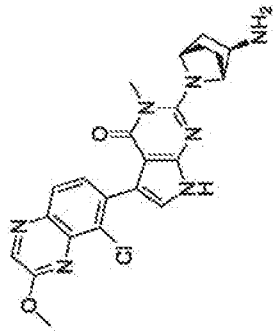
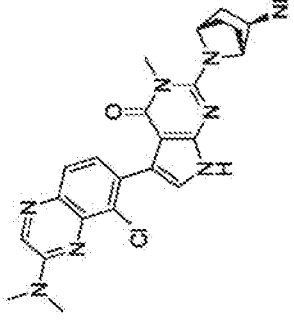
[1942]

162		6-((3*R*,4*S*)-4-氨基-3-氟吡咯烷-1-基)-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 8.45 (3H, s), 7.60 (1H, *J* = 8.8 Hz, d), 7.30 (1H, *J* = 8.8 Hz, d), 5.05 (1H, *J* = 48.8 Hz, d), 4.14 (3H, s), 3.92-3.81 (1H, m), 3.72-3.64 (1H, m), 3.35 (3H, s), 3.32-3.16 (1H, m), 3.01-2.93 (1H, m), 2.13-2.01 (1H, m), 1.59-1.58 (1H, m).	465, 467	3
163		2-((1*R*,2*S*,3*S*,5*S*)-3-氨基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, s), 7.51 (1H, *J* = 8.8 Hz, d), 7.33 (1H, *J* = 8.8 Hz, d), 6.99 (1H, s), 4.57-4.39 (2H, m), 4.15 (3H, s), 3.45 (3H, s), 3.04-2.92 (1H, m), 2.09-1.94 (2H, m), 1.90-1.80 (1H, m), 1.75-1.56 (4H, m).	490, 492	2
164		2-(*rac*-(1*R*,2*S*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.59 (1H, s), 8.38 (1H, s), 7.47 (1H, *J* = 8.8 Hz, d), 7.32 (1H, *J* = 8.8 Hz, d), 6.92 (1H, s), 4.24-4.21 (1H, m), 4.18 (3H, s), 3.95 (1H, *J* = 4.6 Hz, d), 3.46 (3H, s), 2.98-2.91 (1H, m), 1.91-1.54 (5H, m), 1.52-1.44 (1H, m), 1.38-1.28 (2H, m).	424, 426	2

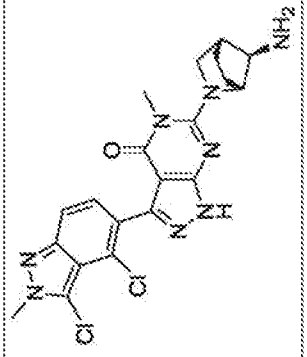
[1943]

165		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-2-((1*S*,2*S*,4*R*)-2-(甲基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.62 (1H, s), 8.38 (1H, s), 7.47 (1H, *J* = 8.8 Hz, d), 7.31 (1H, *J* = 8.8 Hz, d), 6.94 (1H, *J* = 2.2 Hz, d), 4.25-4.14 (2H, m), 4.18 (3H, s), 3.40 (3H, s), 3.16-3.09 (1H, m), 2.27-2.19 (1H, m), 2.24 (3H, s), 2.08-2.01 (1H, m), 1.93-1.85 (1H, m), 1.74-1.64 (1H, m), 1.48-1.41 (1H, m), 0.96-0.89 (1H, m).	438, 440	2
166		2-((1*R*,2*S*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.64 (1H, s), 7.49 (1H, *J* = 8.8 Hz, d), 7.32 (1H, *J* = 8.8 Hz, d), 6.95 (1H, s), 4.26-4.19 (1H, m), 4.13 (3H, s), 3.97-3.92 (1H, m), 3.46 (3H, s), 2.99-2.91 (1H, m), 1.90-1.70 (5H, m), 1.52-1.43 (1H, m), 1.37-1.26 (2H, m).	458, 460	2
167		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(3-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.61 (1H, s), 8.44 (1H, s), 7.74 (1H, *J* = 9.3, 1.2 Hz, dd), 7.50 (1H, *J* = 9.3 Hz, d), 7.25 (1H, s), 4.13-4.08 (1H, m), 4.12 (3H, s), 4.02-3.99 (1H, m), 3.46 (3H, s), 2.31-2.04 (3H, m), 1.95-1.85 (1H, m), 1.71-1.62 (1H, m), 1.52-1.44 (1H, m), 0.92-0.84 (1H, m).	424, 426	2

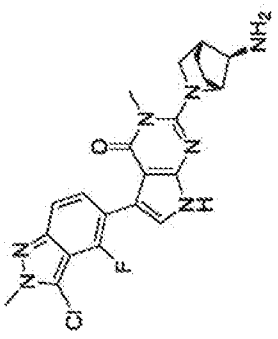
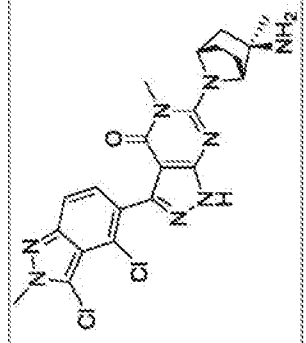
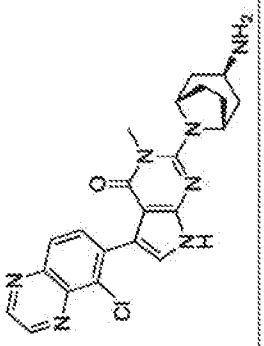
[1944]

168		2-((1*R*,2*S*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-3-甲基-5-(3,4,7-三氯-2-甲基-2*H*-吲唑-5-基)-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.74 (1H, s), 7.47 (1H, s), 7.04 (1H, s), 4.17 (3H, s), 4.14-4.10 (1H, m), 4.03-3.96 (1H, m), 3.50-3.42 (2H, m), 3.39 (3H, s), 2.30-2.21 (1H, m), 2.20-2.10 (1H, m), 1.92-1.84 (1H, m), 1.71-1.60 (1H, m), 1.51-1.44 (1H, m), 0.92-0.83 (1H, m).	492, 494	2
169		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-甲氧基吡嗪-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.84 (1H, br s), 8.66 (1H, s), 7.94 (1H, d, *J* = 8.6 Hz), 7.76 (1H, d, *J* = 8.6 Hz), 7.17 (1H, s), 4.19-4.17 (1H, m), 4.13 (3H, s), 4.05-4.03 (1H, m), 3.52-3.47 (1H, m), 3.43 (3H, s), 2.34-2.26 (1H, m), 2.24-2.18 (1H, m), 2.05-1.68 (3H, m), 1.56-1.50 (1H, m), 0.93-0.88 (1H, m).	452, 454	2
170		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(5-氯-3-(二甲氧基)吡嗪-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.72 (1H, br s), 8.69 (1H, s), 7.69 (1H, d, *J* = 8.5 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 7.06 (1H, s), 4.15-4.13 (1H, m), 4.01-3.99 (1H, m), 3.48-3.43 (1H, m), 3.40 (3H, s), 3.32 (3H, s), 3.28 (3H, s), 2.30-2.23 (1H, m), 2.21-2.15 (1H, m), 1.94-1.88 (1H, m), 1.70-1.64 (2H, m), 1.52-1.46 (1H, m), 0.89-0.83 (1H, m).	465, 467	2

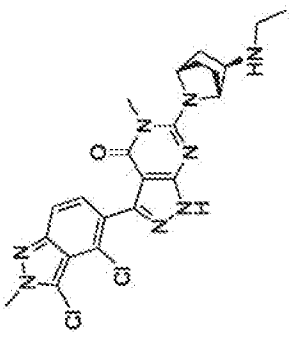
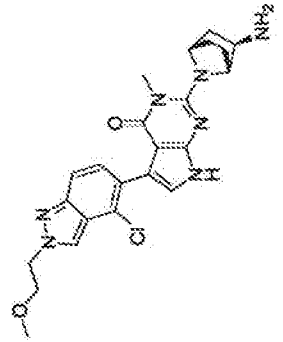
[1945]

171		6-{(1*R*,4*R*,7*R*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基}-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 7.60 13.20 (1H, br s), (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 4.16 (3H, s), 3.95-3.93 (1H, m), 3.79-3.75 (1H, m), 3.28 (3H, s), 3.26-3.24 (1H, m), 3.07 (1H, d, *J* = 9.2 Hz), 2.19-2.14 (1H, m), 2.02-1.84 (3H, m), 1.40-1.33 (1H, m).	459, 461	3
172		2-{(1*R*,4*R*,7*R*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基}-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.51 (1H, br s), 7.49 (1H, d, *J* = 9.0 Hz), 7.32 (1H, d, *J* = 9.0 Hz), 6.90 (1H, s), 4.13 (3H, s), 3.85-3.83 (1H, m), 3.73-3.68 (1H, m), 3.28 (3H, s), 3.25-3.22 (1H, m), 3.01 (1H, d, *J* = 9.0 Hz), 2.18-2.14 (1H, m), 2.00-1.84 (3H, m), 1.40-1.33 (1H, m).	458, 460	2
173		*rac*-2-{(1*R*,2*R*,4*S*)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基}-5-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 7.49 (1H, d, *J* = 9.3 Hz), 7.32 (1H, d, *J* = 9.2 Hz), 6.95 (1H, s), 4.20-4.17 (1H, m), 4.13 (6H, s), 3.78-3.75 (1H, m), 3.41 (3H, s), 2.24-2.17 (1H, m), 1.90-1.81 (2H, m), 1.75-1.66 (1H, m), 1.53-1.46 (1H, m), 1.23 (3H, s), 1.18-1.14 (1H, m).	472, 474	2

[1946]

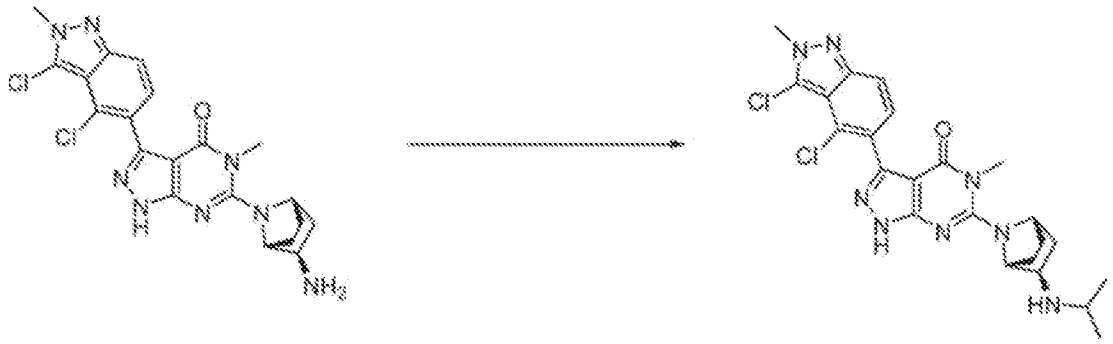
174		2-((1*R*,4*R*,7*R*)-7-氨基-2-氮杂二环[2.2.1]庚烷-2-基)-5-(3-氯-4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.56 (1H, br s), 7.66-7.62 (1H, m), 7.36 (1H, d, *J* = 9.0 Hz), 6.98 (1H, s), 4.12 (3H, s), 3.87-3.84 (1H, m), 3.73-3.68 (1H, m), 3.32 (3H, s), 3.26-3.23 (1H, m), 3.05-3.03 (1H, m), 2.18-2.13 (1H, m), 1.99-1.85 (3H, m), 1.42-1.32 (1H, m).	442, 444	2
175		*rac*-6-{(1*R*,2*R*,4*S*)-2-氨基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基}-3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-5-甲基-1,5-二氢-4*H*-吡咯并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.38 (1H, br s), 7.61 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.8 Hz), 4.31-4.27 (1H, m), 4.17 (3H, s), 3.88-3.84 (1H, m), 3.41 (3H, s), 2.28-2.20 (1H, m), 1.91-1.69 (3H, m), 1.57-1.49 (1H, m), 1.26-1.18 (4H, m).	473, 475	3
176		2-(*endo*-3-氨基-8-氮杂二环[3.2.1]辛烷-8-基)-5-(5-氯吡啶-6-基)-3-甲基-3,7-二氢-4*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.76 (1H, s), 9.06 (1H, d, *J* = 1.8 Hz), 9.00 (1H, d, *J* = 1.8 Hz), 8.03-7.94 (2H, m), 7.22 (1H, s), 4.12 (2H, s), 3.43 (3H, s), 2.34-2.21 (3H, m), 2.18-2.10 (2H, m), 2.00-1.92 (2H, m), 1.58 (2H, d, *J* = 13.2 Hz).	436, 438	2

[1947]

177		3-(3,4-二氯-2-甲基-2*H*-吲唑-5-基)-6-((1*R*,2*R*,4*S*)-2-(乙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4*H*-吡唑并[3,4-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 13.41 (1H, s), 7.61 (1H, d, *J* = 8.9 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 4.29-4.23 (2H, m), 4.17 (3H, s), 3.39 (3H, s), 3.27-3.23 (1H, m), 2.48-2.44 (2H, m), 2.26-2.20 (1H, m), 2.12-2.07 (1H, m), 1.90-1.84 (1H, m), 1.72-1.65 (1H, m), 1.52-1.46 (1H, m), 1.02 (3H, t, *J* = 7.2 Hz), 0.98-0.93 (1H, m).	487, 489	3
178		2-((1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基)-5-(4-氯-2-(2-甲氧基乙基)-2*H*-吲唑-5-基)-3-甲基-3,7-二氢-4*H*-吡喃并[2,3-*d*]嘧啶-4-酮	^{1}H-NMR (DMSO-d_6) δ: 11.63 (1H, br s), 8.40 (1H, d, *J* = 0.6 Hz), 7.49 (1H, dd, *J* = 8.9, 0.9 Hz), 7.32 (1H, d, *J* = 8.9 Hz), 6.94 (1H, s), 4.61 (2H, t, *J* = 5.2 Hz), 4.13 (1H, t, *J* = 4.4 Hz), 4.00 (1H, t, *J* = 5.3 Hz), 3.48-3.44 (1H, m), 3.39 (3H, s), 3.24 (3H, s), 2.29-2.23 (1H, m), 2.19-2.14 (1H, m), 1.94-1.87 (1H, m), 1.71-1.64 (1H, m), 1.52-1.46 (1H, m), 0.88 (1H, dd, *J* = 11.9, 4.6 Hz)	468, 470	2

[1948] 实施例179:3-(3,4-二氯-2-甲基-2H-吲唑-5-基)-6-((1R,2R,4S)-2-(异丙基氨基)-7-氮杂二环[2.2.1]庚烷-7-基)-5-甲基-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮

[1949] [化学式212]

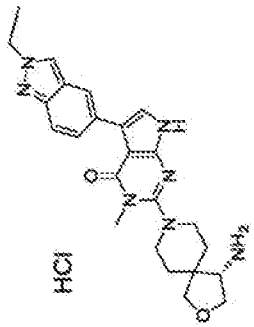
[1950] 

[1951] 在r.t.,向6-[(1S,3R,4R)-3-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-3-(3,4-二氯-2-甲基-吲唑-5-基)-5-甲基-1H-吡唑并[3,4-d]嘧啶-4-酮(20.0mg,0.0435mmol)的DCM(0.400mL)溶液中,加入丙酮(0.0320mL,0.435mmol)和$NaBH(OAc)_3$(27.7mg,0.131mmol)。将混合物在r.t.搅拌18h。然后,将反应物真空浓缩,并将残留物经硅胶柱色谱纯化(梯度洗脱,0-10%MeOH/$CHCl_3$),得到标题化合物(14.1mg)。MS:$[M+H]^+$=501,503.^{1}H-NMR(DMSO-d_6)δ:13.39(1H,s),7.61(1H,d,J=8.9Hz),7.33(1H,d,J=8.9Hz),4.26-4.22(2H,m),4.17(3H,s),3.39(3H,s),2.72-2.66(1H,m),2.30-2.23(1H,m),2.13-2.06(1H,m),1.89-1.67(3H,m),1.54-1.48(1H,m),1.02-0.92(7H,m).

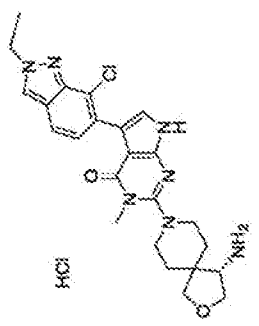
[1952] 利用实施例150中所述的类似方法,制备下面表16的化合物。利用上文所述的类似方法,制备所需的必须具备的取代吲唑类。

[1953]

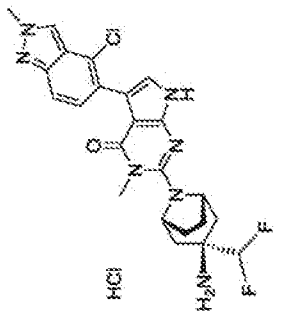
表 16

实施例	结构	名称	NMR 数据	MS: $[M+H]^+$ m/z	备注
180		2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.69 - 11.65 (m, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.67 (dd, *J* = 9.0, 1.6 Hz, 1H), 7.56 - 7.27 (m, 4H), 7.22 (d, *J* = 2.1 Hz, 1H), 4.43 (q, *J* = 7.3 Hz, 2H), 4.07 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.81 - 3.73 (m, 2H), 3.68 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.47 (s, 4H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.29 (s, 1H), 2.92 (t, *J* = 11.2 Hz, 1H), 2.82 (t, *J* = 11.6 Hz, 1H), 1.92 - 1.78 (m, 2H), 1.66 (t, *J* = 14.2 Hz, 2H), 1.51 (t, *J* = 7.3 Hz, 3H).	448	利用 5-溴-1*H*-吲唑制备
181		2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-4-氟-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.76 (br s, 1H), 8.52 (s, 1H), 7.72 (br s, 3H), 7.56 (dd, *J* = 8.9, 7.3 Hz, 1H), 7.38 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.07 (s, 1H), 4.47 (q, *J* = 7.3 Hz, 2H), 4.09 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.86 - 3.69 (m, 3H), 3.55 (dd, *J* = 6.0, 3.4 Hz, 1H),3.41 - 3.31 (m, 2H), 3.33 (s, 3H), 2.93 (t, *J* = 11.6 Hz, 1H), 2.82 (t, *J* = 11.7 Hz, 1H), 1.86 (m, 2H), 1.68 (q, *J* = 13.9 Hz, 2H), 1.52 (q, *J* = 7.3 Hz, 3H).	466	从 5-溴-4-氟-1*H*-吲唑开始制备

[1954]

182		2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(7-氯-2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.78 (d, J = 2.4 Hz, 1H), 8.47 (s, 1H), 8.41 (d, J = 5.5 Hz, 3H), 7.57 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 4.49 (q, J = 7.3 Hz, 2H), 4.09 (dd, J = 10.3, 6.0 Hz, 1H), 3.86 - 3.75 (m, 3H), 3.60 - 3.52 (m, 4H), 3.40 - 3.36 (m, 1H), 3.34 - 3.27 (m, 1H), 2.93 (t, J = 11.8 Hz, 1H), 2.81 (t, J = 11.8 Hz, 1H), 1.95 - 1.82 (m, 2H), 1.75 - 1.64 (m, 2H), 1.52 (t, J = 7.3 Hz, 3H).	482	利用 4-溴-3-氯-2-氟苯甲醛作为原料
183		2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 11.76 (d, J = 2.6 Hz, 1H), 8.50 - 8.38 (m, 4H), 8.33 (s, 1H), 7.61 (dd, J = 8.8, 0.9 Hz, 1H), 7.52 (dd, J = 8.7, 1.5 Hz, 1H), 7.31 (d, J = 2.5 Hz, 1H), 4.44 (q, J = 7.3 Hz, 2H), 4.09 (dd, J = 10.3, 6.0 Hz, 1H), 3.86 - 3.76 (m, 3H), 3.55 (m, 1H), 3.48 (s, 3H), 3.43 – 3.37 (m, 1H), 3.36 - 3.30 (m, 1H), 2.93 (t, J = 11.8 Hz, 1H), 2.81 (t, J = 11.8 Hz, 1H), 1.85 - 1.65 (m, 2H), 1.50-1.25 (m, 2H), 1.52 (t, J = 7.3 Hz, 3H).	448	利用 6-溴-1H-吲唑制备
184		2-[(4S)-4-氨基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2H-吲唑-6-基)-3-甲基-3H,4H,7H-吡咯并[2,3-d]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, 甲醇-d_4) δ : 8.36 (d, J = 2.8 Hz, 1H), 7.49 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 4.54 (q, J = 7.3 Hz, 2H), 4.20 (dd, J = 10.7, 5.5 Hz, 1H), 3.96 (d, J = 9.2 Hz, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.85 (dd, J = 10.7, 2.6 Hz, 1H), 3.66 - 3.61 (m, 1H), 3.57 (s, 3H), 3.52 - 3.42 (m, 2H), 3.10 - 3.01 (m, 1H), 3.01 - 2.93 (m, 1H), 2.03 - 1.94 (m, 2H), 1.89 - 1.76 (m, 2H), 1.63 (t, J = 7.3 Hz, 3H). 未观察到盐的 4 个可交换质子。	466	利用 4-溴-2,3-二氟苯甲醛作为原料

[1955]

185		2-[(*endo*)-3-氟基-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 12.56 (s, 1H), 8.16 (s, 1H), 7.33 (br s, 2H), 7.03 (d, J = 8.7 Hz, 2H), 6.89 (t, J = 6.9 Hz, 1H), 6.69 (td, J = 7.3, 1.1 Hz, 1H), 4.68 (d, J = 6.3 Hz, 2H), 3.96 - 3.83 (m, 2H), 3.19 (dq, J = 7.2, 3.6 Hz, 1H), 2.81 (t, J = 6.4 Hz, 2H), 2.33 (m, 2H), 2.22 - 1.90 (m, 6H), 1.67 (m, 2H).	488	用N-[(*endo*)-3-(二氟甲基)-8-氮杂二环[3.2.1]辛烷-3-基]-2-甲基丙烷-2-亚磺酰胺作为所需的胺
186		2-[(4*S*)-4-氟基-2-氮杂-8-氮杂螺[4.5]癸烷-8-基]-5-(2-乙基-7-氟-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (500 MHz, DMSO-d_6) δ : 12.56 (s, 1H), 8.16 (s, 1H), 7.33 (br s, 2H), 7.03 (d, J = 8.7 Hz, 2H), 6.89 (t, J = 6.9 Hz, 1H), 6.69 (td, J = 7.3, 1.1 Hz, 1H), 4.68 (d, J = 6.3 Hz, 2H), 3.96 - 3.83 (m, 2H), 3.19 (dq, J = 7.2, 3.6 Hz, 1H), 2.81 (t, J = 6.4 Hz, 2H), 2.33 (m, 2H), 2.22 - 1.90 (m, 6H), 1.67 (m, 2H).	466	利用 5- 溴-2,3- 二氟苯甲酸作为原料.

[1956] 利用方法 1-9 中所述的类似方法，制备表 17 中所示的化合物。可将化合物通过研制/从溶液中沉淀直接分离，或者纯化(例如利用质量导向的制备型 HPLC、色谱法、结晶)。在一些情况下，通过用过量 HCl (2N HCl 的 Et_2O 溶液)处理最终化合物的溶液(例如 MeOH 溶液)，然后蒸发至干，将化合物作为盐酸盐分离。

表 17

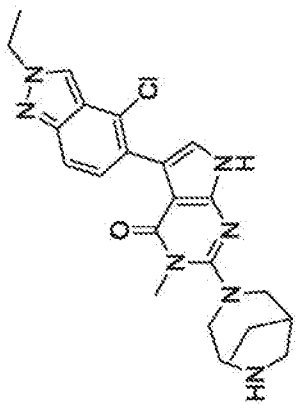
实施例	结构	名称	NMR 数据	MS: $[M+H]^+$ m/z	备注
187		2-[(3*R*,4*S*)-4-氟基-3-氟吡啶-1-基]-5-(7-氯-1,3-苯并噻唑-6-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.92 (1H, d), 9.46 (1H, s), 8.38 (3H, d), 8.04 (1H, d), 7.65 (1H, d), 7.14 (1H, d), 5.07 (1H, d), 3.86-3.76 (1H, m), 3.67-3.50 (2H, m), 3.42 (3H, s), 3.27-3.13 (1H, m), 3.00-2.89 (1H, m), 2.13-2.04 (1H, m), 1.98-1.90 (1H, m).	433	方法 9
188		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(1*S*,6*R*)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.72 (1H, d), 9.63-9.52 (1H, m), 9.13-9.01 (1H, m), 8.41 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.02 (1H, d), 4.85-4.77 (1H, m), 4.32-4.24 (1H, m), 4.20 (3H, s), 3.50 (3H, s), 3.44-3.28 (2H, m), 3.20-3.04 (2H, m), 2.38-2.27 (2H, m), 2.11-1.95 (2H, m), 1.80-1.71 (2H, m).	438	方法 9
189		5-(4-氯-2-甲基-2*H*-吲唑-5-基)-2-[(1*R*,6*S*)-3,9-二氮杂二环[4.2.1]壬烷-9-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.72 (1H, d), 9.64-9.53 (1H, m), 9.15-9.01 (1H, m), 8.41 (1H, s), 7.50 (1H, dd), 7.32 (1H, d), 7.02 (1H, d), 4.85-4.77 (1H, m), 4.33-4.25 (1H, m), 4.20 (3H, s), 3.50 (3H, s), 3.45-3.24 (2H, m), 3.20-3.04 (2H, m), 2.38-2.27 (2H, m), 2.10-1.91 (2H, m), 1.83-1.67 (2H, m).	438	方法 9

[1957] 利用方法 1-9 中所述的类似方法，制备表 18 中所示的化合物。可将化合物通过研制/从溶液中沉淀直接分离，或者纯化(例如利用质量导向的制备型 HPLC、色谱法、结晶)。在一些情况下，通过用过量 HCl (2N HCl 的 Et_2O 溶液)处理最终化合物的溶液(例如 MeOH 溶液)，然后蒸发至干，将化合物作为盐酸盐分离。

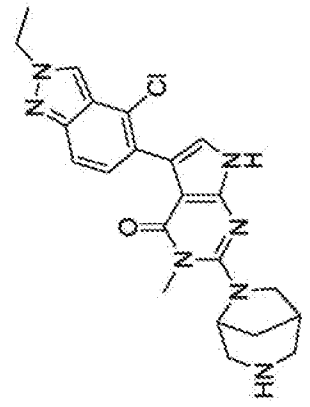
表 18

实施例	结构	名称	NMR 数据	MS: [M+H]+ m/z	备注
190		5-(4-氯-2-乙基-2*H*-吲唑-3-基)-2-(3,6-二氮杂二环[3.2.1]辛烷-3-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (1H, d), 9.66 (1H, s), 9.07 (1H, s), 8.46 (1H, s), 7.52 (1H, dd), 7.32 (1H, d), 7.07 (1H, d), 4.49 (2H, q), 4.15-4.07 (1H, m), 3.55-3.48 (3H, m), 3.43-3.35 (1H, m), 3.34-3.16 (2H, m), 2.81 (1H, d), 2.75-2.69 (1H, m), 1.98 (1H, d), 1.94-1.86 (1H, m), 1.53 (3H, t).	438	方法 2，然后经反相 C18 硅胶色谱纯化，通过手性 SFC 进一步纯化 (45% 恒定 MeOH+0.1% DEA，AD 柱，得到标题化合物，作为较快洗脱的对映体

[1958]

191		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-{3,6-二氮杂二环[3.2.1]辛烷-3-基}-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (1H, d), 9.84 (1H, s), 9.16 (1H, s), 8.46 (1H, s), 7.51 (1H, d), 7.32 (1H, d), 7.06 (1H, d), 4.49 (2H, q), 4.14-4.07 (1H, m), 3.56-3.45 (5H, m), 3.45-3.34 (1H, m), 3.34-3.17 (2H, m), 2.81 (1H, d), 2.75-2.69 (1H, m), 1.97 (1H, d), 1.95-1.85 (1H, m), 1.53 (3H, t).	438.	方法 2，然后经反相 C18 硅胶色谱纯化。通过手性 SFC 进一步纯化 (45% 恒定 MeOH+0.1% DEA、AD 柱，得到标题化合物，作为较慢洗脱的对映体
192		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-{3,6-二氮杂二环[3.2.1]辛烷-6-基}-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (1H, d), 9.79 (1H, d), 8.76 (1H, br. s), 8.45 (1H, s), 7.51 (1H, dd), 7.32 (1H, d), 6.95 (1H, d), 4.65-4.58 (1H, m), 4.49 (2H, q), 3.75-3.60 (3H, m), 3.47 (3H, s), 3.17 (2H, s), 3.11-3.01 (1H, m), 2.72 (1H, s), 1.95 (1H, d), 1.93-1.84 (1H, m), 1.53 (3H, t).	438	方法 2，然后经反相 C18 硅胶色谱纯化。通过手性 SFC 进一步纯化 (40% 恒定 EtOH+0.1% DEA、AD 柱，得到标题化合物，作为较快洗脱的对映体

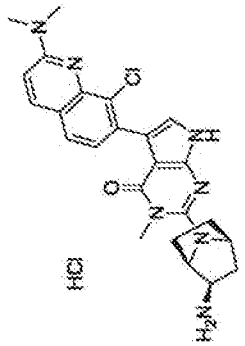
[1959]

193		5-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-(3,6-二氮杂二环[3.2.1]辛烷-6-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (1H, d), 9.57 (1H, d), 8.67 (1H, br. s), 8.45 (1H, s), 7.51 (1H, dd), 7.32 (1H, d), 6.96 (1H, d), 4.63-4.59 (2H, m), 4.52-4.46 (2H, m), 3.79-3.66 (2H, m), 3.61 (1H, d), 3.47 (3H, s), 3.21-3.18 (1H, m), 3.13-2.99 (1H, m), 2.74 (1H, s), 2.00-1.85 (2H, m), 1.54 (3H, d).	438	方法 2，然后经反相 C18 柱色谱纯化，通过手性 SFC 进一步纯化 (40% 恒定 EtOH+0.1% DEA，AD 柱，得到标题化合物，作为较慢洗脱的对映体。
194		2-[(3*S*,4*S*)-4-氨基-3-甲基-2-氧杂-8-氮杂螺[4.5]癸烷-8-基]-5-(4-氯-7-氟-2-甲基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (1H, d), 8.56 (1H, d), 8.09 (3H, br. s), 7.18 (1H, d), 7.12 (1H, d), 4.26-4.20 (4H, m), 3.88 (1H, d), 3.67 (1H, d), 3.53-3.42 (4H, m), 3.42-3.28 (2H, m), 2.94-2.77 (2H, m), 2.00-1.87 (2H, m), 1.78 (1H, d), 1.66 (1H, d), 1.25 (3H, d)	500	方法 2，经反相 C18 硅胶色谱纯化。

[1960]

195		2-[(*endo*)-2-氧基-2-甲基-7-氮杂二环[2.2.1]庚烷-7-基]-5-(4-氯-2-甲基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73 (1H, d), 8.51 (3H, s), 8.40 (1H, s), 7.49 (1H, dd), 7.32 (1H, d), 6.99 (1H, d), 4.34 (1H, t), 4.20 (3H, s), 4.14 (1H, d), 3.43 (3H, s), 2.21-2.10 (1H, m), 2.05-1.98 (1H, m), 1.96-1.87 (1H, m), 1.86-1.76 (1H, m), 1.75-1.69 (1H, m), 1.65 (1H, d), 1.46 (3H, s).	438	方法 9，通过制备 SFC 纯化 (50% MeOH + 0.1% 二乙胺)
196		*rac*-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-2-[2,6-二氮杂螺[3.4]辛烷-6-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮	^{1}H NMR (400 MHz, Me-d3-OD) δ: 8.31 (1H, s), 7.52 (1H, dd), 7.45 (1H, d), 6.95 (1H, s), 4.53 (2H, q), 3.80 (2H, d), 3.76-3.61 (4H, m), 3.58 (2H, t), 3.50 (3H, s), 2.24 (2H, t), 1.64 (3H, t).	438	方法 2.通过反相 C18 硅胶色谱纯化，然后经制备型 HPLC 纯化。
197		2-[(1*R*,2*S*,3*S*,5*S*)-3-氟基-2-氟-8-氮杂二环[3.2.1]辛烷-8-基]-5-(4-氯-2-乙基-2*H*-吲唑-5-基)-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.68 (1H, d), 8.45 (1H, s), 8.30 (3H, br s), 7.51 (1H, dd), 7.31 (1H, d), 6.98 (1H, d), 4.96-4.79 (1H, m), 4.60-4.53 (1H, m), 4.49 (2H, q), 4.31-4.23 (1H, m), 3.76-3.60 (1H, m), 3.46 (3H, s), 2.29-2.19 (1H, m), 2.14-2.00 (2H, m), 1.97-1.88 (1H, m), 1.78-1.67 (2H, m), 1.53 (3H, t).	470	方法 2，然后方法 5，通过反相 C18 硅胶色谱纯化，然后经制备型 HPLC 纯化。

[1961]

198		2-[(1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(二甲氨基)喹啉-7-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	1H NMR (400 MHz, DMSO-d_6) δ: 8.22 (1H, d), 7.72 (1H, d), 7.40 (1H, d), 7.27 (1H, d), 7.11 (1H, s), 4.37 (1H, s), 4.28 (1H, s), 3.83-3.67 (1H, m), 3.40 (3H, s), 3.31 (7H, s), 1.95 (2H, s), 1.88-1.71 (1H, m), 1.65 (1H, d), 1.36 (1H, dd).	464	方法 9
199		2-[(1*R*,2*R*,4*S*)-2-氨基-7-氮杂二环[2.2.1]庚烷-7-基]-5-[8-氯-2-(甲基氨基)喹啉-7-基]-3-甲基-3*H*,4*H*,7*H*-吡咯并[2,3-*d*]嘧啶-4-酮盐酸盐	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (1H, s), 8.53-8.32 (1H, m), 7.84 (1H, s), 7.53 (1H, d), 7.23 (2H, s), 4.39 (1H, s), 4.30 ((1H, s), 3.41 (3H, s), 3.13 (3H, s), 1.96 (2H, s), 1.83 (1H, d), 1.66 (1H, s), 1.38 (1H, dd).	450	方法 9

[1962] 生物学测定

[1963] SHP2生化测定

[1964] 通过测量替代底物6,8-二氟甲基伞形酮基磷酸酯(DiFMUP)向荧光产物6,8-二氟甲基伞形酮(DiFMU)的转化,监测SHP2活性。

[1965] 将SHP2与受试化合物和活化肽pIRS1(H_2N-LN(pY)IDLDLV-(PEG)$_8$-LST(pY)ASINFQK-酰胺)预孵育30min,然后加入6,8-二氟甲基伞形酮基磷酸酯(DiFMUP)(Thermo Fisher D6567)。最终测定浓度为10pM SHP2、0.25μM pIRS1肽,50μM DiFMUP,25mM Bis-Tris丙烷,pH 7.0,150mM NaCl,0.05%(v/v)Tween-20,0.5mM TCEP和5%(v/v)DMSO。然后,通过在BMG Pherastar读数器上以激发360nm/发射450nm监测荧光,历经30min测量反应速率。使用四参数对数曲线拟合,从标准化的剂量响应图,以单一数(in singlicate)计算IC_{50}值。对每种化合物进行1次或多次实验,并将IC_{50}值显示为单一值(对于在单个实验中测量的化合物)或平均值(对于在多个实验中测量的化合物)。

[1966] 结果显示于表19和20中。

[1967] 细胞的pERK抑制测定

[1968] 方法A:

[1969] 利用In-Cell Western测定,测定pERK水平。将HCC827细胞(ATCC,Manassas,USA)以$1x10^4$细胞/孔的密度接种在384-孔板,其含补充10%FBS的RPMI1640培养基,并孵育24小时。将化合物首先用DMSO稀释,然后用无血清的培养基稀释,然后一式四份添加到细胞中,得到0.2%DMSO的终浓度。将板子在含5%CO_2的湿润空气气氛下,于37℃孵育指定的时间。

[1970] 化合物处理后,在室温下,将细胞用福尔马林中性缓冲液固定20分钟。将板子用0.1%Triton-X的PBS溶液洗涤3次,并用Odyssey封闭缓冲液(LI-COR,#927-40000)封闭细胞1小时。振摇封闭缓冲液后,在4℃下,将细胞与用Odyssey封闭缓冲液稀释的phospho-p44/42 ERK抗体(Cell Signalling Technology,#4370,1:200)一起温孵过夜。再洗涤板子,并将细胞与用Odyssey封闭缓冲液稀释的山羊抗-兔IR Dye 800CW(LI-COR,#926-32211,1:800)一起孵育1小时。洗涤并利用离心机完全去除洗涤液后,根据制造商的说明,在Odyssey(LI-COR)上扫描细胞。从每个样品孔的信号中减去空白孔(未添加细胞)的平均信号。然后,用DMSO处理的样品作为对照,将pERK的水平表示为对照的百分比。利用四参数对数曲线拟合,从标准化的剂量-响应图一式四份计算相对IC_{50}值。对每种化合物进行1次或多次实验,并将IC_{50}值显示为一个值(对于在单个实验中测量的化合物)或平均值(对于在多个实验中测量的化合物)。

[1971] 结果显示于表19和20中。

[1972] 方法B:

[1973] 将HCC827细胞(ATCC,Manassas,USA)以$1x10^5$细胞/孔的密度接种在96-孔板,其含补充10%FBS的RPMI培养基,并孵育24小时。将化合物首先用DMSO稀释,然后用无血清的培养基稀释,然后一式三份添加到细胞中,得到终浓度0.1%DMSO。将板子在含5%CO_2的湿润空气气氛下,于37℃孵育指定的时间。

[1974] 化合物处理后,除去培养基,并通过向每个孔中加入50μL裂解缓冲液(Cell Signalling Technology,Beverly,USA)裂解细胞。然后,将板子在室温下振荡孵育25分钟。按照试剂盒说明,使用PathScan(注册商标)phospho-p44/42 MAPK(Thr202/Tyr204)夹心ELISA(Cell Signalling Technology,Beverly,USA)测量裂解液中的pERK水平。简言之,将50μL细胞裂解液添加到96-孔ELISA板中的50μL ELISA样品稀释液中,并在4℃下孵育过夜。

洗涤后，每孔加入100μL检测抗体，并将板子在37℃下孵育1小时。将板子再次洗涤，并在37℃下与每孔100μl HRP-连接的第二抗体一起孵育30分钟。最终洗涤后，每孔添加100μL TMB底物，并将板子在37℃下孵育，以显色。通过每孔加入100μL终止溶液而停止显色。在SpectraMax Gemini读数器(Molecular Devices,Uckfield,UK)上于450nm读板。

[1975] 从每个样品孔的信号中减去空白孔(未加细胞)的平均信号。然后，以DMSO处理的样品作为对照，将pERK的水平表示为“对照百分数”。利用GraphPad Prism版本6(GraphPad软件，La Jolla,USA)产生剂量响应曲线，并用四参数对数曲线拟合进行拟合。

[1976] 结果显示于表19和20中。

[1977] 表19

[1978]

实施例	SHP2 (IC50, •M)	pERK (IC50, •M)	pERK (IC50, •M)
		方法 A	方法 B
1	0.014	0.14	
2	0.014	0.13	
3	0.015	0.21	
4	0.0075	0.12	
5	0.0075	0.16	
6	0.0065	0.58	
7	0.0090	0.17	
8	0.011	0.095	
9	0.094	1.2	
10	0.0085	0.17	
11	0.0063	0.053	
12	0.011	0.12	
13	0.019	0.34	
14	0.024	0.31	
15	0.017	0.50	
16	0.011	0.11	
17	0.043	0.80	
18	0.23		
19	0.35		
20	0.76		
21	0.011	0.32	
22	0.014	2.2	
23	0.12	4.1	
24	0.018	0.14	
25	0.035	0.43	
26	0.011	0.088	
27	0.0070	0.046	
28	0.019	0.68	
29	0.22	2.4	
30	0.0097	0.22	
31	0.040	1.0	
32	0.017	0.92	
33	0.047	0.48	
34	0.16	2.3	
35	0.038	1.0	

[1979]

36	0.0055	0.35	
37	0.012	0.97	
38	0.074	1.4	
39	0.066	0.70	
40	0.096	4.5	
41	0.057	1.8	
42	0.078		
43	0.035	0.72	
44	0.055	1.5	
45	0.11	1.5	
46	0.033	0.42	
47	0.032	0.38	
48	0.085	1.0	
49	0.0045	0.021	
50	0.25	4.7	
51	0.012	0.061	
52	0.18	1.9	
53	0.33	3.1	
54	0.11	1.8	
55	0.074	1.1	
56	0.073	1.1	
57	0.12	2.9	
58	0.099	>10	
59	0.0055	0.048	
60	0.082	3.8	
61	0.098	1.8	
62	0.023	0.36	
63	0.11	4.3	
64	0.042	1.5	
65	0.033	0.43	
66	0.0082	0.082	
67	0.34	3.4	
68	0.041	0.67	
69	0.12	3.0	
70	0.029	0.19	
71	0.26	5.0	
72	0.099	1.9	
73	0.87	>10	
74	0.17	5.4	
75	0.028	2.1	
76	0.031	0.18	
77	0.040	1.9	

[1980]

78	0.0060	0.13	
79	0.0055	0.16	
80	0.011	0.27	
81	0.014	0.78	
82	0.014	0.91	
83	0.011	0.19	
84	0.018	0.55	
85	0.013	0.64	
86	0.059	5.2	
87	0.068	0.58	
88	0.052	4.5	
89	0.014	0.54	
90	0.012	0.74	
91	0.012	0.34	
92	0.0033	0.032	
93	0.0020	0.021	
94	0.0050	0.072	
95	0.0025	0.068	
96	0.0028	0.030	
97	0.0077	0.082	
98	0.010	0.19	
99	0.0045	0.057	
100	0.0060	0.095	
101	0.0015	0.046	
102	0.0090	0.088	
103	0.0020	0.026	
104	0.0027	0.084	
105	0.0050	0.16	
106	0.0050	0.10	
107	0.0070	0.27	
108	0.0040	0.090	
109	0.0065	0.12	
110	0.014	1.7	
111	0.026	0.41	
112	0.013	0.26	
113	0.0045	0.078	
114	0.0055	0.073	
115	0.046	0.49	
116	0.0090	0.10	
117	0.025	0.64	
118	0.049	1.1	
119	0.017	0.29	

[1981]

120	0.029	0.55	
121	0.016	0.21	
122	0.0080	0.14	
123	0.018	0.17	
124	0.019	0.43	
125	0.017	0.26	
126	0.013	0.084	
127	0.0037	0.063	
128	0.011	0.16	
129	0.069	0.98	
130	0.063	0.80	
131	0.028	0.46	
132	0.015	0.25	
133	0.0067	0.046	
134	0.0040	0.083	
135	0.048	0.95	
136	0.03		2.7
137	0.059		45%在3.0μM
138	0.019		1.6
139	0.02		0.097
140	0.017		0.48
141	0.043		64%在10μM
142	0.017		0.11
143	0.022		0.081
144	0.019		0.21
145	0.15		
146	0.057		3.8
147	0.012		0.034
148	0.024		0.025
149	0.29		
150	0.012		0.013
151	0.023		0.52
152	0.029		0.66
153	0.026		0.52
154	0.021		0.92
155	0.0040		
156	0.25		
157	0.0037	0.022	
158	0.25	2.0	
159	0.0035	0.15	

[1982] 表20

[1983]

实施例	SHP2 (IC50, μM)	pERK (IC50, μM) 方法 A	pERK (IC50, μM) 方法 B
160	0.0085	0.23	
161	0.012	0.26	
162	0.042	0.81	
163	0.002	0.012	
164	0.17	6.3	
165	0.084	1.4	
166	0.053		
167	0.013		
168	0.007		
169	0.0033	0.073	
170	0.003	0.016	
171	0.0026	0.02	
172	0.0015	0.016	
173	0.0025	0.14	
174	0.003	0.021	
175	0.012	0.22	
176	0.077	0.66	
177	0.095	1.4	
178	0.005	0.071	
179	0.15	2.1	
180	0.034		0.85
181	0.023		0.21
182	0.036		2.2
183	0.14		
184	0.07		1.1
185	0.18		
186	0.036		
187	0.051		0.8
188	0.041		0.56
189	0.019		0.23
190	0.045		3.3
191	0.092		60%在10uM
192	0.067		0.99
193	0.26		
194	0.016		0.043
195	0.016		0.045
196	0.032		
197	0.012		0.032
198	0.013		0.066
199	0.014		0.11

Abstract

A compound of formula (I):wherein Ring A, Q, R^1,R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11},X, a,b, c and d are as defined in the specification.