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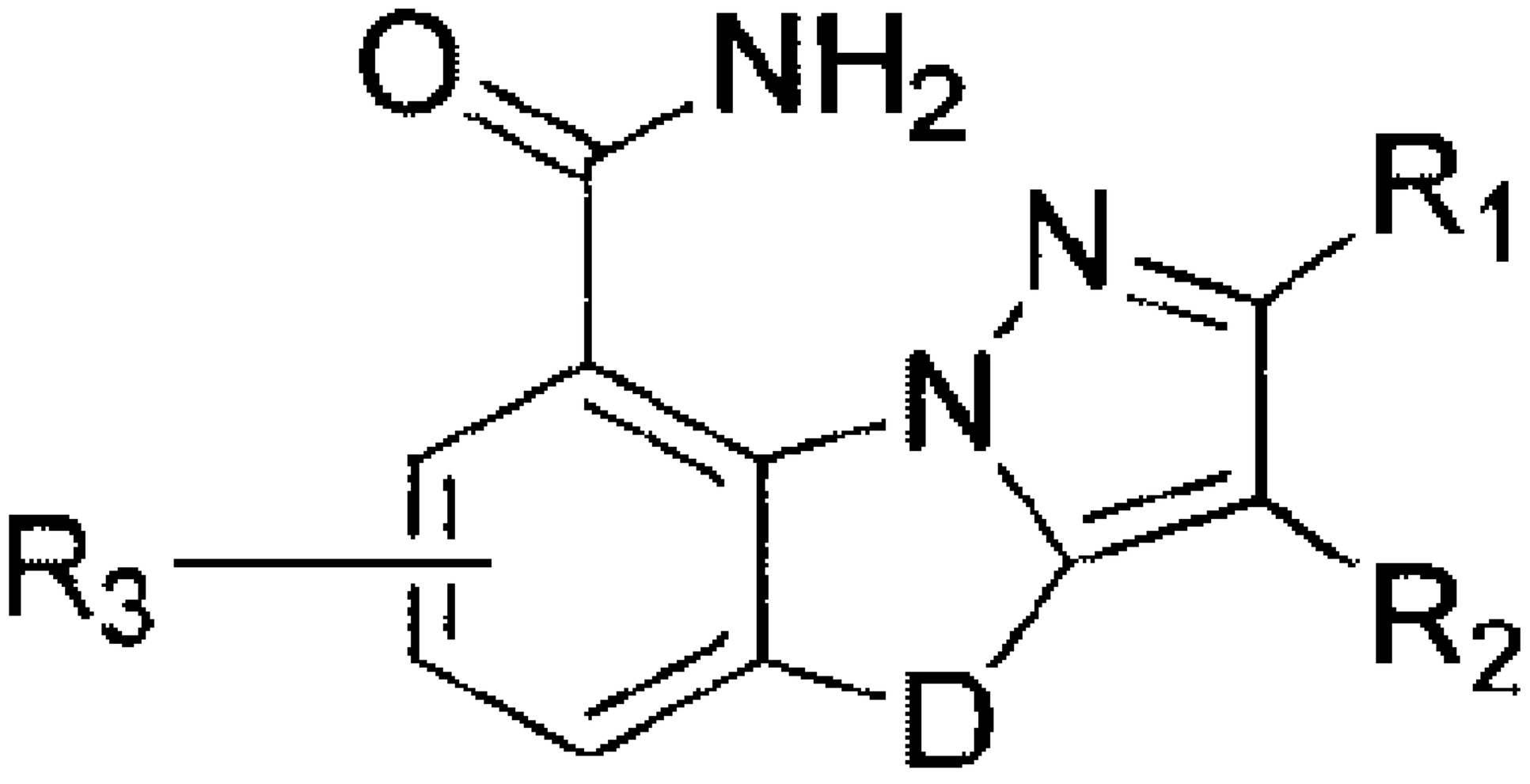
(54) **Titre : ANALOGUES DE COMPOSES DE OF 4H-PYRAZOLO[1,5-A]BENZIMIDAZOLE COMME INHIBITEURS DE PARP**
(54) **Title: ANALOGS OF 4H-PYRAZOLO[1,5-A]BENZIMIDAZOLE COMPOUNDS AS PARP INHIBITORS**



(I)

(57) **Abrégé/Abstract:**
Disclosed is a series of analogues of 4H-pyrazolo[1,5-α]benzimidazole compound as PARP inhibitors. In particular, disclosed in the invention is a compound as shown by formula (I) or a pharmaceutically acceptable salt thereof as a PARP inhibitor.

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Abstract

Disclosed is a series of analogues of 4H-pyrazolo[1,5-α]benzimidazole compound as PARP inhibitors. In particular, disclosed in the invention is a compound as shown by formula (I) or a pharmaceutically acceptable salt thereof as a PARP inhibitor.

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ANALOGS OF 4H-PYRAZOLO[1,5-A]BENZIMIDAZOLE COMPOUNDS AS PARP INHIBITORS

FIELD OF THE INVENTION

This invention relates to a series of analogs of 4H-Pyrazolo[1,5-α]benzimidazole compounds as PARP inhibitors. To be specific, this invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof as PARP inhibitors.

BACKGROUND OF THE INVENTION

PARP is a family of enzymes that catalyzes the addition of an ADP-ribose residue to various target proteins. To date, as many as 18 isoforms have been identified and characterized. Despite the large number of enzymes in the family, PARP-1 is responsible for more than 90% of the ADP-ribosylation within cells.

PARP-1 has long been associated with DNA repair and maintenance of genomic function. Following DNA damage, PARP-1 becomes instantly activated by binding to DNA breaks. After the structural changes, it begins to utilize NAD+ to synthesize poly(ADP) ribose as a signal for the other repairing enzymes (such as DNA ligase III, DNA polymerase beta). This process of PARP-1 binding and activation (known as base excision repair) helps amplify the repair process in which single-strand DNA breaks (SSB) are targeted. SSB are generally initiated by oxidative damages that are caused by cell's own metabolic processes as well as by exogenous chemotherapeutical agents and radiation. It is well-known that many types of anti-cancer therapies, such as DNA alkylating agents, platinum-based drugs, topoisomerase inhibitors and radiotherapy, are concomitant with DNA damages. These therapies are shadowed by the emergence of drug resistance, particularly in PARP-1 dominated DNA repair pathway. Recent studies have confirmed that selective PARP-1 inhibitors greatly enhance the antitumor efficacies of TMZ and cisplatin.

BRCA1 and BRCA2 play an essential role in homologous recombination (HR). DNA breaks arising during DNA replication can only be repaired by HR. In 2005, Bryant and Farmer (Nature, 2005, 913 and 917) independently discovered that cell lines deficient in BACA1 and BACA2 were very sensitive to PARP-1 inhibitors, resulting in cells death. Breast cancer genes BRCA1/2 have long been characterized as tumor suppressor genes that play an indispensable role in the repair of DNA double strand breaks. BRCA1/2 mutation carriers in ovarian cancer and prostate cancer are also at an elevated risk. Therefore PARP-1 inhibitors could also be used as a standalone therapy for such types of tumors that are already deficient in certain types of DNA repair mechanism.

PARP-1 has been an actively pursued oncology target for 30 years and Ferraris has entirely summarized the progress in this field (J. Med. Chem. 2010, 4561). A series compounds are in clinical studies regardless as a single agent or a synergist, such as veliparib (ABT-888), niraparib (MK-4827), BMN-673, CEP-977, BGP-15, E-7016, MP-124 and IND-1022. Recently certain heterocyclic compounds have also been disclosed as being useful in the treatment of a variety of cancers in some patents, for example, WO2014009872 (A1), WO2014019468 (A1),

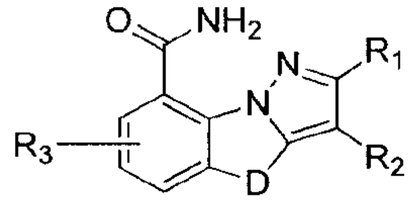
WO2014023390 (A2), WO2013182580, WO2013164061 (A1), EP2656843 (A1).

In addition, PARP-1 inhibition has been an actively pursued drug discovery target in wide ranges of therapeutic areas compassing stroke, cardiac ischemia, inflammation, and diabetes (Pharmacol. Rev. 2002, 54, 375.).

Although efforts have always been made to develop PARP-1 inhibitors for treating cancer and other diseases, satisfactory treatment has not yet been achieved. Thus, there exists a need for the development of new PARP-1 inhibitors.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide compounds shown in formula (I) or pharmaceutically acceptable salts thereof,



(I)

wherein,

D is selected from the group consisting of $-C(R_{d1})(R_{d2})-$, $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O)-, or $-S(=O)_2-$;

R_{1-3}, R_{d1}, and R_{d2} are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, and NH_2, or selected from the group, optionally substituted by R_{01}, consisting of C_{1-10} alkyl, C_{1-10} heteroalkyl, C_{3-10} cyclohydrocarbyl, C_{3-10} heterocyclohydrocarbyl, C_{1-10} alkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl, and C_{1-10} heteroalkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl.

R_{01} is selected from the group consisting of F, Cl, Br, I, CN, OH, SH, NH_2, and R_{02};

R_{02} is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkylamino, N,N-di(C_{1-10} alkyl) amino, C_{1-10} alkyloxyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, C_{3-10} heterocycloalkylamino, C_{3-10} cycloalkyloxyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

the heteroatom or heteroatomic group is separately and independently selected from the group consisting of $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O)-, and $-S(=O)_2-$;

R_{d3-d7} are separately and independently selected from the group consisting of H, and R_{03};

R_{03} is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

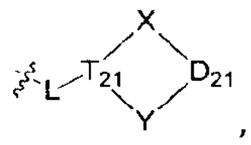
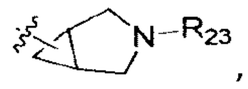
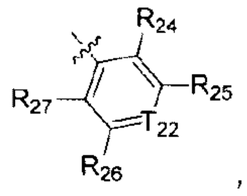
R_{02}, and R_{03} are optionally substituted by R_{001};

R_{001} is selected from the group consisting of F, Cl, Br, I, CN, OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2, CF_3, $(NH_2)CH_2$, $(HO)CH_2$, CH_3, CH_3O, HC(=O), CH_3O C (=O), $CH_3S(=O)_2$, and CH_3S (=O);and

the number of R_{01}, R_{001}, heteroatom, or heteroatomic group is separately and independently selected from 0, 1, 2, or 3.

In an embodiment of this invention, D is selected from -NH-, $-N(CH_3)-$, $-C(F)_2-$, -C(H) (F)- ,and

-C(H) (OH)-.

In an embodiment of this invention, R_{1-3} are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, C_{1-6} alkyl, C_{1-6} alkyloxyl, benzyloxyl, $-CH_2N(R_{21})(R_{22})$,  ,  , and  , in which,

L and D_{21} are separately and independently selected from the group consisting of $-C(R_{d1})(R_{d2})-$, $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, -C(=O)-, -C(=O)O-, -C(=S)-, -S(=O) -, or $-S(=O)_2-$;

L may also be a single bond for a linkage purpose only;

T_{21-22} are separately and independently selected from the group consisting of $C(R_t)$ and N;

X is selected from $(CH2)_n$ optionally substituted by R_{01}, and n is selected from 0, 1, 2, or 3, and preferably 0, 1, or 2;

Y is selected from $(CH2)_m$ optionally substituted by R_{01}, and m is selected from 0, 1, 2, or 3, and preferably 1, 2, or 3;

R_{21-23} and R_{d3-d7} are separately and independently selected from the group consisting of H and R_{03};

R_{24-27}, R_{d1}, R_{d2}, and R_t are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, and NH_2, or selected from the group , optionally substituted by R_{01}, consisting of C_{1-10} alkyl, C_{1-10} heteroalkyl, C_{3-10} cyclohydrocarbyl, C_{3-10} heterocyclohydrocarbyl, C_{1-10} alkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl, and C_{1-10} heteroalkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl;

R_{01} is selected from the group consisting of F, Cl, Br, I, CN, OH, SH, NH_2, and R_{02};

R_{02} is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkylamino, N,N-di(C_{1-10} alkyl)amino, C_{1-10} alkyloxyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, C_{3-10} heterocycloalkylamino, C_{3-10} cycloalkyloxyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

the heteroatom or heteroatomic group is separately and independently selected from the group consisting of $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, -C(=O)O-, -C(=O) -, -C(=S)-, -S(=O) -, and/or $-S(=O)_2-$;

R_{d3-d7} are separately and independently selected from the group consisting of H, and R_{03};

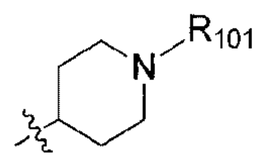
R_{03} is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

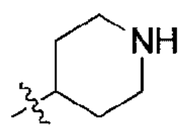
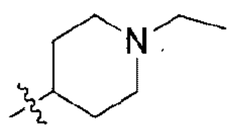
R_{02}, and R_{03} are optionally substituted by R_{001};

R_{001} is selected from the group consisting of F, Cl, Br, I, CN, OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2, CF_3, $(NH_2)CH_2$, $(HO)CH_2$, CH_3, CH_3O, HC(=O), CH_3O C (=O), CH_3S $(=O)_2$, and CH_3S (=O);and

the number of R_{01}, R_{001}, heteroatom, or heteroatomic group is separately and independently selected from 0, 1, 2, or 3.

In an embodiment of this invention, R_1 and R_3 are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, C_{1-3} alkyl, C_{1-3} alkyloxyl, benzyloxyl,

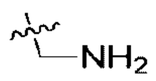
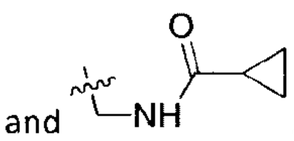
and  , in which R101 is selected from the group consisting of H, methyl, ethyl, n-propyl, or isopropyl.

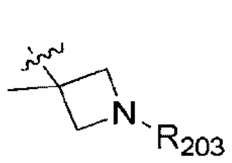
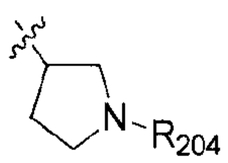
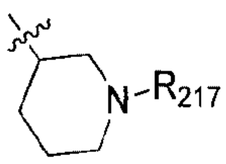
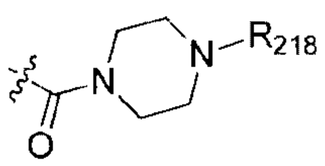
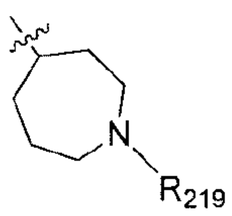
In an embodiment of this invention, R_1 is selected from the group consisting of H, methyl, methyloxyl, benzyloxyl,  , and  .

In an embodiment of this invention, R_3 is selected from the group consisting of H, F, Cl, Br, CN, and methyl.

In an embodiment of this invention, R_2 is selected from $-CH_2N(R_{201})(R_{202})$, in which R_{201} and R_{202} are separately and independently selected from the group consisting of H, C_{1-3} alkyl, C_{1-3} alkylacyl, C_{3-6} cycloalkylacyl, or C_{3-6} cycloalkyl.

In an embodiment of this invention, R_{201} and R_{202} are separately and independently selected from the group consisting of H or cyclopropylacyl.

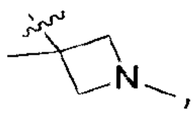
In an embodiment of this invention, R_2 is selected from the group consisting of  and  .

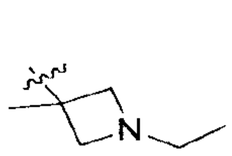
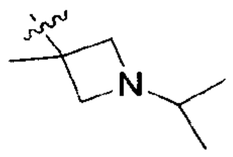
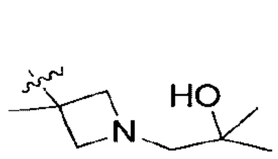
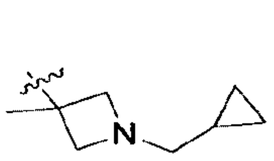
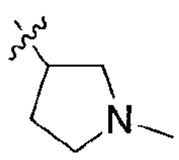
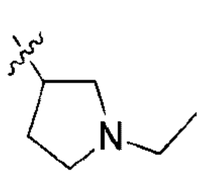
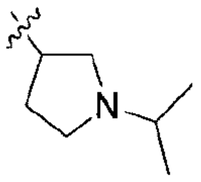
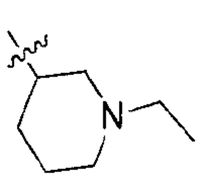
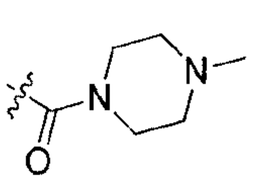
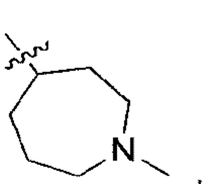
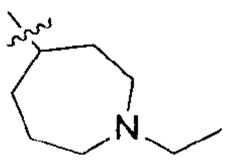
In an embodiment of this invention, R_2 is selected from the group consisting of  ,  ,  ,  , and  , in which R_{203}, R_{204}, R_{217}, and R_{218} are separately and independently selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl, or cyclopropylmethylene, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, or methyloxyl, and the number of substituents is 0, 1, 2, or 3.

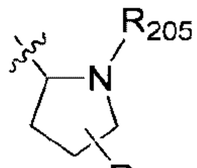
In an embodiment of this invention, R_{203} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, $-CH_2C(CH_3)(CH_3)(OH)$, and cyclopropylalkylene.

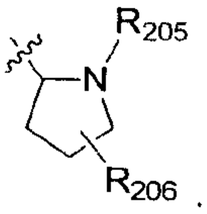
In an embodiment of this invention, R_{204} is selected from the group consisting of methyl, ethyl, n-propyl, and isopropyl.

In an embodiment of this invention, $R_{217-219}$ are separately and independently selected from the group consisting of methyl and ethyl.

In an embodiment of this invention, R_2 is selected from the group consisting of  ,

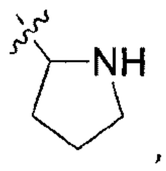










and


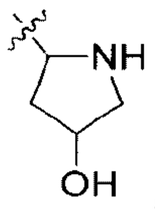
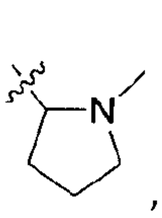
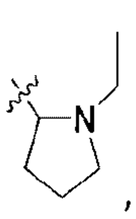
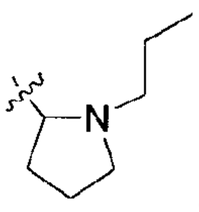


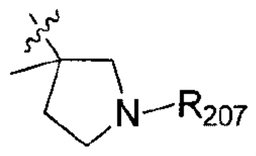
In an embodiment of this invention, R_2 is selected from  , in which R_{205} and R_{206} are separately and independently selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl, or cyclopropylmethylene, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, or methyloxyl, and the number of substituents is 0, 1, 2, or 3.

In an embodiment of this invention, R_{205} and R_{206} are separately, independently and preferably selected from the group consisting of H, methyl, ethyl, n-propyl, and isopropyl, and R_{206} is also preferably selected from the group consisting of F, Cl, Br, I, CN, OH, and NH_2.

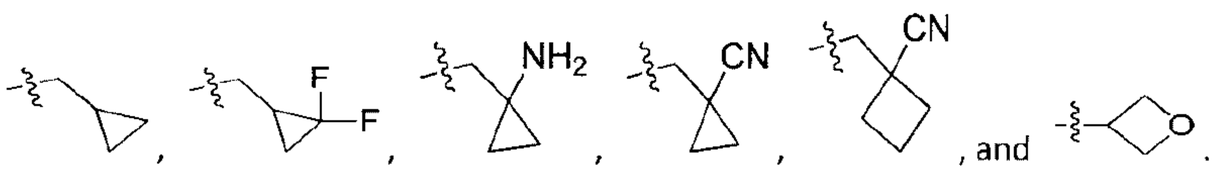
In an embodiment of this invention, R_2 is selected from .

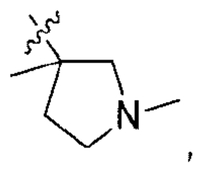
In an embodiment of this invention, R_2 is selected from the group consisting of  ,

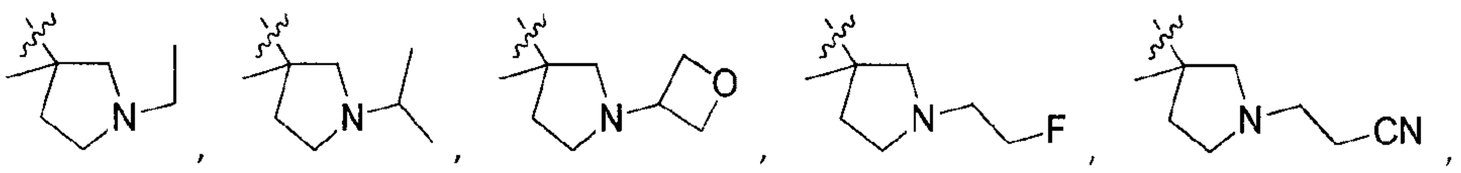



and


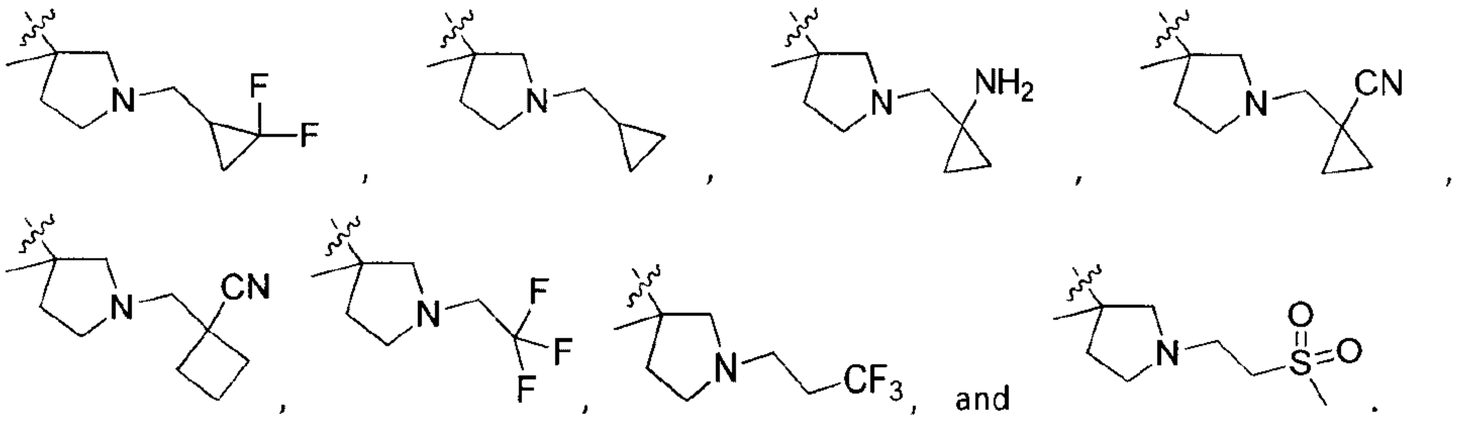
In an embodiment of this invention, R_2 is selected from  , in which R_{207} is selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl, cyclopropylmethylene, cyclobutyl, cyclobutylmethylene, oxacyclobutyl or oxacyclobutylalkylene, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, CF_3, methyloxyl, and methylsulfonyl, and the number of substituents is 0, 1, 2, or 3.

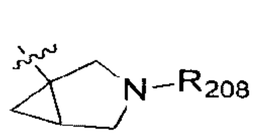
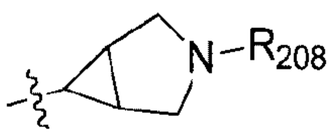
In an embodiment of this invention, R_{207} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2S(=O)_2CH_3$, $-CH_2CH_2CN$,



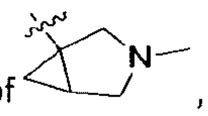
In an embodiment of this invention, R_2 is selected from the group consisting of  ,

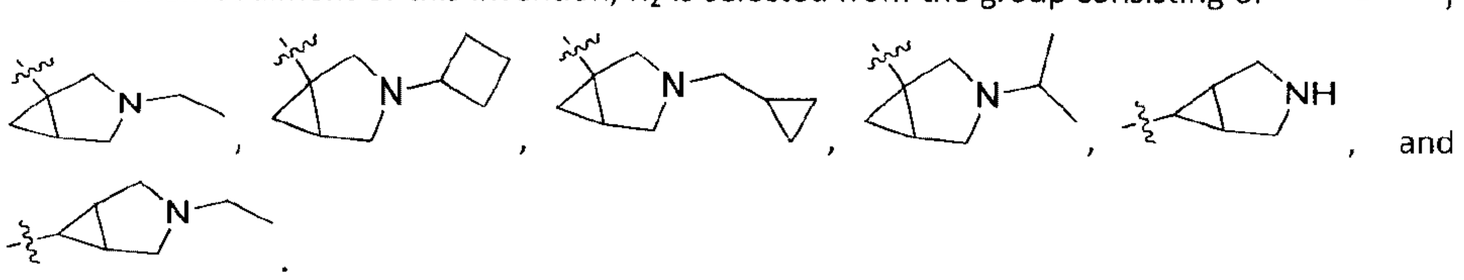


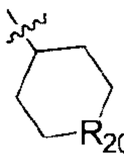


In an embodiment of this invention, R_2 is selected from the group consisting of  or  , in which R_{208} is selected from the group consisting of H, substituted or unsubstituted $C_{1\text{-}4}$ alkyl, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, CF_3, methyloxyl, and methylsulfonyl, and the number of substituents is 0, 1, 2, or 3.

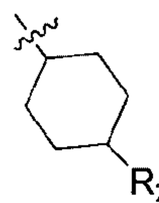
In an embodiment of this invention, R_{208} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, cyclopropylmethylene, and cyclobutyl.

In an embodiment of this invention, R_2 is selected from the group consisting of  ,

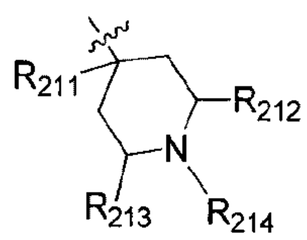


In an embodiment of this invention, R_2 is selected from  , in which R_{209} is selected from the group consisting of $-C(R_{d1})(R_{d2})-$, $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O)-, or $-S(=O)_2-$.

In an embodiment of this invention, R_{209} is selected from the group consisting of O and $S(=O)_2$.

In an embodiment of this invention, R_2 is selected from  , in which R_{210} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, N,N-di(C_{1-3} alkyl)amino, and C_{1-3} alkylamino.

In an embodiment of this invention, R_{210} is selected from the group consisting of dimethylamino, methylamino, H, F, Cl, Br, I, CN, OH, and NH_2.

In an embodiment of this invention, R_2 is selected from  , in which $R_{211-214}$ are selected from the group consisting of H, or substituted or unsubstituted C_{1-4} alkyloxylcarbonyl, C_{1-4} alkyl, 3-6 membered cycloalkyl, 3-6 membered cycloalkylmethylene, or unsaturated 5-6 membered heterocyclohydrocarbyl, wherein the substitutent includes R_{215}, and $R_{211-213}$ are also selected from the group consisting of H, F, Cl, Br, I, CN, OH, and NH_2, in which the cycloalkyl or unsaturated heterocyclohydrocarbyl has O, S or NR_{216} with a number of 0, 1 or 2 wherein

R_{216} is selected from the group consisting of H and C_{1-4}alkyl substituted by R_{215},

R_{215} is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, ethyl, methyloxyl, ethyloxyl, formyl, acetyl, methylsulfonyl, ethylsulfonyl, methyloxylcarbonyl, ethyloxylcarbonyl, dimethylamino, diethylamino, dimethylaminocarbonyl, diethylaminocarbonyl, oxo,

the number of R_{215} is 1, 1, 2, or 3,

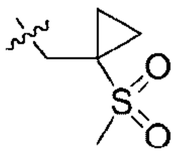
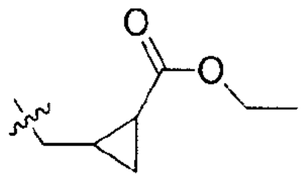
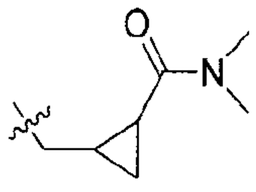
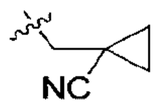
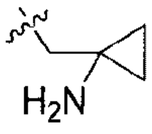
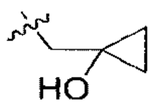
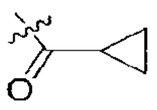
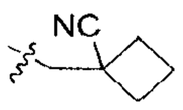
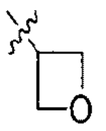
optionally, R_{212} and R_{213} may join together to form a linker selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$;

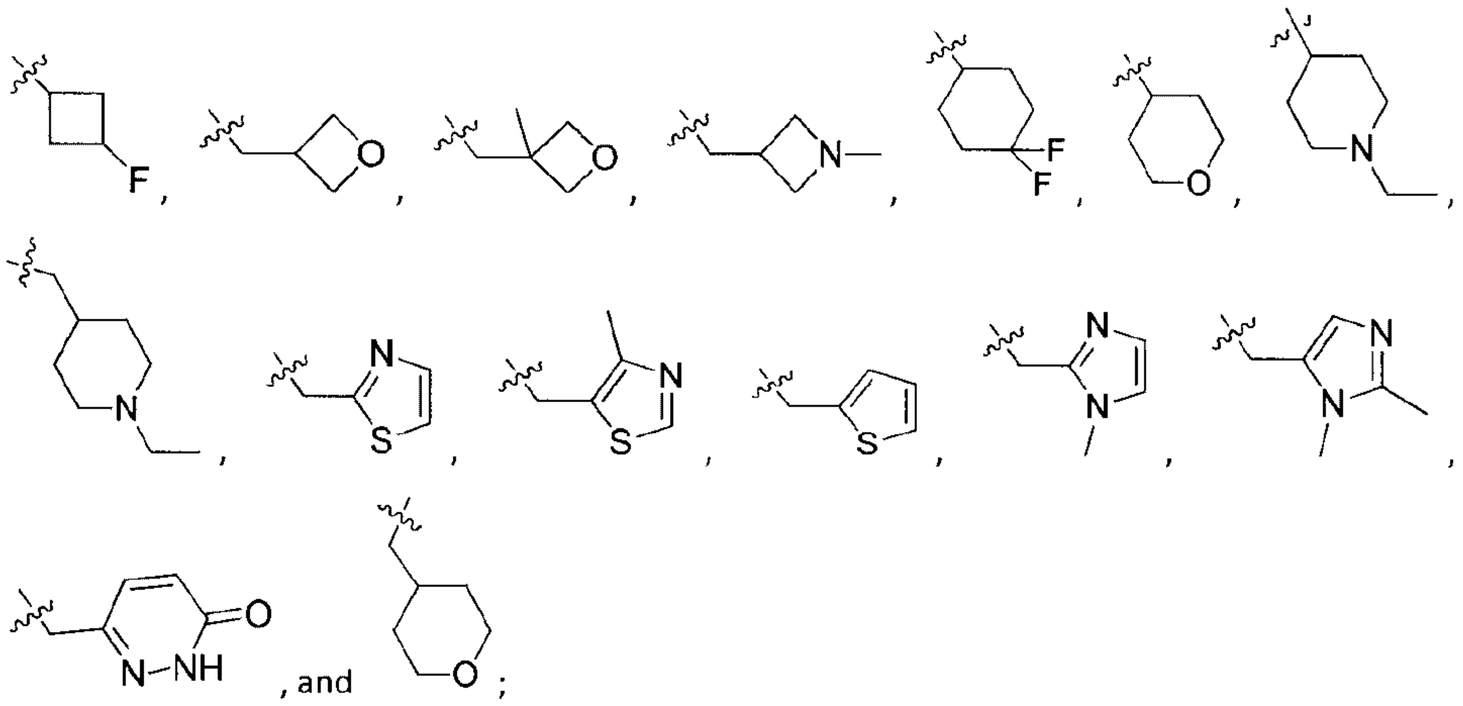
In an embodiment of this invention,

R_{211} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NH_2, methyl, ethyl, hydroxylmethyl, and methyloxylcarbonyl,

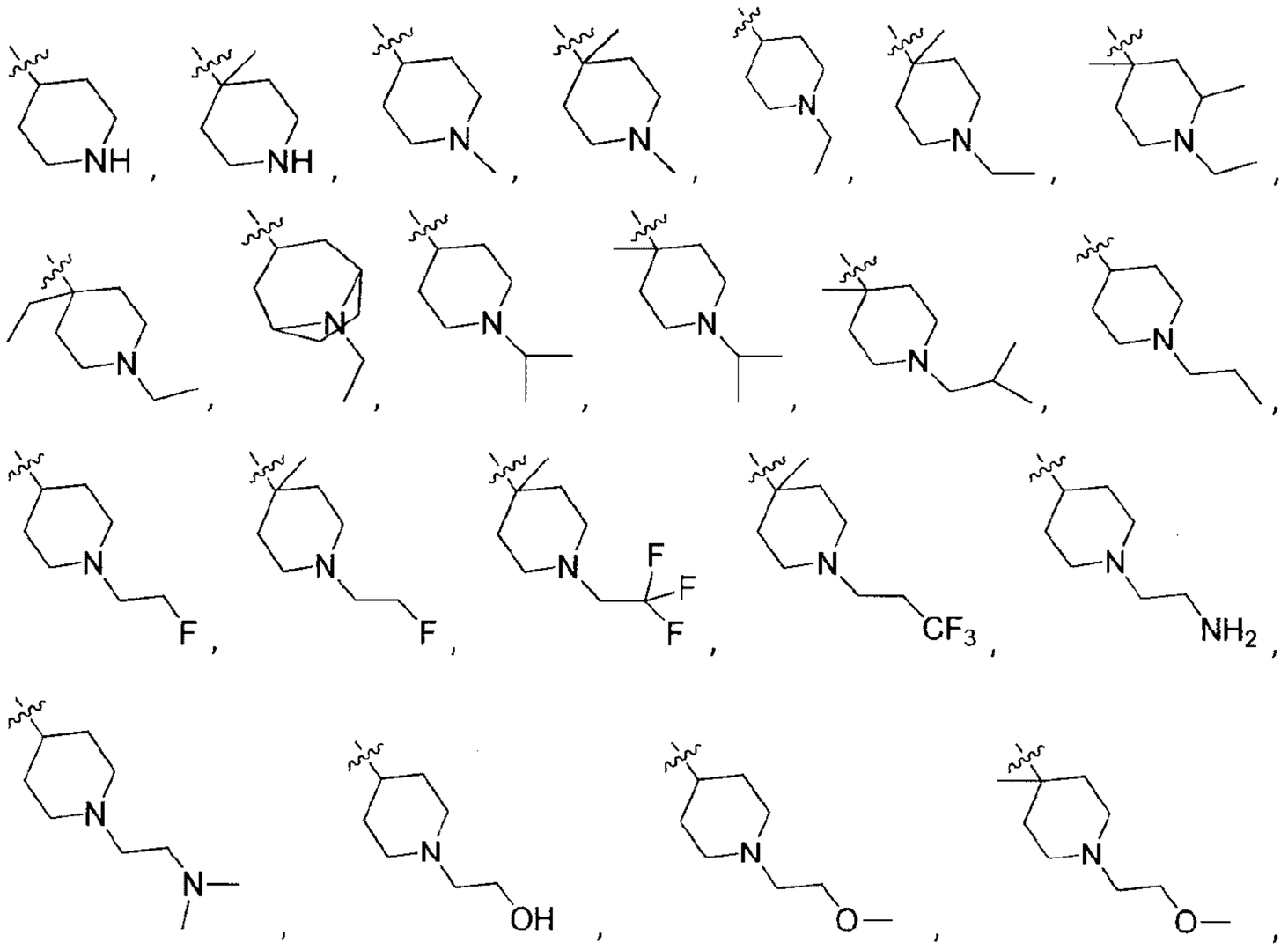
R_{212} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NH_2, and methyl,

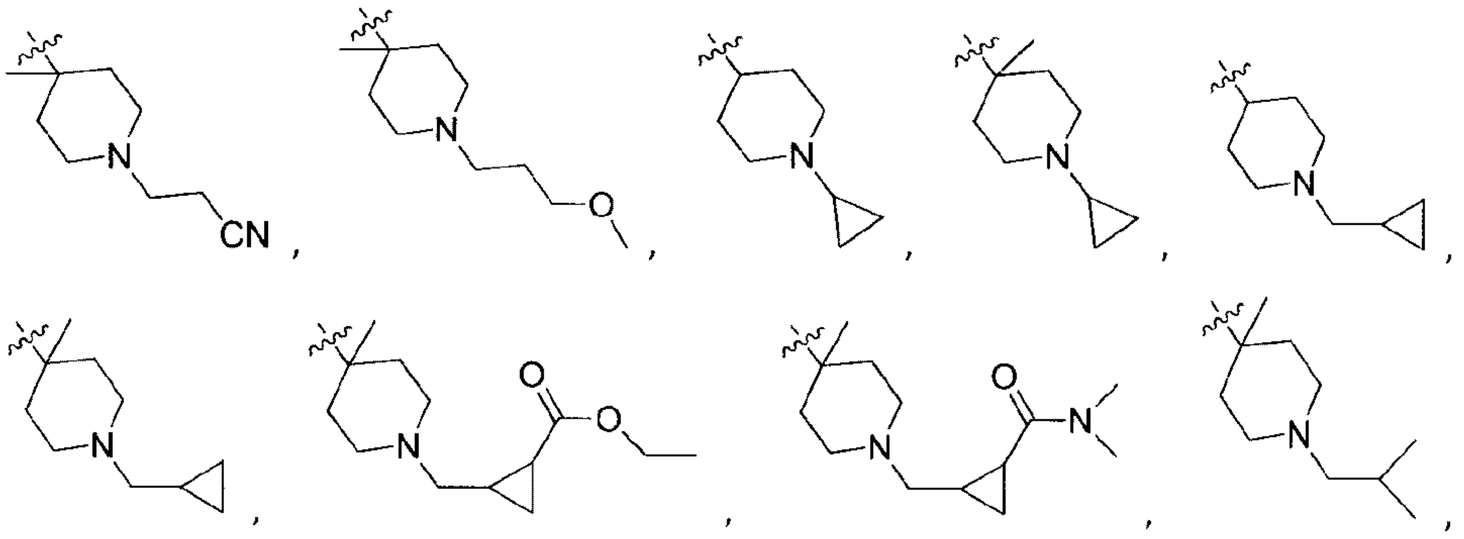
R_{213} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, and NH_2,

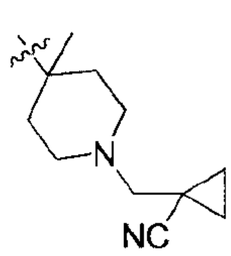
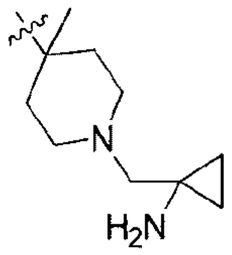
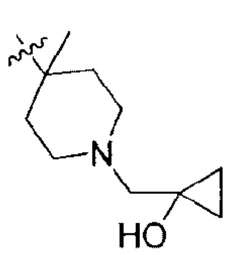
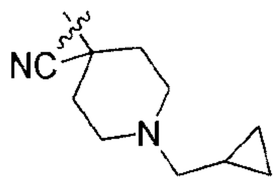
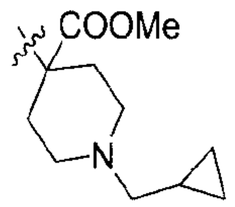
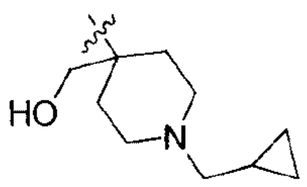
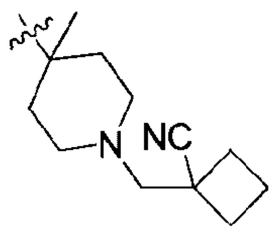
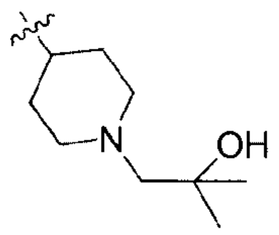
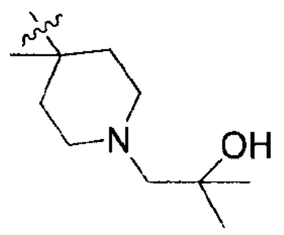
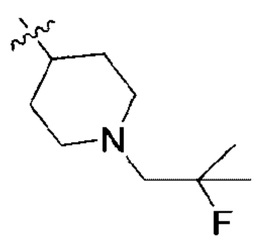
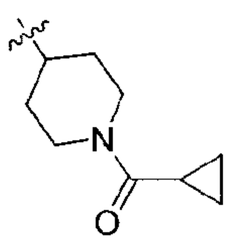
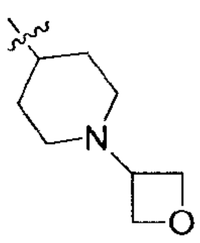
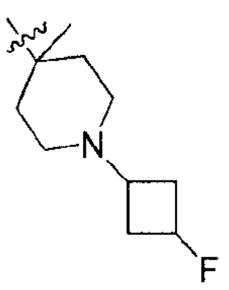
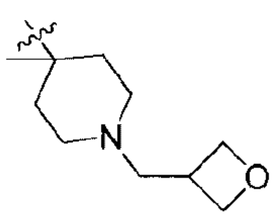
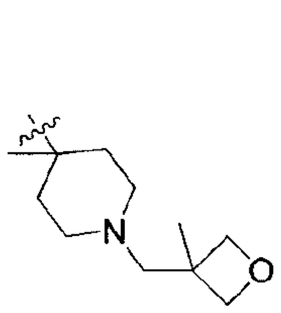
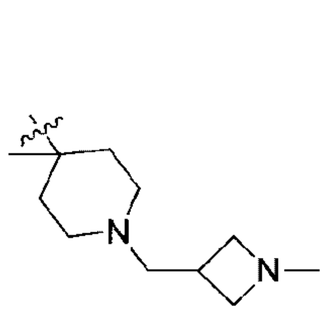
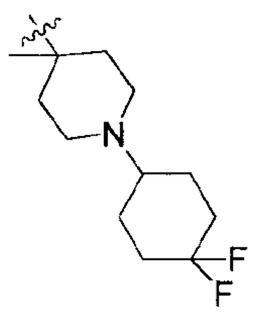
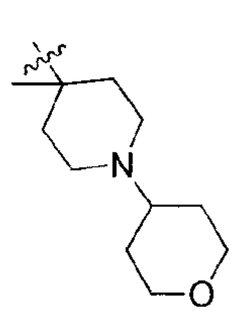
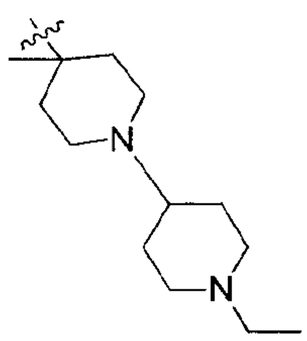
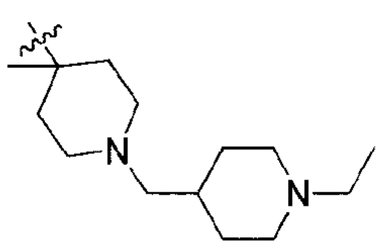
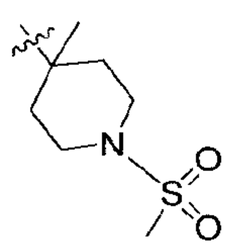
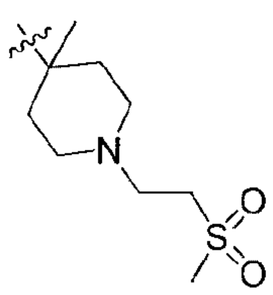
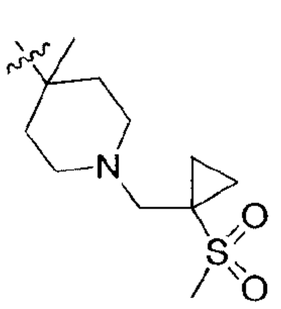
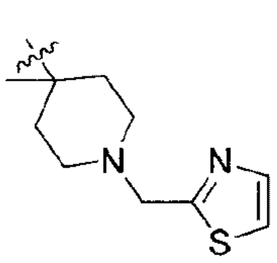
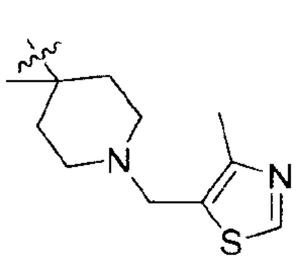
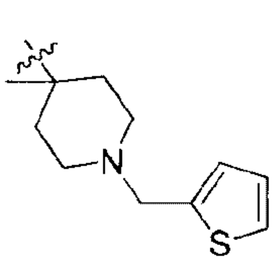
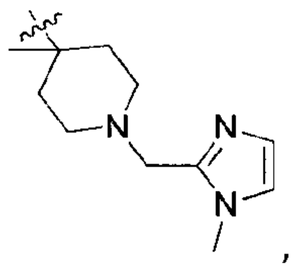
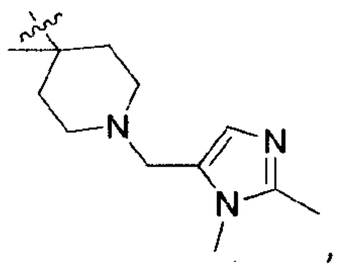
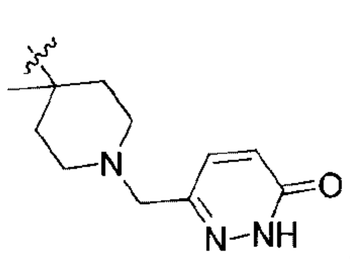
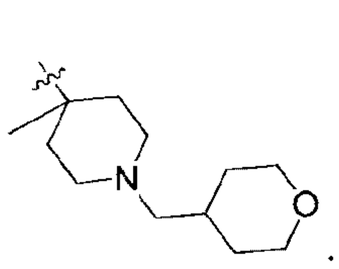
R_{214} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, $-CH_2C(OH)(CH_3)_2$, $-CH_2C(F)(CH_3)_2$, $-CH_2CH_2F$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2OH$, $-CH_2CH_2CN$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CH_2N(CH_3)_2$, $-S(=O)_2CH_3$, $-CH_2CH_2S(=O)_2CH_3$,  , cyclopropyl, cyclopropylmethylene,  ,  ,  ,  ,  ,  ,  ,  .



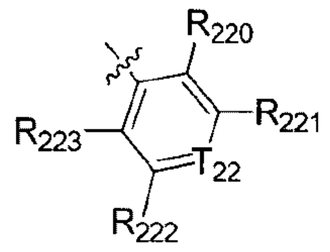
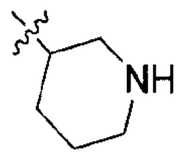
In an embodiment of this invention,R_2 is selected from the group consisting of





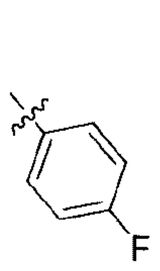
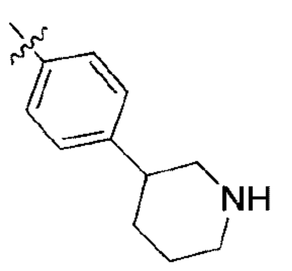
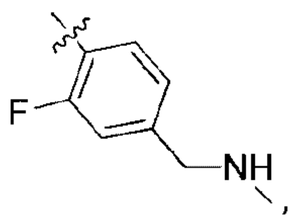
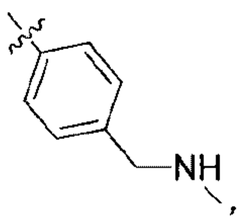
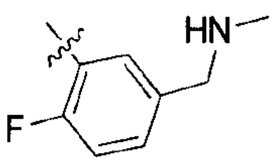
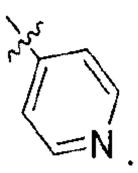































, and .

In an embodiment of this invention, R_2 is selected from  , in which T_{22} is selected from the group consisting of N or $C(R_{224})$, and $R_{220-224}$ are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, C_{1-3} alkylamino-C_{1-3} alkyl, and  .

In an embodiment of this invention, the C_{1-3} alkylamino-C_{1-3} alkyl is selected from methylaminomethylene.

In an embodiment of this invention,

R_2 is selected from the group consisting of  ,  ,  ,  ,  , and  .

In an embodiment of this invention, the compounds or pharmaceutically acceptable salts thereof are selected from:

1) 6-fluoro-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
2) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
3) 6-fluoro-3-(1-(2-fluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
4) 3-(1-cyclopropylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
5) 3-(1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
6) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
7) 6-fluoro-3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
8) 3-(1-(cyclopropylcarbonyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
9) 6-fluoro-3-(1-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
10) 6-fluoro-3-(1-isopropylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
11) 6-fluoro-3-(1-(oxetan-3-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

12) 6-fluoro-3-(1-propylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
13) 3-(1-(2-aminoethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
14) 3-(1-(2-(dimethylamino)ethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
15) 6-fluoro-3-(1-(2-methoxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
16) 6-fluoro-3-(1-(2-hydroxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
17) 3-(1-ethylpiperidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
18) 3-(1-ethylazepan-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
19) 6-fluoro-3-(1-methylazepan-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
20) 6-fluoro-3-(1-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
21) 3-(1-ethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
22) 6-fluoro-3-(1-isopropylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
23) 6-fluoro-3-(pyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
24) 6-fluoro-3-(1-propylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;6-fluoro-3-(1-methylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
25) 3-(1-ethylpyrrolidin-2-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
26) 3-(1-ethylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
27) 6-fluoro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
28) 3-(3-ethyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
29) 3-(3-cyclobutyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
30) 3-(3-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
31) 6-fluoro-3-(3-isopropyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
32) 3-(3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
33) 3-(3-ethyl-3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
34) 3-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
35) 6-fluoro-3-(4-hydroxypyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
36) 3-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
37) 3-cyano-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
38) 3-(aminomethyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
39) 3-(cyclopropanecarboxamidomethylene)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
40) 6-fluoro-3-(4-fluorophenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
41) 6-fluoro-3-(2-fluoro-4-((methylamino)methylene)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyraz

ole-8-carboxamide;

42) 6-fluoro-3-(4-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

43) 6-fluoro-3-(2-fluoro-5-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

44) 6-fluoro-3-(pyridin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

45) 6-fluoro-3-(4-(piperidin-3-yl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

46) 6-fluoro-3-(tetrahydro-2H-pyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

47) 3-(4-(dimethylamino)cyclohexyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

48) 6-fluoro-3-(4-methylpiperazin-1-carbonyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

49) 3-(1-(cyclopropylmethyl)piperidin-4-yl)-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxamide;

50) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4-hydroxy-4H-pyrazolo[1,5-α]indole-8-carboxamide;

51) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

52) 6-fluoro-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

53) 3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

54) 3-(1-cyclopropyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide ;

55) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

56) 3-(1-(cyclopropylmethylene)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

57) 3-(1-(4,4-difluorocyclohexyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

58) 6-fluoro-3-(4-methyl-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

59) 6-fluoro-3-(1-(2-fluoroethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

60) 6-fluoro-3-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

61) 6-fluoro-3-(4-methyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

62) 3-(1-((1-cyanocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

63) 3-(1-((1-cyanocyclobutyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

64) 6-fluoro-3-(4-methyl-1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

65) 6-fluoro-3-(4-methyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

66) 3-(1-((1-aminocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
67) 6-fluoro-3-(4-methyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
68) 6-fluoro-3-(1-(2-methoxyethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
69) 6-fluoro-3-(1-((1-hydroxycyclopropyl)methyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
70) 6-fluoro-3-(4-methyl-1-((3-methyloxetan-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
71) 6-fluoro-3-(1-(3-methoxypropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
72) 6-fluoro-3-(4-methyl-1-((1-(methylsulfonyl)cyclopropyl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
73) 6-fluoro-3-(4-methyl-1-(thiazol-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
74) 6-fluoro-3-(4-methyl-1-(methylsulfonyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
75) 6-fluoro-3-(1-(3-fluorocyclobutyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
76) 6-fluoro-3-(4-methyl-1-(thiophen-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
77) 3-(1-((1-ethylpiperidin-4-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
78) 6-fluoro-3-(4-methyl-1-((1-methylazetidin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
79) ethyl 2-((4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidin-1-yl)methyl)cyclopropanecarboxylate;
80) 3-(1-((2-(dimethylcarbamoyl)cyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
81) 6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
82) 6-fluoro-3-(4-methyl-1-((4-methylthiazol-5-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
83) 6-fluoro-3-(4-methyl-1-((1-methyl-1H-imidazol-2-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
84) 3-(1-((1,2-dimethyl-1H-imidazol-5-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide
85) 3-(1'-ethyl-4-methyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
86) 6-fluoro-3-(4-methyl-1-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
87) 3-(1-(2-cyanoethyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

88) 6-chloro-3-(1-ethyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
89) 3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
90) 3-(1,3-dimethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
91) 6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
92) 3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
93) 6-fluoro-3-(3-methyl-1-(oxetan-3-yl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
94) 6-fluoro-3-(1-(2-fluoroethyl)-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
95) 3-(1-((2,2-difluorocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
96) 6-fluoro-3-(3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
97) 6-fluoro-3-(3-methyl-1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
98) 6-fluoro-3-(3-methyl-1-(3,3,3-trifluoropropyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
99) 3-(1-((1-aminocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
100) 3-(1-((1-cyanocyclobutyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
101) 3-(1-((1-cyanocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
102) 3-(1-(2-cyanoethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
103) 3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
104) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
105) 6-fluoro-3-(4-methyl-1,1-dioxido-2H-thiopyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
106) 3-(1,4-diethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
107) 3-(4-cyano-1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
108) 3-(1-(cyclopropylmethyl)-4-(hydroxymethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
109) Methyl
4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-1-(cyclopropylmethyl)piperidine-4-carboxylate;

110) 3-(1-(cyclopropylmethyl)-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
111) 3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
112) 6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
113) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
114) 3-(1,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
115) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
116) 3-(1-ethyl-2,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
117) 3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
118) 6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
119) 3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
120) 3-(1,3-dimethylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
121) 3-(1-ethyl-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
122) 6-fluoro-3-(1-isopropyl-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
123) 3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
124) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
125) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
126) 2-(benzyloxy)-6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
127) 6-fluoro-2-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
128) 2-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide.

DEFINITIONS

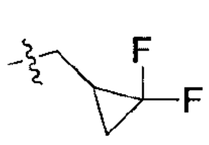
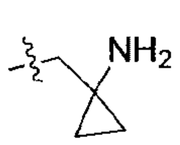
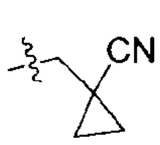
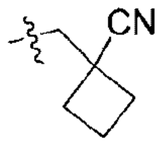
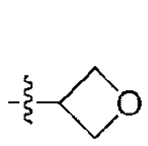
C_{1-10} is selected from the group consisting of C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10}; C_{3-10} is selected from the group consisting of C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10}.

C_{1-10} alkyl, C_{1-10} heteroalkyl, C_{3-10} cyclohydrocarbyl, C_{3-10} heterocyclohydrocarbyl, C_{1-10} alkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl, or C_{1-10} heteroalkyl substituted by C_{3-10} cyclohydrocarbyl or C_{3-10} heterocyclohydrocarbyl include, but are not limited to:

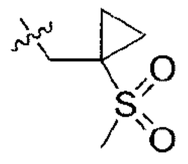
C_{1-10} alkyl, C_{1-10} alkylamino, N,N-di(C_{1-10} alkyl) amino, C_{1-10} alkyloxyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, C_{3-10} heterocycloalkylamino, C_{3-10} cycloalkyloxyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

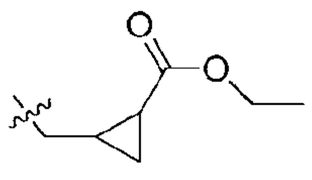
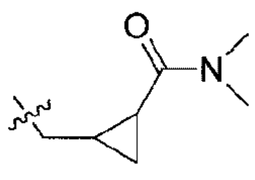
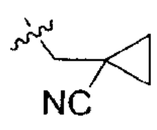
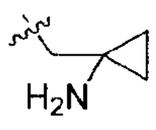
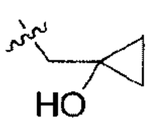
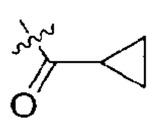
methyl, ethyl, n-propyl, isopropyl, $-CH_2C(CH_3)(CH_3)(OH)$, cyclopropyl, cyclobutyl, propylmethylene, cycropropylacyl, benzyloxyl, trifluoromethyl, aminomethyl, hydroxylmethyl, methyloxyl, formyl, methyloxylcarbonyl, methylsulfonyl, methylsulfinyl, ethyloxyl, acetyl, ethylsulfonyl, ethyloxylcarbonyl, dimethylamino, diethylamino, dimethylaminocarbonyl, and diethylaminocarbonyl;

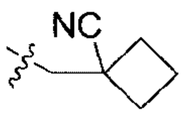
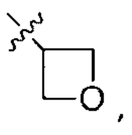
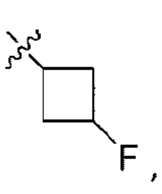
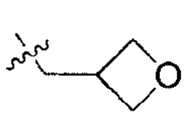
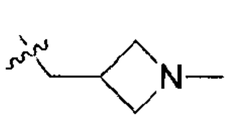
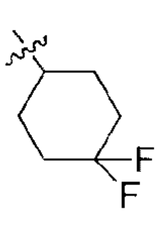
$N(CH_3)_2$, $NH(CH_3)$, $-CH_2CF_3$, -CH2CH_2CF_3, $-CH_2CH_2F$, $-CH_2CH_2S(=O)_2CH_3$, $-CH_2CH_2CN$, ,

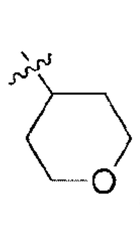
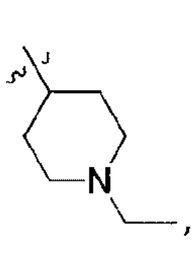
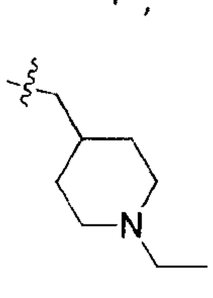
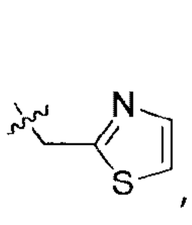
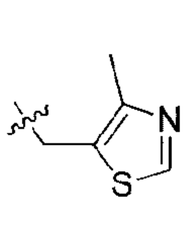
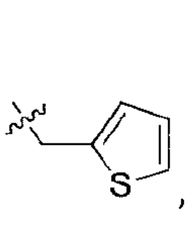
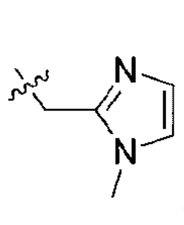
 ,  ,  ,  ,  , $-CH_2CH(OH)(CH3)_2$,

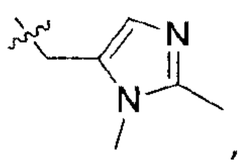
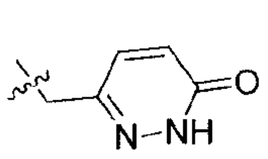
$-CH_2CH(F)(CH_3)_2$, $-CH_2CH_2F$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$,

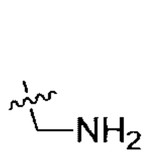
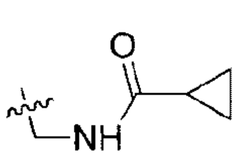
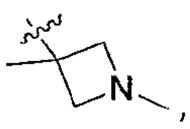
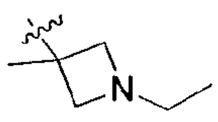
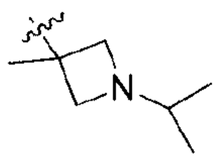
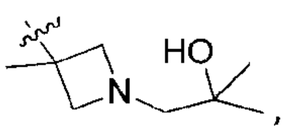
$-CH_2CH_2CH_2OCH_3$, $-CH_2CH_2N(CH_3)_2$, $-S(=O)_2CH_3$, $-CH_2CH_2S(=O)_2CH_3$,  ,

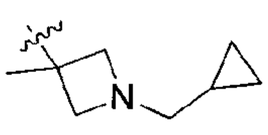
 ,  ,  ,  ,  ,  ,

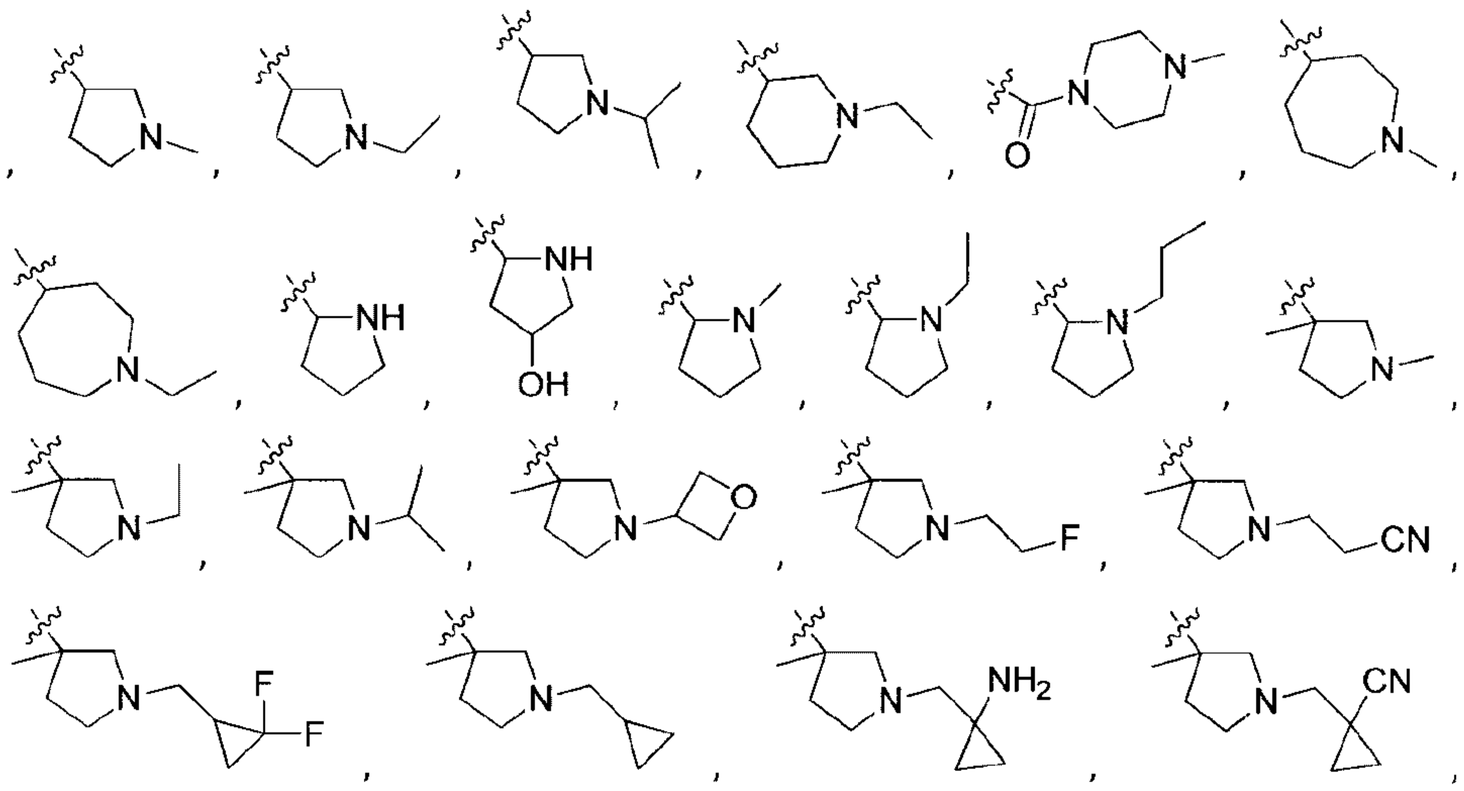
 ,  ,  ,  , ,  ,  ,

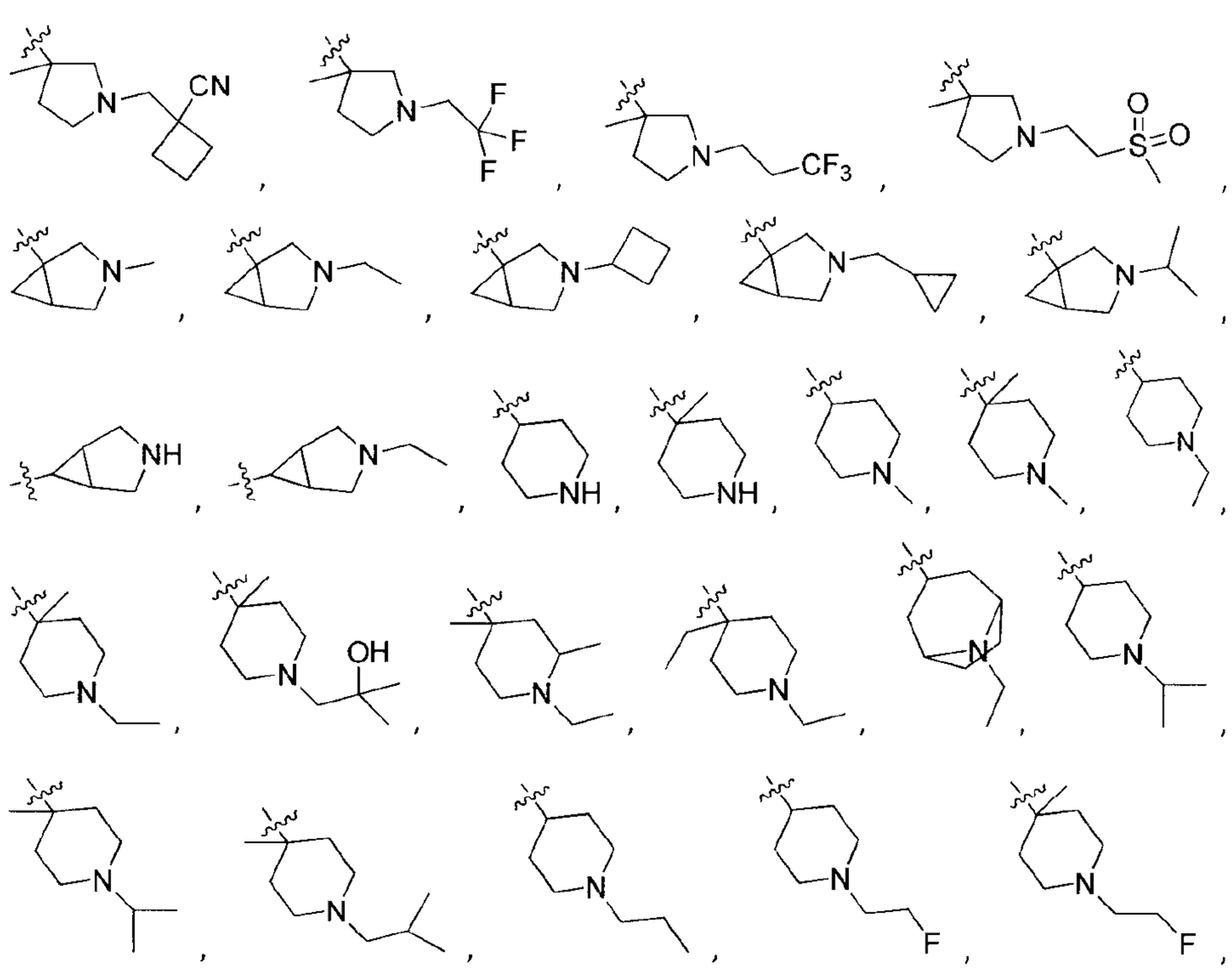
 ,  ,  ,  ,  ,  ,  ,

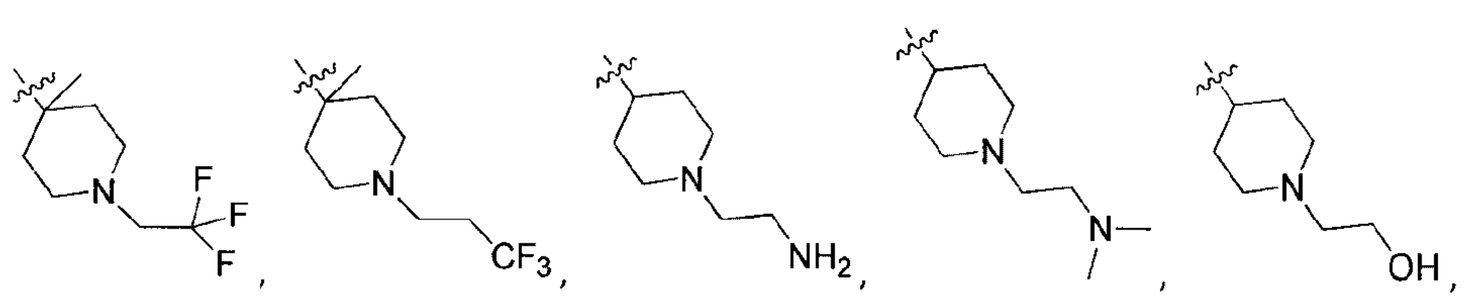
 ,  ;

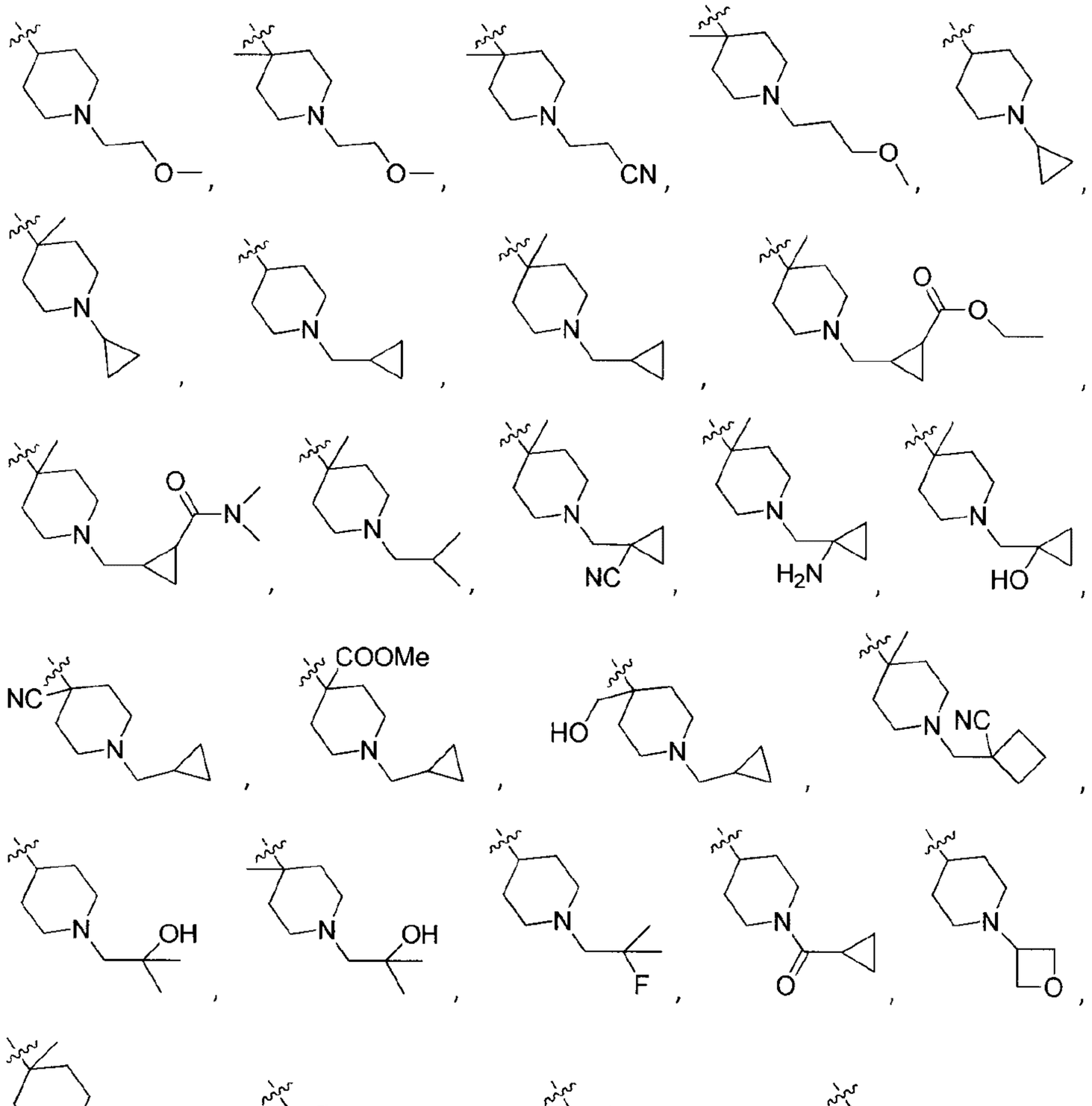
 ,  ,  ,  ,  ,  ,

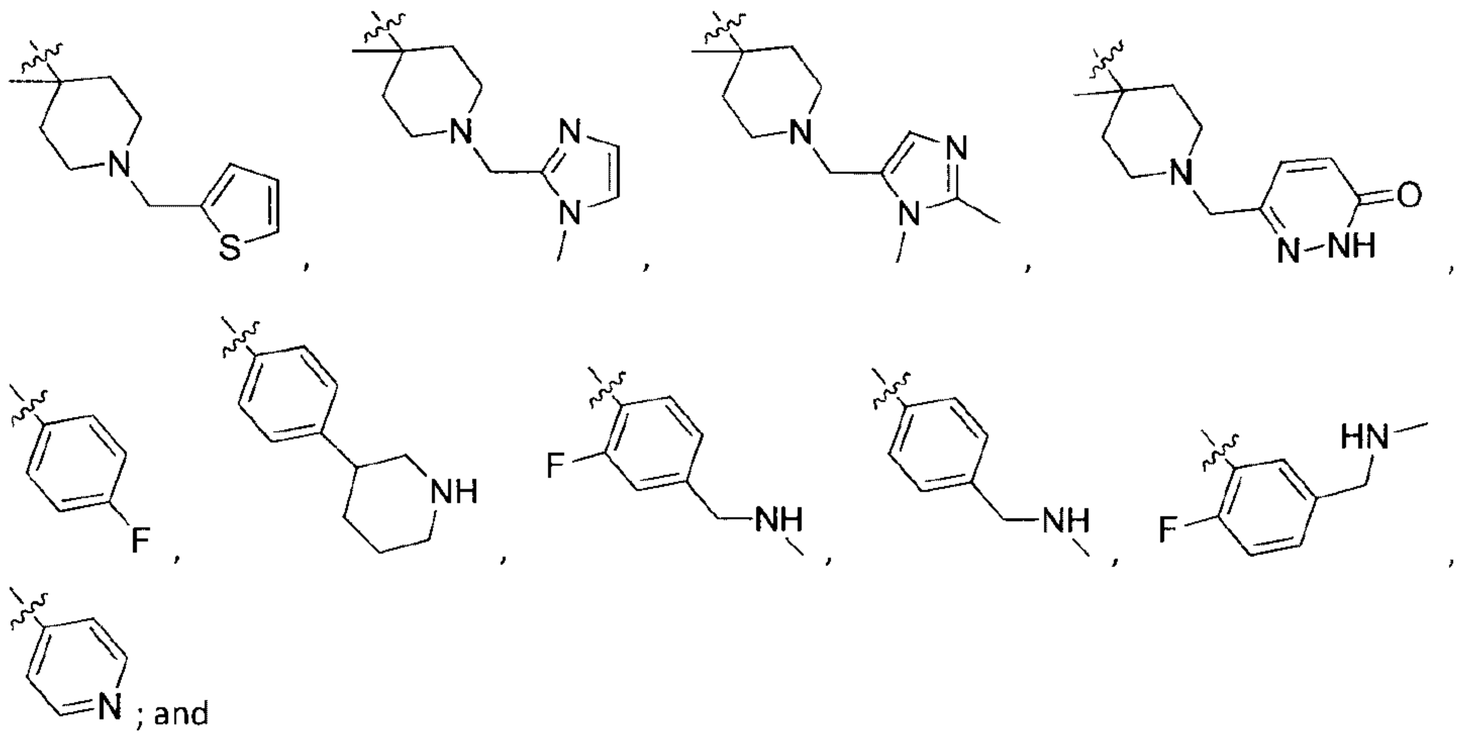
 ,











; and

phenyl, thiazolyl, biphenyl, naphthyl, cyclopentyl, furyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-oxolanyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, imidazolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 4H-pyranyl, pyridyl, piperidinyl, 1,4-dioxanyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3 5-trithianyl, 1,3,5-triazinyl, benzofuranyl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, purinyl, quinolinyl, iso-quinolinyl, cinnolinyl, or quinoxalinyl;

The term "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salt" is meant to include a salt of a compound of the invention which is prepared by a relatively nontoxic acid or base and the compound of the invention having particular substituents. When the compound of the invention contains a relatively acidic functional group, a base addition salt can be obtained by contacting a neutral form of such compounds with a sufficient amount of a desired base, either neat or in a suitable inert solvent. Examples of the pharmaceutically acceptable base addition salts include salts of sodium, potassium, calcium, ammonium, organic amine, or magnesium, or similar salts. When the compound of the invention contains a relatively basic functional group, an acid addition salt can be obtained by contacting a neutral form of such compounds with a sufficient amount of a desired acid, either neat or in a suitable inert solvent. Examples of the pharmaceutically acceptable acid addition salts include salts of inorganic acids including hydrochloric, hydrobromic, nitric, carbonic, hydrocarbonic, phosphoric, hydrophosphoric, dihydrophosphoric, sulfuric, hydrosulfuric, hydriodic, or phosphorous acids and the like; as well as salts of organic acids including acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic acid, or the like; and also salts of amino acids (such as arginate and the like), and salts of organic acids like glucuronic acid and the like (see, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition

salts.

The neutral form of the compound is preferably regenerated by contacting the salt with a base or acid and then isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms thereof in certain physical properties, such as solubility in polar solvents.

As used herein, "pharmaceutically acceptable salts" refers to derivatives of the compounds of the invention wherein the parent compound is modified by making a salt with an acid or base. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; alkali or organic salts of acidic groups such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydrobromic, hydrochloric, hydroiodide, hydroxyl acids, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic acid.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile or the like are preferred.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an in vivo environment.

Certain compounds of the invention can exist in unsolvated forms or solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and all are encompassed within the scope of the present invention. Certain compounds of the invention may exist in polycrystalline or amorphous forms.

Certain compounds of the invention may possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all encompassed within the scope of the present invention.

The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr, J. Chem. Ed. 1985, 62: 114-120. Solid and broken wedges are used to denote the absolute configuration of a stereocenter unless otherwise noted. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are included within the scope of the invention.

Compounds of the invention can exist in particular geometric or stereoisomeric forms. The invention contemplates all such compounds, including *cis*- and *trans*-isomers, (-)- and (+)-enantiomers, (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, the racemic mixtures thereof, and other mixtures thereof, such as enantiomerically or diastereomerically enriched mixtures, and all these mixtures as falling within the scope of the invention. Additional asymmetric carbon atoms can be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Optically active (*R*)- and (*S*)-isomers and *D* and *L* isomers can be prepared by chiral synthons or chiral reagents, or other conventional techniques. If a particular enantiomer of a compound of the present invention is desired, it can be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resultant diastereomeric mixture is separated and the auxiliary group is cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group (such as an amino group) or an acidic functional group(such as a carboxyl group) diastereomeric salts can be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers. In addition, separation of enantiomers and diastereomers is frequently accomplished by chromatography employing chiral, stationary phases, optionally in combination with chemical derivatization (e.g., formation of carbamates from amines).

The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the invention, regardless of radioactivity, are intended to be encompassed within the scope of the present invention.

The term "pharmaceutically acceptable carrier or vehicle" refers to any formulation or carrier medium that is capable of delivery of an effective amount of an active agent of the invention withouttoxic side effects on a host or patient. Representative carriers include water, oils, both vegetable and mineral, cream bases, lotion bases, ointment bases and the like. These bases include suspending agents, thickeners, penetration enhancers, and the like. Their formulation is well known to those in the art of cosmetics and topical pharmaceuticals.

The term "excipients" conventionally means carriers, diluents and/or vehicles needed in formulating effective pharmaceutical compositions.

The terms "effective amount" or "therapeutically effective amount" for a drug or pharmacologically active agent refers to a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the oral dosage forms of the present disclosure, an "effective amount" of an active agent of the composition refers to the amount of the active agent required to provide the desired effect when used in combination with the other active agent of the composition. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of a recipient, and also a particular active agent, and an appropriate effective amount in an individual case may be determined by one of ordinary skill in the art using routine experimentation.

The terms "active ingredient," "therapeutic agent," "active substance," or "active agent" mean a chemical entity which can be effective in treating a targeted disorder, disease or condition.

The term "substituted" means that any one or more hydrogens on a designated atom is replaced with a substituent including deuterium and a variant of hydrogen, provided that the designated atom's valency is normal, and that the substituted compound is stable. When a substituent is keto (i.e., =O), it means that 2 hydrogen atoms are replaced. Keto substituents are not present on aromatic moieties. The term "optionally substituted" means that the designated atom can be substituted or unsubstituted, and unless otherwise stated, the species and number of the substituents may be arbitrary provided that they can be achieved in Chemistry.

When any variable (e.g., R) occurs more than once in the constituent or structure of a compound, its definition at each occurrence is independent. Thus, for example, if a group is substituted with 0-2 Rs, then said group may optionally be substituted with up to two R groups and R at each occurrence has independent options. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating via which atom such substituent is bonded to the compound of a general formula including unspecified ones, then such substituent may be bonded via any atom therein. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Substituents of the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents," and they can be one or more selected from, but not limited to the following groups: -R', -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', NR' C(O)NR"R"', -NR"$C(O)_2$R', -NR""'-C(NR'R"R'")=NR"", NR"" C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", NR"SO_2R', -CN, –NO_2, -N_3, -$CH(Ph)_2$, and fluoro(C_1-C_4)alkyl, with a number of substitutents ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"', R"" and R""' are each preferably independently hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', R"" and R""' groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion on substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups constituted by carbon atoms bonding to groups other than hydrogen groups, such as haloalkyl (e.g., -CF_3 and –CH_2CF_3) and acyl (e.g., -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3, and the like).

Similar to the substituents described for the alkyl radical, substituents of the aryl and heteroaryl groups are generically referred to as "aryl group substituents." The substituents are selected from, for example: -R', -OR', -NR'R", -SR', -halogen, -SiR'R"R"', OC(O)R', -C(O)R', -CO2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', NR' C(O)NR"R"', -NR"$C(O)_2$R', -NR""'-C(NR'R"R'")=NR"", NR"" C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", NR"SO_2R', -CN, –NO_2, -N_3, -$CH(Ph)_2$,

fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, etc., with a number of substitutents ranging from zero to the total number of open valences on the aromatic ring; where R', R", R"', R"" and R""' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', R"" and R""' groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula –T-C(O)-(CRR')q-U-, wherein T and U are independently selected from –NR-, -O-, -CRR'- or a single bond, and q is an integer from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula –A(CH_2)rB-, wherein A and B are independently selected from –CRR'-, -O-, -NR-, -S-, -S(O)-, $S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer from 1 to 4. One of the single bonds of the thus formed new ring may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula –A(CH_2)rB-, where s and d are separately and independently selected from integers from 0 to 3, and X is –O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or –$S(O)_2$NR'-. The substituents R, R', R" and R'" are separately, preferably and independently selected from hydrogen and substituted or unsubstituted (C_1-C_6)alkyl.

The term "hydrocarbyl" or its hyponyms (such as alkyl, alkenyl, alkynyl and phenyl etc.) by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated, and may be mono-, di-, or multi-substituted, and can include di- or multi-valent radicals, having the designated number of carbon atoms (e.g., C_1-C_{10} meaning one to ten carbons). "Hydrocarbyl" include, but are not limited to, aliphatic hydrocarbyl and aromatic hydrocarbyl, and the aliphatic hydrocarbyl include linear and cyclic ones, specifically including but not limited to, alkyl, alkenyl, and alkynyl, and the aromatic hydrocarbyl include, but are not limited to, 6-12 membered aromatic hydrocarbyl, for example, benzene, and naphthalene, etc. In some embodiments, the term "alkyl" means a straight or branched chain radical, or combinations thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals. Examples of saturated hydrocarbon radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, isobutyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of radicals such as n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, butenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

The term "heterohydrocarbyl" or its hyponymshyponyms (such as heteroalkyl, heteroalkenyl, heteroalkynyl and heteroaryl etc.) by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In some embodiments, the term "heteroalkyl," by itself or in combination with another term, means a stable straight or branched chain hydrocarbyl radical, or combinations

thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In a typical embodiment, the heteroatoms are selected from the group consisting of B, O, N and S, wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) B, O, N and S may be placed at any internal position of the heterohydrocarbyl group (except the position at which the hydrocarbyl group is attached to the remainder of the molecule). Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

The terms "cyclohydrocarbyl," "heterocyclohydrocarbyl" or "cyclohydrocarbylheteroyl" or its hyponyms (such as aryl, heteroaryl, arylheteroyl,cycloalkyl, heterocycloalkyl, cycloalkylheteroyl, cycloalkenyl, heterocycloalkenyl, cycloalkenylheteroyl, cycloalkynyl, heterocycloalkynyl and cycloalkynylheteroyl, etc.) by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "hydrocarbyl," "heterohydrocarbyl" or "hydrocarbylheteroyl," respectively. Additionally, for heterohydrocarbyl or heterocyclohydrocarbyl (such as heteroalkyl and heterocycloalkyl), a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Non-limiting examples of heterocycle moieties include 1 –(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuranindol-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1–piperazinyl, and 2-piperazinyl.

The term "halo" or "halogen," by themselves or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, the term "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic substituent that may be mono-, di- or poly-substituted, and can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms. In an exemplary embodiment, the heteroatom is selected from B, N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents of any of the above-described aryl and heteroaryl ring systems are selected from the acceptable substituents

described below.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthio, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom, e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like.

"Ring or cyclo" means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The so-called ring includes fused ring moieties. The number of atoms in a ring is typically defined as the number of members of the ring. For example, a "5- to 7-membered ring" means there are 5 to 7 atoms in the encircling arrangement. Unless otherwise specified, the ring optionally includes one to three heteroatoms. Thus, the term "5- to 7-membered ring" includes, for example phenyl, pyridinyl and piperidinyl. The term "5- to 7-membered heterocycloalkyl ring," on the other hand, include pyridinyl and piperidinyl, but not phenyl. The term "ring" further includes a ring system comprising at least one ring, wherein each "ring" is independently defined as above.

As used herein, the term "heteroatom" includes atoms other than carbon (C) and hydrogen (H), including e.g., oxygen (O), nitrogen (N) sulfur (S), silicon (Si), germanium (Ge), aluminum (Al) and boron (B), etc.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction (such as a nucleophilic substitution reaction). For example, representative leaving groups include triflate, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "protecting group" includes but is not limited to "amino-protecting group," "hydroxy-protecting group" or "thiol-protecting group." The term "amino-protecting group" means a protecting group suitable for preventing side reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl, trichloroacetyl or trifluoroacetyl; alkoxycarbonyl groups, such as tert-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS); and the like. The term "hydroxy-protecting group" means a protecting group suitable for preventing side reactions at a hydroxy group. Representative hydroxy-protecting groups include, but are not limited to, alkyl groups, such as methyl, ethyl, and tert-butyl; acyl groups, for example alkanoyl groups, such as acetyl; arylmethyl groups, such as benzyl (Bn), p-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM); silyl groups, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS); and the like.

Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy,

and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. 3-7 cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. The term "Halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

The term "heterocycle" or "heterocyclo" is intended to mean a stable monocyclic or bicyclic or bicyclic heterocyclic ring which may be saturated, partially unsaturated or unsaturated (aromatic), and include carbon atoms and 1, 2, 3, or 4 ring heteroatoms independently selected from the group consisting of N, O and S in which any of the above-defined heterocyclic rings may be fused to a benzene ring to form a bicyclic group. The nitrogen and sulfur heteroatoms may optionally be oxidized (i. e., NO and S (O) p). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or other substituents already defined herein). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on a carbon or on a nitrogen atom if the resultant compound is stable. A nitrogen atom in the heterocycle may optionally be quaternized. In a preferred embodiment, when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. In another preferred embodiment, the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group"or "heteroaryl" is intended to mean a stable 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, or 10-membered bicyclic heterocyclic aromatic ring which includes carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting of N, O and S. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or other substituents already defined herein). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., NO and S (O) p). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is to be noted that a bridge always converts a monocyclic ring into a tricyclic ring. In a bridged ring, the substituents on the ring may also be present on the bridge.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1, 5,2-dithiazinyl, dihydrofuro [2, 3-b] tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl,

pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2, 4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2, 3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds.

The compounds of the present invention can be prepared in a number of synthetic methods known to one skilled in the art, including the specific embodiments described below, the embodiments formed by combining them with other chemical synthetic methods known in the art, andequivalents well known to those skilled in the art. Preferred embodiments include, but are not limited to, examples of the invention.

All solvents used herein are commercially available and are used without further purification. Reactions are typically run in anhydrous solvents under an inert atmosphere of nitrogen. Proton NMR data are recorded on Bruker Avance III 400 (400 MHz) spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Agilent 1200 series plus 6110 (& 1956A). LC/MS, or Shimadzu MS includes a DAD:SPD-M20A (LC) and Shimadzu Micromass 2020 detector. The mass spectrometer is equipped with an electrospray ion source (ESI) operated in a positive or negative mode.

The following abbreviations are used herein: aq represents aqueous; HATU represents *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate; EDC represents *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, *m*-CPBA represents 3-chloroperoxybenzoic acid; eq. represents equivalent; CDI represents carbonyl diimidaole; DCM represents dichloromethane; PE represents petroleum ether; DIAD represents diisopropyl azodicarboxylate; DMF represents *N*,*N*-dimethylformamide; DMSO represents dimethylsulfoxide; EtOAc represents ethyl acetate; EtOH represents ethanol; MeOH represents methanol; CBz represents benzyloxycarbonyl, a amine protecting group; BOC represents *tert*-butylcarbonyl, an amine protecting group; HOAc represents acetic acid; $NaCNBH_3$ represents sodium cyanoborohydride; r.t. represents room temperature; O/N represents overnight; THF represents tetrahydrofuran; Boc_2O represents di-*tert*-butyl dicarbonate; TFA represents trifluoroacetic acid; DIPEA represents diisopropylethylamine; $SOCl_2$ represents sulfurous dichloride; CS_2 represents carbon disulfide; TsOH represents 4-methylbenzenesulfonic acid; NFSI represents *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide; NCS represents *N*-chlorosuccinimide; *n*-Bu_4NF represents tetrabutylammonium fluoride; *i*-PrOH represents 2-propanol and mp represents melting point.

Compounds were named either manually or by using ChemDraw®, or using vendors catalogue name if commercially available.

HPLC analyses werere performed on a Shimadzu LC20AB system with a Shimadzu SIL-20A Autosampler and a Shimadzu DAD:SPD-M20A Detector. The column used was a Xtimate™ C18, 3 μm, 2.1 x 300 mm. Method 0-60AB_6 min included: applying a linear gradient, starting elution at 100% A (A: 0.0675% TFA in water) and ending elution at 60% B (B: 0.0625% TFA in MeCN) overall for 4.2 min and then eluting at 60% B for 1.0 min. The column was then re-equilibrated over 0.8 min to 100:0 with a total run time of 6 min. Method 10-80AB_6 min included: applying a linear gradient, starting elution at 90% A (A: 0.0675% TFA in water) and

ending elution at 80% B (B: 0.0625% TFA in MeCN) overall for 4.2 min and then eluting at 80% B for 1.0 min. The column was then re-equilibrated over 0.8 min to 90:10 with a total run time of 6 min. The column temperature was at 50 °C with a flow rate of 0.8 mL/min. The Diode Array Detector scanned from 200-400 nm.

Thin layer chromatography (TLC) was performed on Silica gel GF254 from Sanpont-group and UV was typically used to visualize the spots. Additional visualization methods were also employed in some cases. In these cases the TLC plate was developed with iodine (prepared by adding approximately 1 g of I_2 to 10 g silica gel and thoroughly mixing), vanillin (prepared by dissolving about 1 g vanillin in 100 mL 10% H_2SO_4), ninhydrin (available commercially from Aldrich), or Magic Stain (prepared by thoroughly mixing $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, 5 g $(NH_4)_2Ce(IV)(NO_3)_6$, 450 mL H_2O and 50 mL concentrated H_2SO_4) to visualize the compound. Flash chromatography was performed using 40-63 μm (230-400 mesh) silica gel from Silicycle following analogous techniques to those disclosed in Still, W. C.; Kahn, M.; and Mitra, M. Journal of Organic Chemistry, 1978, 43, 2923-2925. Typical solvents used for flash chromatography or thin layer chromatography were mixtures such as dichloromethane/methanol, ethyl acetate/methanol and hexanes/ethyl acetate.

Preparative chromatography was performed on a Gilson-281 Prep LC 322 System using a Gilson UV/VIS-156 Detector. The column used was a Agella Venusil ASB Prep C18, 5 μm, 150 x 21.2 mm or Phenomenex Gemini™ C18, 5 μm, 150 x 30 mm or Boston Symmetrix™ C18, 5 μm, 150 x 30 mm or Phenomenex Synergi™ C18, 4 μm, 150 x 30 mm. Narrow gradients with acetonitrile/water, with the water containing 0.05% HCl or 0.25% HCOOH or 0.5% $NH_3\bullet H_2O$, were used to elute the compounds at a flow rate of approximately 25 mL/min and a total run time of 8 - 15 min.

SFC analyses were performed on an Agilent 1260 Infinity SFC system with an Agilent 1260 Autosampler and an Agilent DAD:1260 Detector. The column used was Chiralcel™ OD-H 250 x 4.6 mm I.D., 5um or Chiralpak™ AS-H 250 x 4.6mm I.D., 5 μm or Chiralpak™ AD-H 250 x 4.6 mm I.D., 5um. Method OD-H_5_40_2.35ML Column included: Chiralcel™ OD-H 250 x 4.6 mm I.D., 5 μm Mobile phase: 40% ethanol (0.05% DEA) in CO_2 Flow rate: 2.35 mL/min Wavelength: 220 nm. Method AS-H_3_40_2.35ML Column included: Chiralpak™ AS-H 250 x 4.6 mm I.D., 5 μm Mobile phase: 40% methanol (0.05% DEA) in CO_2 Flow rate: 2.35 mL/min Wavelength: 220 nm. Method OD-H_3_40_2.35M Column included: Chiralcel™ OD-H 250 x 4.6 mm I.D., 5 μm Mobile phase: 40% methanol (0.05% DEA) in CO_2 Flow rate: 2.35 mL/min Wavelength: 220 nm. Method AD-H_2_50_2.35ML Column included: Chiralpak™ AD-H 250 x 4.6 mm I.D., 5 mm Mobile phase: 50% methanol (0.1% MEA) in CO_2 Flow rate: 2.35 mL/min Wavelength: 220 nm.

Preparative SFC analysis was performed on a Waters Thar 80 Pre-SFC System using a Gilson UV Detector. The column used was Chiralcel™ OD-H 250 x 4.6 mm I.D., 5 m or Chiralpak™ AD-H 250 x 4.6mm I.D., 5m. Narrow gradients with ethanol or methanol in CO_2, with the ethanol or methanol containing 0.05% $NH_3\bullet H_2O$ or 0.05% DEA or 0.1% MEA, were used to elute the compound at a flow rate between 40-80 mL/min and a total run time between 20-30 min.

The PARP-1 inhibitors provided herein can be used for the treatment of wide rages of diseases comprising cancer, stroke, cardiac ischemia, inflammation, and diabetes. The PARP-1 inhibitors can be used as a standalone agent or in combination with other chemotherapeutical agents to enhance the effect of these standard chemotherapeutical agents.

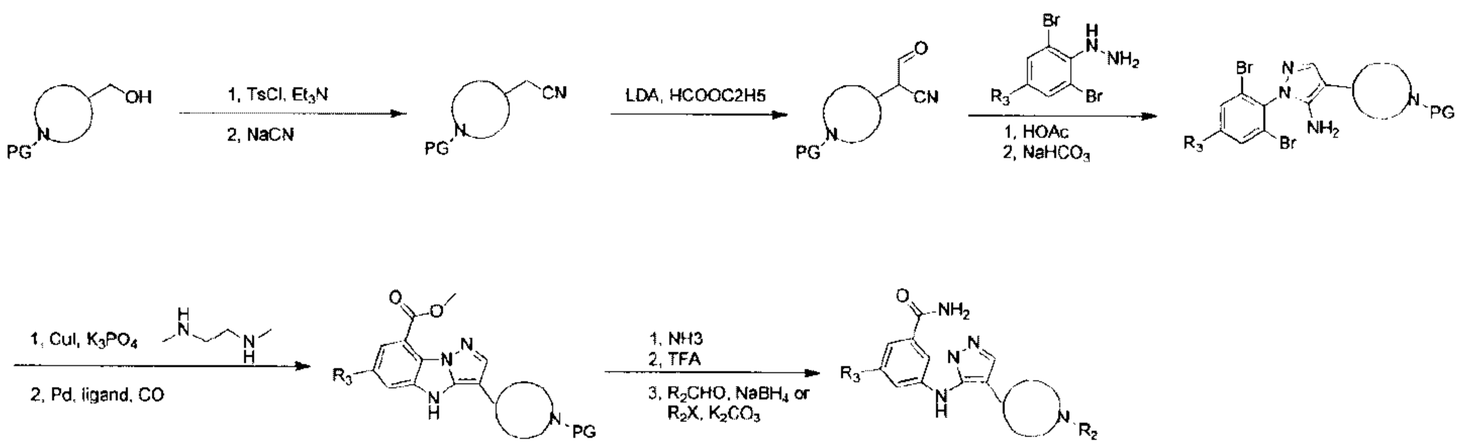
Cancers that can be treated by the PARP-1 inhibitors include, but are not limited to breast

cancer, ovarian cancer, pancreatic cancer, prostate cancer, clone cancer, and leukemia, etc.

DETAILED DESCRIPTION OF THE INVENTION

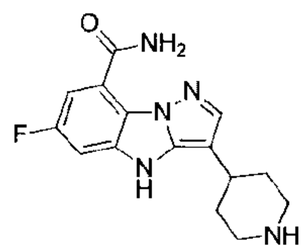
To describe the present invention in more detail, the following examples are provided. However, the scope of the present invention is not limited to these.

Scheme A



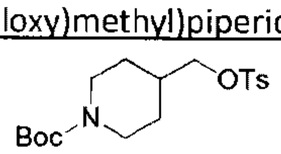
Example 1

6-fluoro-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 1A

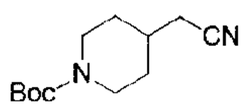
tert-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (10 g, 46.5 mmol), Et_3N (5.64 g, 55.8 mmol) and DMAP (1.13 g, 9.3 mmol) in DCM (100 mL) was added in protions TosCl (9.73 g, 51.2 mmol) at 0℃ under N_2 atmosphere. After stirring at 17℃ for 2 h, water (100 mL) was added to quench. The aqueous layer was extracted with DCM (100 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by column chromatography to give the title compound (17 g, 99% yield) as a white solid. LCMS (ESI) m/z: 370 (M+1).

Example 1B

tert-butyl 4-(cyanomethyl)piperidine-1-carboxylate

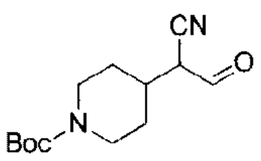


A mixture of **EXAMPLE 1A** (19 g, 55.7 mmol), sodium cyanide (8.19 g, 167 mmol) in

dimethylsulfoxide (100 mL) was reacted at 100℃ for 16 h. After being cooled to room temperature, the mixture was diluted with water (200ml). The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with water (50 mL), and brine (50 mL), then dried over Na_2SO_4, filtered and evaporated to provide the title compound (11 g) which could be used directly in the next step without further purification. LCMS (ESI) m/z: 225 (M+1)

Example 1C

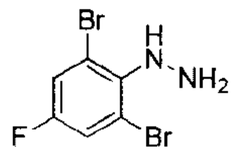
tert-butyl 4-(1-cyano-2-oxoethyl)piperidine-1-carboxylate



To a mixture of **EXAMPLE 1B** (11 g, 49 mmol), t-BuOK (32.9 g, 294 mmol) in DMF (80 mL) was added dropwise a solution of ethyl formate (21.7 g, 294 mmol) in DMF(50 mL) at -10℃ under N_2 atmosphere. After the dropwise addition completed, the mixture was stirred at 17℃ for 16 h, and then neutralized with 1N HCl. The aqueous layer was extracted with EtOAc (100mL x 4). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound (11g, 89%) which could be used directly in the next step without further purification. LCMS (ESI) m/z: 253 (M+1)

Example 1D

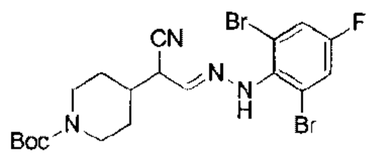
(2,6-dibromo-4-fluorophenyl)hydrazine



To a solution of 2,6-dibromo-4-fluoroaniline (5 g, 18.6 mmol) in 35 ml 20% aq HCl (35 mL) was added dropwise a solution of $NaNO_2$ (1.41 g, 20.45 mmol) in water (40 mL) at -5℃ with a rate of the dropwise addition to keep the internal temperature below 5℃. After 0.5h, the above-mentioned solution was added dropwise into a solution of $SnCl_2$ (10.49 g, 46 mmol) in concentrate HCl solution (40 mL) at -15℃. After the dropwise addition completed, the mixture was allowed to warm to 35℃ and stirred for 12 h. The mixture was cooled to 0℃ and adjusted to pH=9 with concentrate ammonia aqueous solution. The aqueous layer was extracted with EtOAc (150 mL x 3). The organic layers were washed with water (100 mL), dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by column chromatography to provide the title compound (4 g, yield :76%). ^{1}H NMR (400 MHz, CDCl3-d): δ ppm 3.91(br.s.,1H), 5.37(br.s.,1H), 7.31 (d, J=7.37Hz, 2H).

Example 1E

tert-butyl 4-(1-cyano-2-(2-(2,6-dibromo-4-fluorophenyl)hydrazono)ethyl)piperidine-1-carboxylate

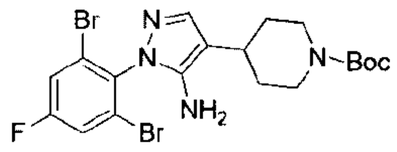


A mixture of **EXAMPLE 1C** (3.5 g, 13.87 mmol) and **EXAMPLE 1D** (3.94 g, 13.87 mmol) in EtOH (30 mL) was stirred at 80℃ for 0.5h. After removal of solution in vacuum, the residue was purified

by column chromatography to provide the title compound as a white solid (3.8 g, 53%). LCMS (ESI) m/z: 519 (M+1).

Example 1F

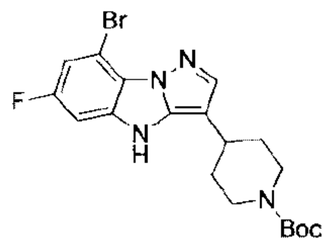
tert-butyl 4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazol-4-yl)piperidine-1-carboxylate



A mixture of **EXAMPLE 1E** (3.8 g, 7.33 mmol) and Et_3N (1.48 g, 14.67 mmol) in EtOH (30 mL) was stirred at 80℃ for 16h. The mixture was evaporated under vacuum to provide the title compound which could be used directly in the next step without further purification. (3.8 g, 100%).

Example 1G

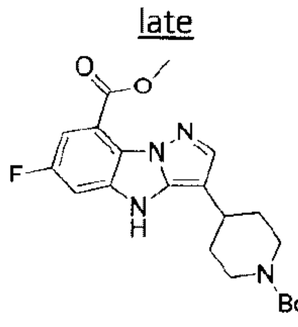
tert-butyl 4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)piperidine-1-carboxylate



A mixture of **EXAMPLE 1F** (2.4 g, 4.63 mmol), N^1,N^2-dimethylethane-1,2-diamine (40.83 mg, 0.463 mmol), CuI (88 mg, 0.463 mmol) and K_3PO_4 (983 mg, 4.63 mmol) in DMF (30 mL) was stirred at 60℃ for 1h by microwave under N_2 atmosphere. The mixture was cooled to room temperature and then filtrated through a pad of celite, and the filtrate was evaporated under vacuum to give a residue which was purified by column chromatography to provide the title compound as a white solid (0.4 g, 15%). LCMS (ESI) m/z: 437, 439 (M, M+2).

Example 1H

methyl 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxylate

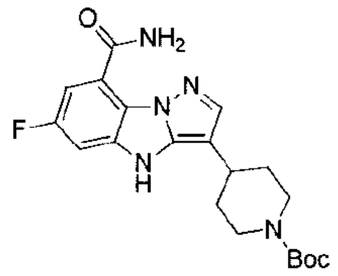


A mixture of **EXAMPLE 1G** (200 mg, 0.457 mmol), $Pd(OAc)_2$ (10.27 mg, 0.0457 mmol), $Pd(dppf)Cl_2$ (33.46 mg, 0.0457 mmol), Xantphos (53 mg, 0.0914 mmol), DPPP (38 mg, 0.0914 mmol), PPh_3 (24 mg, 0.0914 mmol) and Et_3N (232 mg, 2.29 mmol) in DMF (40 mL) and MeOH (20 mL) was stirred at 120℃ for 12h under CO atmosphere (3 MPa). The mixture was cooled to room temperature and then filtrated through a pad of celite. The filtrate was evaporated to give the residue which was purified by column chromatography to provide the title compound as a white solid (100 mg, 52%). LCMS (ESI) m/z: 417 (M+1).

Example 1I

tert-butyl

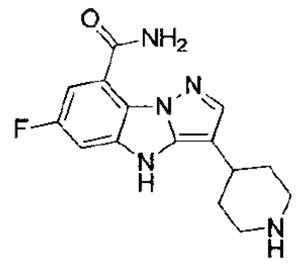
4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)piperidine-1-carboxylate



A mixture of **EXAMPLE 1H** (100 mg, 0.24 mmol) and NH_3-MeOH (30 mL) in DMF (100 mL) was reacted at 120℃ for 16h in a closed tube. The mixture was cooled and then removed of solution in vacuum, and the residue was purified by column chromatography to provide the title compound as a white solid (70 mg, 73%). LCMS (ESI) m/z: 402 (M+1).

Example 1J

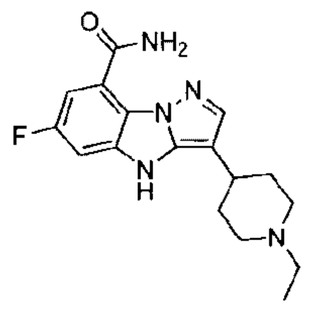
6-fluoro-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixed solution of EXAMPLE 1I (70 mg, 0.174 mmol) in DCM (3 mL) and TFA (1 mL) was stirred at 15℃ for 1h, and removed of solution in vacuum. The residue was purified by prep-HPLC to provide the title compound (25 mg, 49%). ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.93-1.96 (m, 2 H), 2.37 – 2.36 (d, 2 H), 3.09 – 3.22 (m, 3 H), 3.31 – 3.53 (t, 2 H), 7.37 - 7.39 (m, 1 H), 7.68-7.74 (m, 2 H). LCMS (ESI) m/z: 302 (M+1).

Example 2

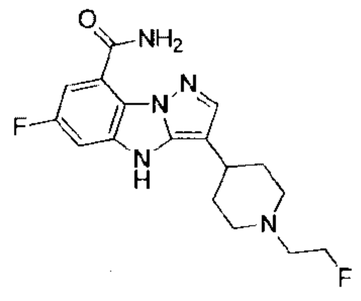
3-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of **EXAMPLE 1J** (750 mg, 2.49 mmol) and acetaldehyde (1.1 g, 24.9 mmol) in MeOH (15 mL) was stirred at 50℃ for 0.5h. Thereafter, $NaCNBH_3$ (3.13 g, 49.8 mmol) was added thereto. The resulting mixture was stirred at 50℃ for 16h. After removal of solution in vacuum, the residue was purified by column chromatography to provide the title compound as a white solid.(563.1 g, 69%). ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.31-1.34 (t, 3 H), 1.94-1.97 (m, 2 H), 2.27-2.31 (d, 2 H), 2.82 (t, 2 H), 2.97-3.02 (m, 3H), 3.47-3.48 (d, 2 H), 7.34-7.37 (m, 1 H), 7.67-7.72 (m, 2 H). LCMS (ESI) m/z: 330 (M+1).

Example 3

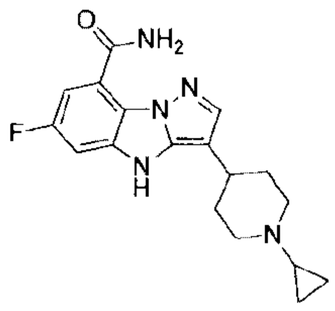
6-fluoro-3-(1-(2-fluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of **EXAMPLE 1J** (112 mg, 0.372 mmol), 1-bromo-2-methoxyethane (71 mg, 0.558 mmol) and potassium carbonate (154 mg, 1.116 mmol) in acetonitrile (20 mL) was stirred at 40℃ for 16 hours. The mixture was cooled and filtrated, and the filtrate was evaporated under vacuum to give a residue which was purified by prep-HPLC to provide the title compound (4.6 mg, 3.6%). ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.94 - 2.15 (m, 2 H), 2.17 - 2.37 (m, 2 H), 2.86 - 3.07 (m, 3 H), 3.27 - 3.32 (m, 1 H), 3.35 - 3.39 (m, 1 H), 3.46 - 3.61 (m, 2 H), 4.71 - 4.80 (m, 1 H), 4.89 (br. s., 1 H), 7.28 - 7.41 (m, 1 H), 7.60 - 7.76 (m, 2 H), 8.24 - 8.69 (m, 1 H). LCMS (ESI) m/z: 348 (M+1).

Example 4

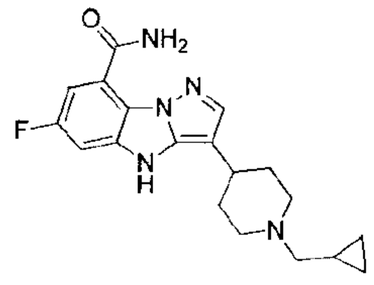
3-(1-cyclopropylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of (1-ethoxycyclopropoxy)trimethylsilane (115 mg, 0.663 mmol), **EXAMPLE 1J** (40 mg, 0.133 mmol), HOAc (79 mg, 1.33 mmol) and $NaCNBH_3$ (83 mg, 1.33 mmol) in MeOH (10 mL) was stirred at 66℃ for 7 h. The mixture was cooled and then removed of solution in vacuum, and the residue was purified by prep-HPLC to provide the title compound (19.6 mg, 43%). ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 0.70-0.79 (m, 4 H), 1.84-1.92 (m, 2 H), 2.18-2.28 (t, 3 H), 2.85-2.94 (m, 3 H), 3.42-3.45 (d, 2H), 7.33-7.35 (m, 1 H), 7.65-7.68 (m, 2H), 8.395 (s, 1 H). LCMS (ESI) m/z: 342 (M+1).

EXAMPLE 5

3-(1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

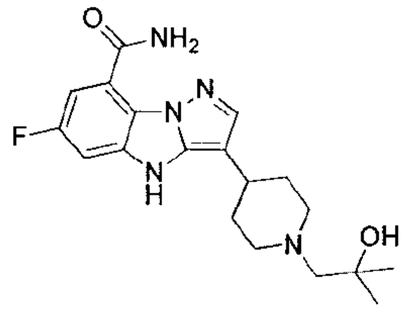


A mixture of **EXAMPLE 1J** (12 mg, 0.04 mmol), cyclopropanecarbaldehyde (5.58 mg, 0.08mmol) and $NaCNBH_3$ (50 mg, 0.8 mmol) in MeOH (2 mL) was stirred at 10℃ for 16 h. Thereafter, tetraisopropoxytitanium (17 mg, 0.06 mmol) was added thereto and continuously stirred for 1 hour. After removal of solution in vacuum, the residue was purified by prep-HPLC to provide the title compound (5.2 mg, 37%). ^{1}H NMR (400 MHz, METHANOL-d4) □ ppm 0.40-0.44 (m, 2H),

0.75-0.79 (m, 1H), 1.12-1.13 (m, 1H), 2.04 (s, 2H), 2.32-2.36 (d, 2H), 2.9-3.12 (m, 5 H), 3.68 (s, 2H), 7.36-7.39 (m, 1 H), 7.68-7.73 (m, 2 H), 8.50 (s, 1H). LCMS (ESI) m/z: 356 (M+1).

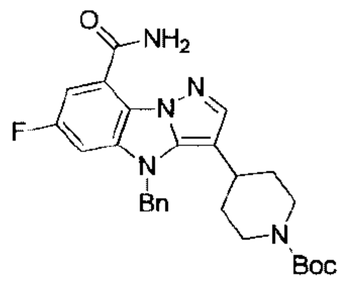
Example 6

6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



EXAMPLE 6A

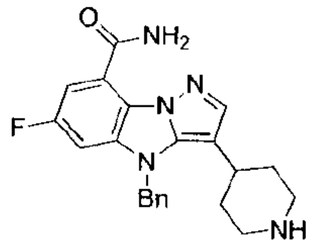
tert-butyl 4-(4-benzyl-8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)piperidine-1-carboxylate



A mixture of **EXAMPLE 1I** (100 mg, 0.25 mmol), (bromomethyl)benzene (127 mg, 0.748 mmol) and potassium carbonate (103 mg, 0.748 mmol) in acetonitrile (4 mL) was stirred at 60℃ for 4 hours. The mixture was cooled and filtered and the filtrate was evaporated under vacuum to give a residue which was purified by silica gel chromatography to provide the title compound (112.6 mg, 91.8%). LCMS (ESI) m/z: 492 (M+1).

Example 6B

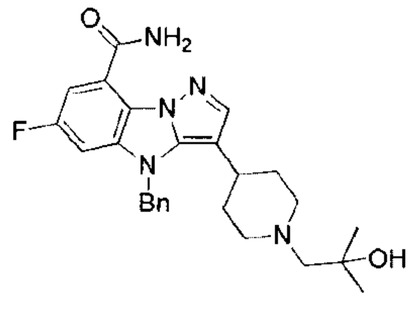
4-benzyl-6-fluoro-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture solution of **EXAMPLE 6A** (112.6 mg, 0.229 mmol) in DCM (9 mL) TFA (3 mL) was stirred at 12℃ for 2 hours. After removal of solution in vacuum, the title compound (115 mg, 100%) was provided as yellow solid which could be used directly in the next step without further purification. LCMS (ESI) m/z: 392 (M+1).

Example 6C

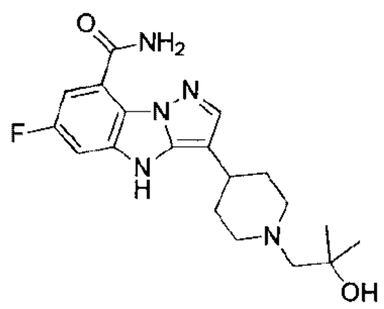
4-benzyl-6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of **EXAMPLE 6B** (115 mg, 0.229 mmol), 2,2-dimethyloxirane（50 mg, 0.690 mmol）and Et_3N (116 mg, 1.15mmol) in ethanol (5ml) was heated at 120℃ under microwave for 1 hour. The mixture was cooled and removed of solution in vacuum, and then the residue was purified by silica gel chromatography to provide the title compound. LCMS (ESI) m/z: 464 (M+1).

Example 6D

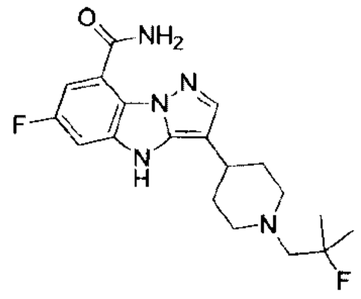
6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of **EXAMPLE 6C** (32 mg, 0.069mmol) and Pd/C (25 mg) in Methanol (30 mL) was hydrogenated at 50℃ for 4 hours under H_2 (1 atm). The mixture was cooled and filtered, and the filtrate was evaporated under vacuum. Thereafter the residue was purified by prep-HPLC to provide the title compound (8.2 mg, 32.2%). ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.38 (s, 6 H), 2.10 - 2.30 (m, 4 H), 3.12 (s, 5 H), 3.57 - 3.73 (m, 2 H), 7.29 - 7.39 (m, 1 H), 7.61 - 7.69 (m, 1 H), 7.69 - 7.75 (m, 1 H), 8.54 (br. s., 1 H). LCMS (ESI) m/z: 374 (M+1).

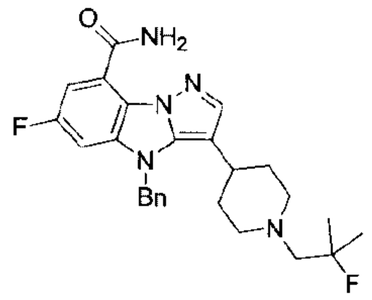
Example 7

6-fluoro-3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 7A

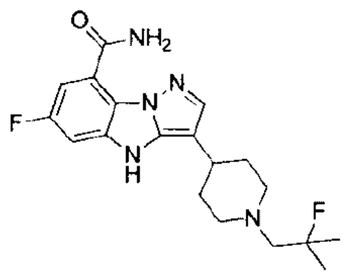
4-benzyl-6-fluoro-3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



To a mixture of **EXAMPLE 6C** (32 mg, 0.069 mmol) in DCM (10 mL) was added dropwise a solution of DAST（33 mg, 0.207 mmol） in DCM (2 mL) at 0℃ under N_2 atmosphere. After the dropwise addition was completed, the mixture was stirred at 17℃ for 16h, and then quenched with saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel chromatography to provide the title compound (27 mg, 84.4%). LCMS (ESI) m/z: 466 (M+1).

Example 7B

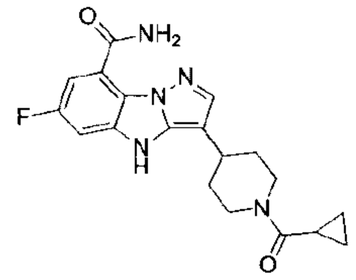
6-fluoro-3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of **EXAMPLE 7A** (27 mg, 0.058mmol) and Pd/C (30 mg) in Methanol (20 mL) was hydrogenated at 45℃ for 16 hours under H_2 (1 atm). The mixture was cooled and filtered and the filtrate was evaporated. The residue was purified by prep-HPLC to provide the title compound (2.1 mg, 10%). ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.42 (s, 3 H), 1.48 (s, 3 H), 1.90 - 2.03 (m, 2 H), 2.04 - 2.16 (m, 2 H), 2.51 - 2.67 (m, 2 H), 2.72 - 2.90 (m, 3 H), 3.23 - 3.31 (m, 2 H), 7.32 - 7.41 (m, 1 H), 7.63 - 7.75 (m, 2 H), 8.27 - 8.59 (m, 1 H). LCMS (ESI) m/z: 376 (M+1)

Example 8

3-(1-(cyclopropylcarbonyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

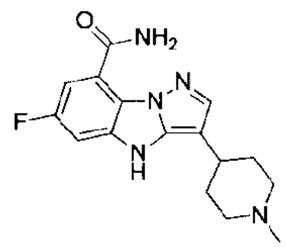


A mixture of **EXAMPLE 1J** (52 mg, 0.125 mmol), cyclopropanecarboxylic acid (13 mg, 0.150 mmol), Et_3N (50.5 mg, 0.5 mmol) and HATU (47.5 mg, 0.125 mmol) in acetonitrile (5 mL) was stirred at 50℃ for 3 hours. After the mixture was cooled and removed of solution in vacuum, the residue was purified by prep-HPLC to provide the title compound (12.7 mg, 27.3%). LCMS: 370 [M+1]. ^{1}H NMR (400 MHz, DMSO-d_6) ppm 0.72 (d, J=7.53 Hz, 4 H), 1.42 - 1.69 (m, 2 H), 1.88 - 2.07 (m, 3 H), 2.65 - 2.77 (m, 1 H), 2.86 - 2.98 (m, 1 H), 3.14 - 3.29 (m, 1 H), 4.26 - 4.50 (m, 2 H), 7.43 - 7.50 (m,

1 H), 7.51 - 7.59 (m, 1 H), 7.76 (s, 1 H). LCMS (ESI) m/z: 370 (M+1).

Example 9

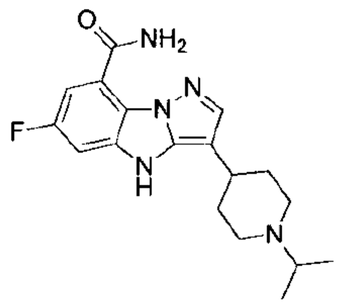
6-fluoro-3-(1-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.98-2.01 (d, 2 H), 2.29-2.31 (d, 2 H), 2.83 (s, 1 H), 3.01-3.04 (d, 2 H), 3.48 (d, 2H), 7.36-7.39 (m, 1 H), 7.68-7.73 (m, 2 H), 8.49 (s, 1 H). LCMS (ESI) m/z: 316 (M+1).

Example 10

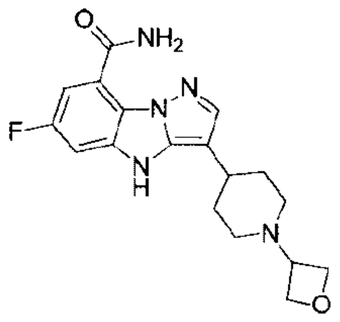
6-fluoro-3-(1-isopropylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.38-1.40 (d, 6 H), 2.02-2.05 (d, 2 H), 2.36-2.40 (d, 2 H), 3.06 (m, 1 H), 3.19-3.22 (t, 2H), 3.51-3.55 (m, 3 H), 7.35-7.38 (m, 1 H), 7.66-7.72 (m, 2 H), 8.51(s, 1 H). LCMS (ESI) m/z: 344 (M+1).

Example 11

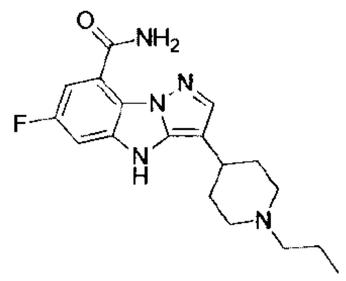
6-fluoro-3-(1-(oxetan-3-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.79 (m, 2 H), 1.82 - 1.99 (m, 4 H), 2.58 - 2.69 (m, 1 H), 2.70 - 2.81 (m, 2 H), 3.36 - 3.45 (m, 1 H), 4.45 (s, 2 H), 4.51 - 4.58 (m, 2 H), 7.36 - 7.44 (m, 1 H), 7.45 - 7.53 (m, 1 H), 7.65 - 7.75 (m, 1 H). LCMS (ESI) m/z: 358 (M+1).

Example 12

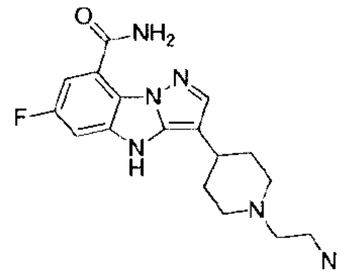
6-fluoro-3-(1-propylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, METHANOL-d4) δ ppm 1.02-1.06 (t, 3H), 1.76-1.82 (m, 2 H), 2.00-2.03 (d, 2 H), 2.31-2.34 (d, 2 H), 3.01-3.05 (m, 5 H), 3.57-3.58 (d, 2 H), 7.36-7.39 (m, 1 H), 7.68-7.73 (m, 2 H), 8.51(s, 1 H). LCMS (ESI) m/z: 344 (M+1).

Example 13

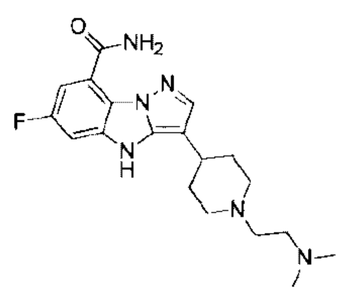
3-(1-(2-aminoethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.80 - 1.98 (m, 2 H), 2.06 - 2.17 (m, 2 H), 2.30 - 2.46 (m, 2 H), 2.68 - 2.85 (m, 3 H), 3.05 - 3.19 (m, 4 H), 7.30 - 7.38 (m, 1 H), 7.69 (br. s., 2 H), 8.28 - 8.67 (m, 1 H). LCMS (ESI) m/z: 345 (M+1).

Example 14

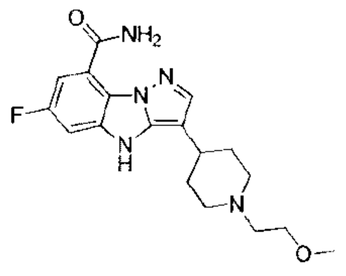
3-(1-(2-(dimethylamino)ethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.83 - 1.98 (m, 2 H), 2.05 - 2.18 (m, 2 H), 2.36 - 2.48 (m, 2 H), 2.68 (s, 6 H), 2.80 (t, *J*=6.46 Hz, 3 H), 2.97 - 3.07 (m, 2 H), 3.11 - 3.25 (m, 2 H), 7.25 - 7.40 (m, 1 H), 7.57 - 7.75 (m, 2 H). LCMS (ESI) m/z: 373 (M+1).

Example 15

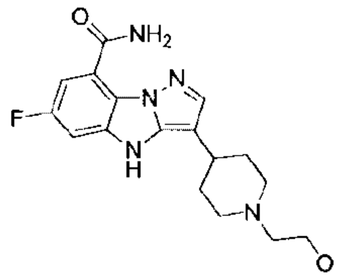
6-fluoro-3-(1-(2-methoxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d4) ppm 2.00 - 2.18 (m, 2 H), 2.22 - 2.38 (m, 2 H), 2.94 - 3.08 (m, 1 H), 3.08 - 3.22 (m, 2 H), 3.33 - 3.38 (m, 2 H), 3.44 (s, 3 H), 3.56 - 3.70 (m, 2 H), 3.71 - 3.82 (m, 2 H), 7.19 - 7.38 (m, 1 H), 7.53 - 7.64 (m, 1 H), 7.68 (s, 1 H), 8.42 - 8.66 (m, 1 H). LCMS (ESI) m/z: 360 (M+1).

Example 16

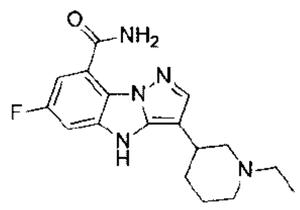
6-fluoro-3-(1-(2-hydroxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 2.04 - 2.20 (m, 2 H), 2.25 - 2.37 (m, 2 H), 2.98 - 3.10 (m, 1 H), 3.12 - 3.24 (m, 2 H), 3.25 - 3.31 (m, 2 H), 3.62 - 3.75 (m, 2 H), 3.89 - 3.99 (m, 2 H), 7.25 - 7.38 (m, 1 H), 7.57 - 7.66 (m, 1 H), 7.69 (s, 1 H), 8.50 - 8.62 (m, 1 H). LCMS (ESI) m/z: 346 (M+1).

Example 17

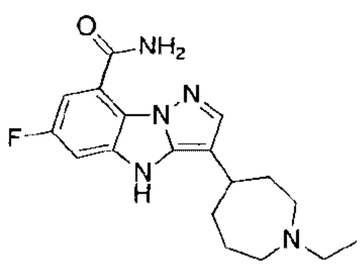
3-(1-ethylpiperidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 1 and 2, substituting tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.38 (t, 3 H), 1.85-2.00 (m, 2 H), 2.13-2.26 (m, 2 H), 2.94-3.03 (m, 2 H), 3.21-3.24 (m, 3 H), 3.59-3.73 (m, 2 H), 7.37-7.39 (dd, 1 H), 7.66-7.69 (dd, 1 H), 7.76 (s, 1 H), 8.52 (bs, 1 H). LCMS (ESI) m/z: 331 (M+1).

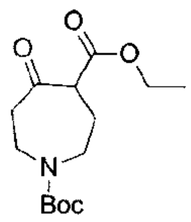
Example 18

3-(1-ethylazepan-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 18A

1-tert-butyl 4-ethyl 5-oxoazepane-1,4-dicarboxylate

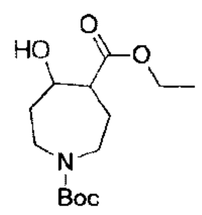


To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (50 g, 251 mmol) and BF_3-Et_2O (49.86 g,

351 mmol) in THF (500 ml) was added dropwise ethyl 2-diazo (40.09 g, 351 mmol) at -40℃ under N_2 atmosphere. After the dropwise addition was completed, the mixture was stirred at -40℃ for 2h and then warmed to 15℃ and stirred for 16h. After the reaction completed, the mixture was quenched with K_2CO_3 aqueous solution (500 mL). The aqueous layer was extracted with EtOAc (500 mL x 2). The combined organic layers were washed with water, and brine, thereafter dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph on silica gel to provide the title compound (45 g, yield: 63%). LCMS (ESI) m/z: 286 (M+1).

Example 18B

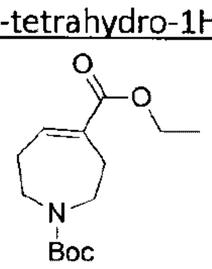
1-tert-butyl 4-ethyl 5-hydroxyazepane-1,4-dicarboxylate



To a solution of **EXAMPLE 18A** (45 g, 157.7 mmol) in MeOH (420 ml) was added $NaBH_4$ (7.16 g, 189 mmol) in portions at 0℃. After stirring at 0℃ for 1 h, the resultant mixture was quenched with water (400 mL) and the aqueous phase was extracted with EtOAc (400 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph on silica gel to provide the title compound (22.3 g, yield:49%). LCMS (ESI) m/z: 288 (M+1).

Example 18C

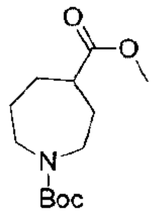
1-tert-butyl 4-ethyl 2,3,6,7-tetrahydro-1H-azepine-1,4-dicarboxylate



To a solution of **EXAMPLE 18B** (21 g, 73 mmol), DBU (22 g, 146 mmol) in toluene (200 mL) was added dropwise MsCl (14.56 g, 128 mmol). After the dropwise addition was completed, the mixture was stirred at 110℃ for 2 h, and cooled to room temperature, and then water (200 mL) was added to quench. The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph on silica gel to provide the title compound (13 g, yield:66%). LCMS (ESI) m/z: 270 (M+1).

Example 18D

1-tert-butyl 4-methyl azepane-1,4-dicarboxylate

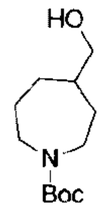


A mixture of **EXAMPLE 18C** (13 g, 48.27 mmol) and Pd/C (1 g) in MeOH (130 mL) was hydrogenated at 15℃ for 16h under H_2 (1 atm). The mixture was filtered and the filtrate was

evaporated to provide the title compound which could be used directly in the next step without further purification (10.7 g, yield: 82%). LCMS (ESI) m/z: 258 (M+1).

Example 18E

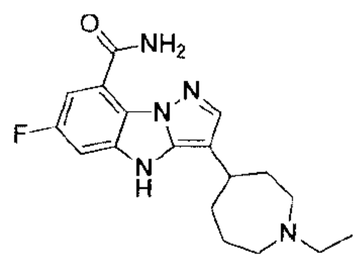
tert-butyl 4-(hydroxymethyl)azepane-1-carboxylate



To a solution of **EXAMPLE 18D** (10.7 g, 39 mmol) in THF (200 mL) was added $LiAlH_4$ (1.48 g, 39 mmol) in portions at 0℃. After stirring at 0℃ for 30 mins, the resultant mixture was quenched with water (10 mL), 15% aq NaOH (10 mL), water (30 mL). The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatograph on silica gel to provide the title compound (7 g, yield: 77%). LCMS (ESI) m/z: 230 (M+1).

Example 18F

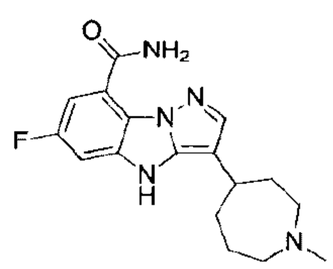
3-(1-ethylazepan-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 1 and 2, substituting tert-butyl 4-(hydroxymethyl)azepane-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.38-1.42 (t, 3 H), 1.93-1.96 (m, 2 H), 1.99-2.12 (m, 2 H), 2.32-2.34 (m, 2 H), 3.15-3.30 (m, 1 H), 3.32-3.33 (m, 2 H), 3.33-3.53 (m, 4 H), 7.38-7.40 (dd, 1 H), 7.69-7.73 (dd, 1 H), 7.74 (s, 1 H), 8.50 (bs, 1 H). LCMS (ESI) m/z: 344 (M+1).

Example 19

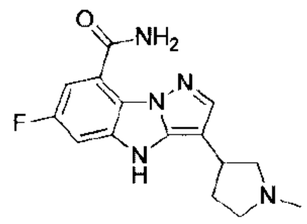
6-fluoro-3-(1-methylazepan-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 18. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.95-2.10 (m, 3 H), 2.26-2.35 (m, 3 H), 2.96 (s, 1 H), 3.14-3.17 (m, 1 H), 3.36-3.49 (m, 4 H), 7.38-7.40 (dd, 1 H), 7.69-7.72 (dd, 1 H), 7.74 (s, 1 H), 8.47 (bs, 1 H). LCMS (ESI) m/z: 330 (M+1).

Example 20

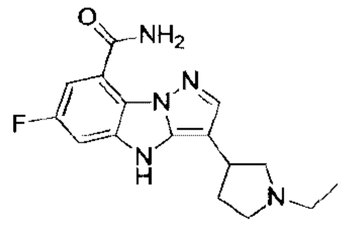
6-fluoro-3-(1-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 1 and 2, substituting tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (MeOD, 400 MHz) δ: 2.29-2.35 (m, 1 H), 2.59-2.62 (m, 1 H), 2.99 (s, 3 H), 3.32-3.36 (m, 1 H), 3.53-3.55 (m, 2 H), 3.76-3.81 (m, 2 H), 7.40-7.42 (dd, 1 H), 7.70-7.73 (dd, 1 H), 7.80 (s, 1 H), 8.50 (bs, 1 H). LCMS (ESI) m/z: 302 (M+1).

Example 21

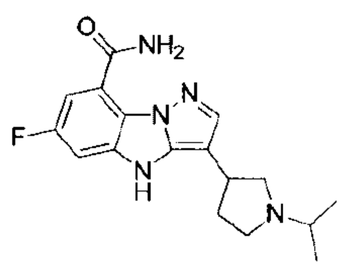
3-(1-ethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 20, substituting tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (MeOD, 400 MHz) δ: 2.29-2.35 (m, 1 H), 2.59-2.62 (m, 1 H), 2.99 (s, 3 H), 3.32-3.36 (m, 1 H), 3.53-3.55 (m, 2 H), 3.76-3.81 (m, 2 H), 7.40-7.42 (dd, 1 H), 7.70-7.73 (dd, 1 H), 7.80 (s, 1 H), 8.50 (bs, 1 H). LCMS (ESI) m/z: 316 (M+1).

Example 22

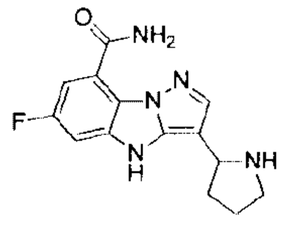
6-fluoro-3-(1-isopropylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 20, substituting tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.42-1.44 (d, 6 H), 2.25-2.31 (m, 1H), 2.57-2.60 (m, 1 H), 3.32-3.33 (m, 1 H), 3.44-3.55 (m, 3 H), 3.68-3.71 (m, 1 H), 7.41-7.43 (dd, 1 H), 7.71-7.74 (dd, 1 H), 7.82 (s, 1 H), 8.55 (bs, 1 H). LCMS (ESI) m/z: 330 (M+1).

Example 23

6-fluoro-3-(pyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

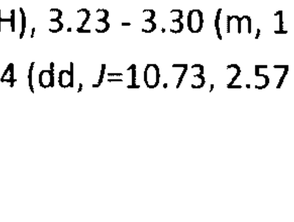


This example was prepared as described in Example 1, substituting tert-butyl

2-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 2.17 - 2.31 (m, 1 H), 2.33 - 2.51 (m, 2 H), 2.52 - 2.67 (m, 1 H), 3.48 (t, *J*=7.28 Hz, 2 H), 7.40 (dd, *J*=8.03, 2.26 Hz, 1 H), 7.65 (dd, *J*=10.79, 2.26 Hz, 1 H), 7.94 (s, 1 H), 8.55 (br. s., 1 H). LCMS (ESI) m/z: 288 (M+1).

Example 24

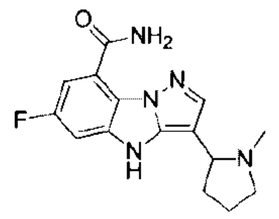
6-fluoro-3-(1-propylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 2, substituting tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.93 (t, *J*=7.34 Hz, 3 H), 1.54 - 1.79 (m, 2 H), 2.23 (d, *J*=5.02 Hz, 2 H), 2.37 - 2.53 (m, 2 H), 2.76 (br. s., 1 H), 3.05 (br. s., 2 H), 3.65 (br. s., 1 H), 4.31 (br. s., 1 H), 7.44 (dd, *J*=8.09, 2.32 Hz, 1 H), 7.73 (dd, *J*=10.92, 2.38 Hz, 1 H), 7.94 (s, 1 H), 8.54 (br. s., 1 H). LCMS (ESI) m/z: 330 (M+1).

Example 25

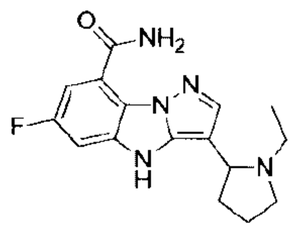
6-fluoro-3-(1-methylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 2, substituting tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 2.25 - 2.41 (m, 2 H), 2.47 - 2.67 (m, 2 H), 2.82 (s, 3 H), 3.23 - 3.30 (m, 1 H), 3.66 - 3.79 (m, 1 H), 4.50 - 4.58 (m, 1 H), 7.43 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.64 (dd, *J*=10.73, 2.57 Hz, 1 H), 7.95 - 8.02 (m, 1 H), 8.52 (br. s., 1 H). LCMS (ESI) m/z: 302 (M+1).

Example 26

3-(1-ethylpyrrolidin-2-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

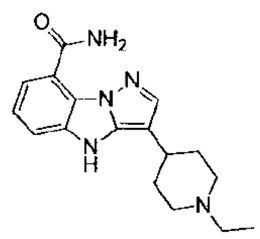


This example was prepared as described in Example 2, substituting tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.30 (t, *J*=7.28 Hz, 3 H), 2.26 - 2.37 (m, 2 H), 2.46 - 2.61 (m, 2 H), 2.98 - 3.09 (m, 1 H), 3.25 (d, *J*=10.29 Hz,

2 H), 3.68 - 3.80 (m, 1 H), 4.55 (t, *J*=8.78 Hz, 1 H), 7.42 (dd, *J*=8.16, 2.26 Hz, 1 H), 7.64 (dd, *J*=10.73, 2.32 Hz, 1 H), 7.97 (s, 1 H), 8.54 (br. s., 1 H). LCMS (ESI) m/z: 316 (M+1).

Example 27

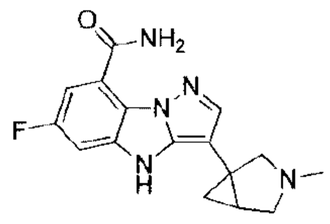
3-(1-ethylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 1, substituting (2,6-dibromophenyl)hydrazine for (2,6-dibromo-4-fluorophenyl)hydrazine. ^{1}H-NMR (400 MHz, METHANOL-d4) δ ppm 1.16-1.20 (t, 3H), 1.84-1.87 (m, 2H), 2.07-2.11 (d, 2H), 2.16-2.19 (d, 2H), 2.51-2.56 (q, 2H), 2.70-2.75 (m, 1H), 3.11-3.13 (d, 2H), 7.40-7.44 (t, 1 H), 7.61-7.63 (m, 1 H), 7.70 (s, 1H), 7.99-8.02 (m, 1 H). LCMS (ESI) m/z: 312 (M+1).

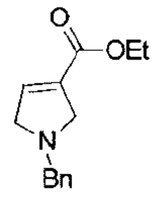
Example 28

6-fluoro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 28A

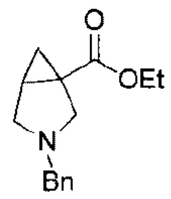
ethyl 1-benzyl-2,5-dihydro-1H-pyrrole-3-carboxylate



To a solution of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (4.5 g, 61 mmol) and ethyl propiolate (5.0 g, 51 mmol) in DCM (150 mL) was added dropwise Et_3N (0.4 mL, 5.2 mmol) at 0℃. After the dropwise addition was completed, the reaction mixture was stirred at 0℃ for 1h and warmed to 20℃ and stirred for 24h, and then quenched with saturated $NaHCO_3$ (100 mL). The aqueous phase was extracted with DCM (250 mL x 2). The combined organic layers were washed with brine (150 mL x 2) and dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (10 g, yield: 80%) as a yellow oil. LCMS (ESI) m/z: 232 (M+1).

Example 28B

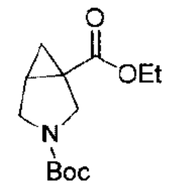
ethyl 3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylate



To a mixture of $(CH_3)_3SOI$ (21.5 g, 97.7 mmol) in DMSO (150 mL) was added portion wise 60% NaH (3.5 g, 87.5 mmol) at 0℃-5℃ under N_2 atmosphere. After the addition was completed, the mixture was stirred at 19℃ for 2h, and thereafter a solution of EXAMPLE 28A (9 g, 38.9 mmol) was added thereto portionwise at 0℃-5℃. The mixed reaction solution was stirred at 19℃ for 15h, and then quenched with saturated $NaHCO_3$ (300 mL). The aqueous phase was extracted with DCM (500 mL x 2). The combined organic layers were washed with brine (200 mL x 2) and dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (5.4 g, yield: 32%) as a yellow oil. LCMS (ESI) m/z: 246 (M+1).

Example 28C

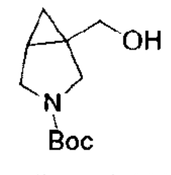
3-tert-butyl 1-ethyl 3-azabicyclo[3.1.0]hexane-1,3-dicarboxylate



A mixture of EXAMPLE 28B (5.4 g, 22 mmol), BOC_2O (10 g, 46 mmol) and 10% Pd/C (600 mg) in MeOH (100 mL) was hydrogenated at 19℃ for 15h under H_2 (1 atm). The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatograph to provide the title compound (5.3 g, yield: 94%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (t, J=4.96 Hz, 1 H), 1.25 (t, J=7.15 Hz, 3 H), 1.39 - 1.48 (m, 9 H), 1.56 (dd, J=8.34, 4.58 Hz, 1 H), 1.79 (s, 1 H), 1.94 - 2.10 (m, 1 H), 3.41 (dd, J=10.73, 3.45 Hz, 1 H), 3.50 - 3.82 (m, 3 H), 4.07 - 4.19 (m, 2 H), 4.25 (d, J=7.15 Hz, 1 H), 5.05 (s, 1 H), 6.61 (t, J=1.88 Hz, 1 H), 7.14 (s, 1 H), 7.28 - 7.38 (m, 1 H)

Example 28D

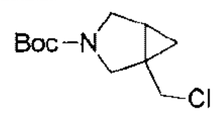
tert-butyl 1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate



A mixture of EXAMPLE 28C (5.3 g, 20.7 mmol) and 1N LiOH (50 mL, 50 mmol) in THF (25 mL) and MeOH (50 mL) was stirred at 60℃ for 2 hours. The mixture was cooled to room temperature and thereafter extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (50 mL x 2), brine (50 mL x 2), dried over Na_2SO_4 and evaporated to give the residue. The residue was dissolved in THF (100 mL), and thereto was added dropwise 10M BH_3-DMS (10 mL, 100 mmol) at 0℃ under N_2 atmosphere. After the dropwise addition was completed, the mixture was stirred at 19℃ for 15h, and after completion of the reaction quenched with MeOH (100 mL). The solution was evaporated under vacuum. The residue was purified by column chromatograph to provide the title compound (3.5 g, yield: 89%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.51 (br. s., 1 H, 0.78 (dd, J=8.09, 5.08 Hz, 1 H), 1.37 - 1.47 (m, 10 H), 3.42 (d, J=10.29 Hz, 2 H, 3.48 - 3.78 (m, 4 H).

Example 28E

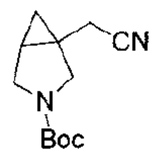
tert-butyl 1-(chloromethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate



To a mixture of EXAMPLE 28D (3.5 g, 16.43 mmol), DMAP (200 mg, 1.6 mmol) and Et_3N (5 mL, 36.14 mmol) in DCM (100 mL) was added portionwise TosCl (3.7 g, 19.47 mmol) at 0℃. After being stirred at 24℃ for 15h, the mixture ws quenched with water (100 mL). The aqueous layer was extracted with DCM (250 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (2.6 g, yield: 68%), as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.68 (t, J=4.64 Hz, 1 H), 0.90 (dd, J=8.16, 5.27 Hz, 1 H), 1.39 - 1.55 (m, 10 H), 3.36 - 3.46 (m, 2 H), 3.48 - 3.77 (m, 4 H).

Example 28F

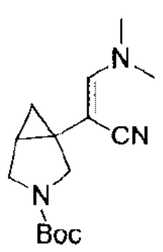
tert-butyl 1-(cyanomethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate



A mixture of EXAMPLE 28E (2.6 g, 11 mmol), NaCN (1.57 g, 32 mmol) and KI (1.87 g, 11 mmol) in DMSO (40 mL) was stirred at 100-120℃ for 2h. After being cooled to room temperature, the mixture was partitioned between EtOAc (200 mL) and Na_2CO_3 aqueous solution (120 mL). The aqueous layer was extracted with EtOAc (100mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (2.4 g, yield: 96%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.47 - 0.72 (m, 1 H), 0.81 - 0.96 (m, 1 H), 1.34 - 1.55 (m, 10 H), 2.53 - 2.80 (m, 2 H), 3.30 (d, J=10.54 Hz, 1 H), 3.38 - 3.84 (m, 1 H). LCMS (ESI) m/z: 167 (M-55).

Example 28G

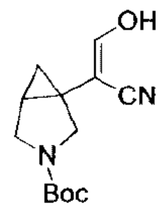
tert-butyl 1-(1-cyano-2-(dimethylamino)vinyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate



A mixture of 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (3.8 g, 21.8 mmol) and EXAMPLE 28F (2.4 g, 10.8 mmol) in DMF (20 mL) was stirred at 70 ℃ for about 10 h. After being cooled to room temperature, the resultant mixture was evaporated off solvent under vacuum to provide the title compound which could be used directly in the next step without further purification.

Example 28H

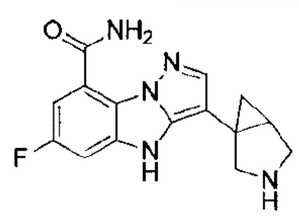
tert-butyl 1-(1-cyano-2-hydroxyvinyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate



A solution of EXAMPLE 28G (3.0 g, crude, 10.8 mmol) in a mixture of THF/HOAc/Water (1/1/1) (45 mL) was stirred at 24℃ for 5h. After removal of solution in vacuum, the residue was partitioned between saturated $NaHCO_3$ (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (100 mL x 2), brine (100 mL x 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound (1.4 g, yield: 52%) as a yellow oil. LCMS (ESI) m/z: 195 (M-55).

Example 28I

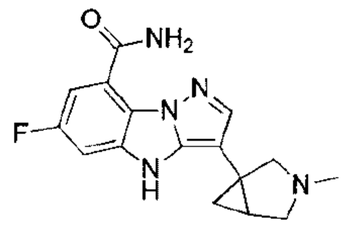
3-(3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in EXAMPLEs 1E-1J.

Example 28J

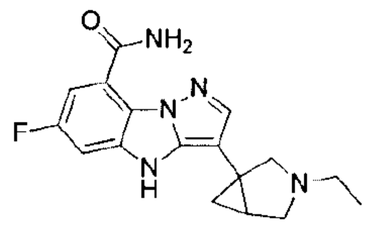
6-fluoro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, Methanol-d_4) δ ppm 1.32 (d, J=6.40 Hz, 2 H), 2.05 (td, J=6.37, 3.95 Hz, 1 H), 2.93 (s, 3 H), 3.47 (d, J=11.04 Hz, 1 H), 3.59 (dd, J=11.11, 3.83 Hz, 1 H), 3.67 - 3.76 (m, 1 H), 3.85 (d, J=11.04 Hz, 1 H), 7.32 (dd, J=8.16, 2.51 Hz, 1 H), 7.58 (dd, J=10.79, 2.51 Hz, 1 H), 7.77 (s, 1 H), 8.52 (s, 1 H). LCMS (ESI) m/z: 314 (M+1).

Example 29

3-(3-ethyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

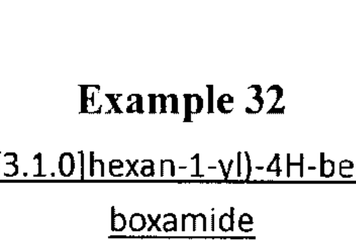


This example was prepared as the method described in Example 28. ^{1}H-NMR (400 MHz, Methanol-d_4) δ ppm 1.27 - 1.37 (m, 5 H), 1.95 - 2.11 (m, 1 H), 3.22 (q, J=7.19 Hz, 2 H), 3.41 (d, J=10.92 Hz, 1 H), 3.48 - 3.57 (m, 1 H), 3.69 (s, 1 H), 3.86 (d, J=10.92 Hz, 1 H), 7.33 (dd, J=8.16, 2.51

Hz, 1 H), 7.64 (dd, J=10.85, 2.57 Hz, 1 H), 7.79 (s, 1 H), 8.51 (s, 1 H). LCMS (ESI) m/z: 328 (M+1).

Example 30

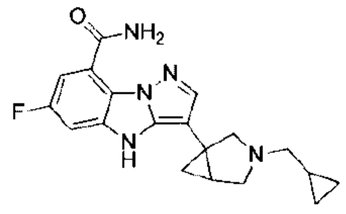
3-(3-cyclobutyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 28. ^{1}H-NMR (400 MHz, DMSO-d_6+ D_2O) 0.77 (dd, J=7.91, 4.14 Hz, 1 H), 1.22 (t, *J*=4.14 Hz, 1 H), 1.51 - 1.68 (m, 3 H), 1.77 - 1.96 (m, 4 H), 2.47 (br. s., 2 H), 2.88 (d, *J*=8.78 Hz, 1 H), 2.98 - 3.13 (m, 2 H), 7.44 (dd, *J*=8.41, 2.51 Hz, 1 H), 7.52 (dd, *J*=10.98, 2.57 Hz, 1 H), 7.71 (s, 1 H). LCMS (ESI) m/z: 354 (M+1).

Example 31

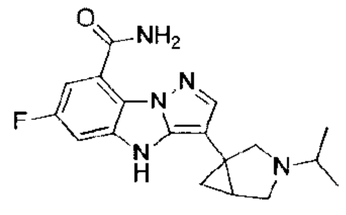
3-(3-(cyclopropylmethyl)-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 28. ^{1}H NMR (400 MHz, METHANOL-d4) □ ppm 0.32-0.35 (m, 2 H), 0.65-0.68 (m, 2 H), 1.06 (m, 1 H), 1.16-1.19 (m, 1 H), 1.39-1.42 (t, 1 H), 1.92 – 1.94 (m, 1 H), 2.84-2.85 (d, 2 H), 3.18-3.21 (m, 1 H), 3.56-3.59 (d, 2 H), 3.73-3.75 (d, 2 H), 7.35-7.39 (dd, 1 H), 7.68-7.71 (dd, 1 H), 7.78 (s, 1 H), 8.55 (s, 1 H). LCMS (ESI) m/z: 354 (M+1).

Example 32

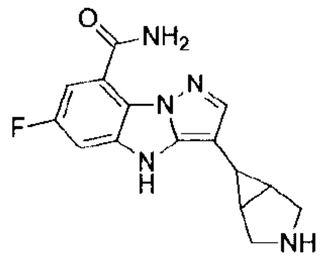
6-fluoro-3-(3-isopropyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 28. ^{1}H-NMR (400 MHz, MethanoL-d_4) 1.25 - 1.43 (m, 8 H), 2.00 - 2.15 (m, 1 H), 3.39 (s, 1 H), 3.49 (d, J=11.04 Hz, 1 H), 3.62 (d, J=3.89 Hz, 1 H), 3.71 (s, 1 H), 3.90 (d, J=10.92 Hz, 1 H), 7.29 - 7.40 (m, 1 H), 7.64 (dd, J=10.85, 2.57 Hz, 1 H), 7.79 (s, 1 H), 8.52 (br. s., 1 H). LCMS (ESI) m/z: 342 (M+1).

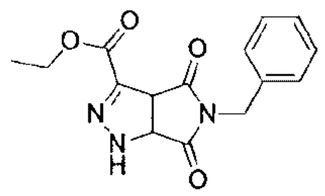
Example 33

3-(3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 33A

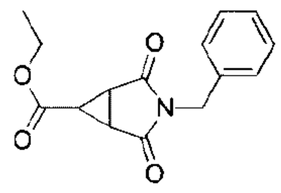
ethyl 5-benzyl-4,6-dioxo-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrazole-3-carboxylate



A mixture of 1-benzyl-1H-pyrrole-2,5-dione (5.0 g, 26.7 mmol) and 2-propionyldiazenecarbaldehyde (2.9 ml, 28.0 mmol) in toluene (30 mL) was stirred at 30℃ for 5h. After removal of solution in vacuum, the residue was purified by silica gel chromatography to provide the title compound (7.67 g, yield 95.4%). LCMS (ESI) m/z: 302 (M+1).

Example 33B

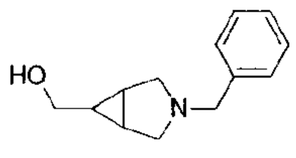
ethyl 3-benzyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate



EXAMPLE 33A (7.67 g, 25.5 mmol) was heated to 190℃ for 1 hour. The residue was purified by chromatography to provide the title compound (5.353 g, 76.9%) as white solid. LCMS (ESI) m/z: 274 (M+1).

Example 33C

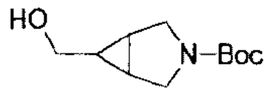
(3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl)methanol



To a suspension of $LiAlH_4$ (3.055 g, 80.4 mmol) in THF (50 mL) was added dropwise a solution of EXAMPLE 33B (5.353 g, 19.6 mmol) in 30 ml of THF at 0℃ under N_2 atmosphere. After refluxing for 16h, the reaction mixture was quenched with saturated Na_2SO_4 aqueous solution (5 mL). The organic layer was dried over Na_2SO_4, filtrated and evaporated to give the residue which was purified by chromatography to provide the title compound (1.42 g, 35.8%). LCMS (ESI) m/z: 204 (M+1).

Example 33D

tert-butyl 6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

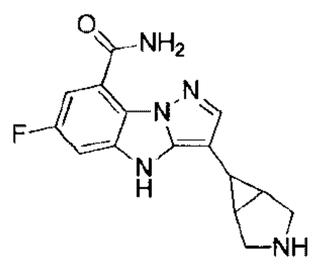


A mixture of EXAMPLE 33C (1.42 g, 7.0 mmol), Boc_2O (1.81 g, 8.4 mmol) and 10% Pd/C (200 mg)

in methanol (80 mL) was hydrogenated at 25℃ for 16h under H_2 (1 atm). The mixture was filtered and the filtrate was evaporated to give the residue which was purified by chromatography to provide the title compound **4** (1.14 g, 76%). LCMS (ESI) m/z: 214 (M+1).

Example 33E

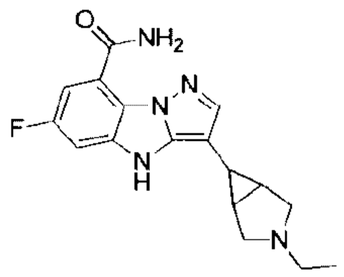
3-(3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 1E-1J. ^{1}H NMR (400 MHz, METHANOL-d4) ppm 1.86 - 1.95 (m, 1 H), 2.12 - 2.22 (m, 2 H), 3.49 - 3.65 (m, 4 H), 7.34 - 7.42 (m, 1 H), 7.64 - 7.74 (m, 2 H), 8.42 - 8.61 (m, 1 H). LCMS (ESI) m/z: 300 (M+1).

Example 34

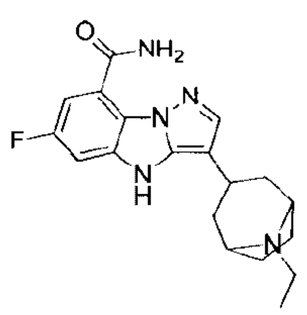
3-(3-ethyl-3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 28. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.26 (s, 3 H), 1.95 - 2.02 (m, 2 H), 2.11 - 2.18 (m, 1 H), 2.85 - 2.95 (m, 2 H), 2.96 - 3.08 (m, 2 H), 3.42 - 3.58 (m, 2 H), 7.30 - 7.38 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.65 - 7.70 (m, 1 H). LCMS (ESI) m/z: 328 (M+1).

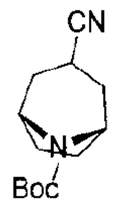
Example 35

3-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 35A

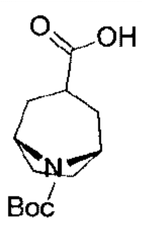
tert-butyl -3-cyano-8-azabicyclo[3.2.1]octane-8-carboxylate



To a mixture of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (10 g, 44.389 mmol) in DME (300 mL) and EtOH (6.7 mL) was added portionwise t-BuOK (20 g, 177.557 mmol) and TOSMIC (17.33 g, 88.778 mmol) at 0℃ under N_2 atmosphere. After being stirred at 60℃ for 16 h, the resultant mixture was quenched with water (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (6.08 g, yield: 57.96%) as a white solid. LCMS (ESI) m/z: 327 (M+1).

Example 35B

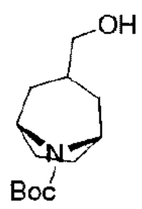
8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid



A solution of EXAMPLE 35A (6.58 g, 27.845 mmol) and KOH (9.36 g, 167.069 mmol) in a mixture of EtOH/H_2O (1:1, 200 mL) was stirred at 80℃ for 4 h. The resultant mixture was diluted with water (100 mL) and the aqueous phase was adjusted to pH 3 – 4 with 2 N HCl, and thereafter extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated to provide the title compound as a white solid which was used directly in the next step without further purification (6.01 g, yield: 84.53%).

Example 35C

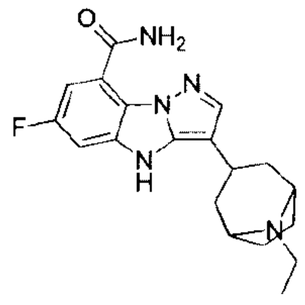
tert-butyl 3-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate



To a solution of EXAMPLE 35B (6 g, 23.529 mmol) in THF (60 mL) was added BH_3-DMS at 0℃ under N_2 atmosphere. After the mixture was stirred at 25℃ for 16h, MeOH (100 mL) was added to quench. The resultant mixture was evaporated, and the residue was purified by column chromatograph to provide the title compound (5.2 g, yield: 92.69%). LCMS (ESI) m/z: 242 (M+1).

Example 35D

3-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

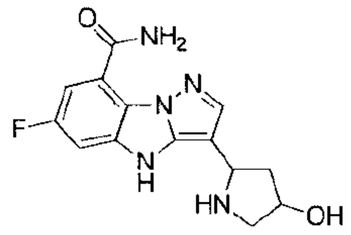


This example was prepared as described in Examples 1E-1J and 2. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.42-1.45 (t, 3 H), 2.18-2.36 (m, 8 H), 3.16-3.18 (m, 2 H), 3.36-3.42 (m, 1 H), 4.13 (s, 2 H),

7.36-7.37 (dd, 1 H), 7.61-7.66 (dd, 1 H), 7.68 (s, 1 H), 8.62 (bs, 1 H). LCMS (ESI) m/z: 356 (M+1).

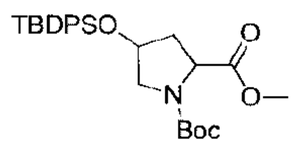
Example 36

6-fluoro-3-(4-hydroxypyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 36A

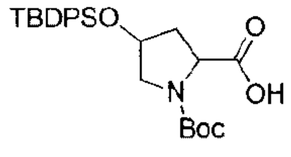
1-(tert-butyl) 2-methyl 4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate



To a mixture of 1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2 g, 8.13 mmol), imidozole (1.1 g, 16.26 mmol) in anhydrous DCM (50 mL) was added portionwise TBDPSCl (2.68 g, 9.76 mmol) at 0℃ under N_2 atmosphere. After being stirred at 15℃ for 4 hours, the reaction mixture was washed with water (10 mL x 2) and dried over Na_2SO_4, filtered and evaporated to provide the title compound (3.9 g, yield: 99%) as a courless oil which could be used directly in the next step without further purification.

Example 36B

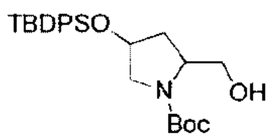
1-(tert-butoxycarbonyl)-4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-2-carboxylic acid



A mixture of EXAMPLE 36A (3.9 g, 8.1 mmol) and LiOH (1 g, 24.2 mmol) in a mixed solution of H_2O (20 mL), MeOH (5 mL) and THF (20 mL) was stirred at 15℃ for 16h. The mixture was diluted with water (50 mL) and adjusted to pH 4 – 5 with 1 N HCl, and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to provide the title compound (3.7 g, yield: 97%) which was used directly in the next step without further purification.

Example 36C

tert-butyl 4-((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate

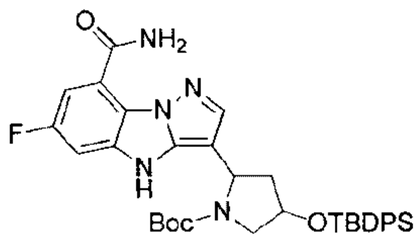


To a mixture of EXAMPLE 36B (3.7 g, 7.89 mmol), Et_3N (2.2 g, 15.8 mmol) in THF (100 mL) was added isopropyl carbonochloridate (1.2 g, 9.5 mmol) at 0℃ under N_2 atmosphere. After being stirred at 15℃ for 4h, the mixture was cooled to 0℃ and $NaBH_4$ (1.2 g, 31.56 mmol) was added thereto. The reaction mixture was stirred at 15℃ for 64 hours. After removal of solution in vacuum, the residue was partitioned between water (50 mL) and DCM (50 mL). The aqueous

layer was extracted with DCM (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (3.5 g, yield: 100%). LCMS (ESI) m/z: 456 (M+1).

Example 36D

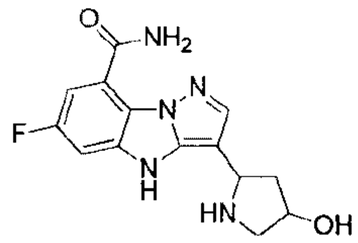
tert-butyl 4-((tert-butyldiphenylsilyl)oxy)-2-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl) pyrrolidine-1-carboxylate



This example was prepared as described in Examples 1E-1J. LCMS (ESI) m/z: 642 (M+1).

Example 36E

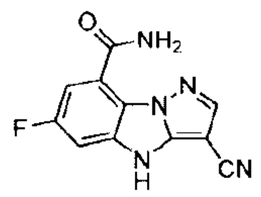
6-fluoro-3-(4-hydroxypyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 36D (50 mg, 0.078 mmol) in HBr/HOAc (0.5 mL) was stirred at 15℃ for 6 hours. The resultant mixture was evaporated, and the residue was purified by prep-HPLC to provide the title compound (10 mg, yield: 43%). ^{1}H NMR (400MHz, DMSO-d_6) = 8.36 (br. s., 1 H), 8.06 - 7.86 (m, 1 H), 7.53 (d, *J*=9.9 Hz, 2 H), 4.91 (dd, *J*=6.1, 11.5 Hz, 1 H), 4.56 (br. s., 1 H), 3.45 (d, *J*=8.8 Hz, 1 H), 3.06 (d, *J*=12.7 Hz, 1 H), 2.48 - 2.41 (m, 1 H), 2.21 (dd, *J*=5.8, 13.0 Hz, 1H). LCMS (ESI) m/z: 304 (M+1).

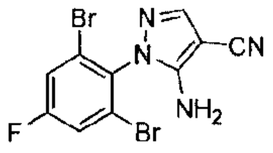
Example 37

3-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 37A

5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazole-4-carbonitrile

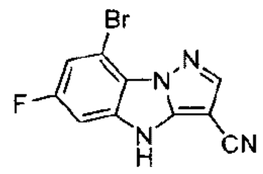


A mxiture of EXAMPLE 1D (4g, 14 mmol) and 2-(ethoxymethylene)malononitrile (2.24g, 18.31 mmol) in EtOH (30 mL) was stirred at 80℃ for 1.5h. The mixture was evaporated under vacuum to provide the title compound (2.8 g, 56%) which could be used directly in the next step

without further purification.

Example 37B

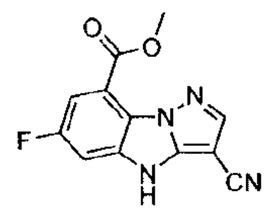
8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carbonitrile



A mixture of EXAMPLE 37A (2.8 g, 7.78 mmol), N^1,N^2-dimethylethane-1,2-diamine (68 mg, 0.777 mmol), CuI (148 mg, 0.777 mmol) and K_3PO_4 (1.65 g, 7.78 mmol) in DMF (30 mL) was stirred at 60℃ for 24h under N_2 atmosphere. The mixture was cooled to room temperature and filtered and the filtrate was evaporated to give the residue which was washed with MeOH and water and then dried under vacuum to provide the title compound (1.7g, 78%) which was used directly in the next step without further purification.

Example 37C

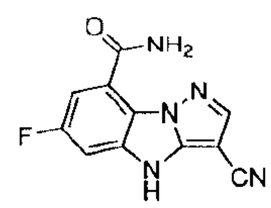
methyl 3-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxylate



A solution of EXAMPLE 37B (1 g, 3.58 mmol), $Pd(OAc)_2$ (161 mg, 0.72 mmol), $Pd(dppf)Cl_2$ (526 mg, 0.72 mmol), Xantphos (420 mg, 0.72 mmol), DPPP (296 mg, 0.72 mmol), PPh_3 (188 mg, 0.72 mmol) and Et_3N (1.8 g, 18 mmol) in DMF (30 mL) and MeOH(10 mL) was stirred at 120℃ for 12h under CO atmosphere (3 MPa). After being cooled to room temperature, the mixture was filtered and the filtrate was evaporated to give the residue which was washed with DCM and and dried. The resultant title compound (0.5 g, 54%) was used directly in the next step without further purification.

Example 37D

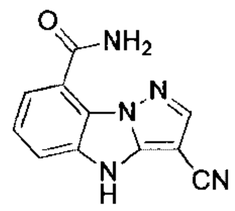
3-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 37C (20 mg, 0.077 mmol) and NH_4OH (5 mL) in DMF (1 mL) and MeOH (1mL) was stirred at 120℃ for 4h. After removal of solution in vacuum, the resultant residue was purified by prep-HPLC to provide the title compound (2.99 mg, 16%). ^{1}H- NMR (400 MHz, MeOD-d4) δ ppm 7.52(dd,J=7.91Hz,1 H), 7.80 (dd, J=10.67Hz, 1 H), 8.19 (s, 1 H). LCMS (ESI) m/z: 244 (M+1).

Example 38

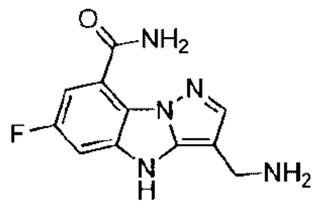
3-cyano-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 37. ^{1}H NMR (400 MHz, D2O) ppm 7.54-7.58 (t, 1H), 7.75-7.77 (d, 1 H), 8.10-8.12 (d, 1H), 8.23 (S, 1 H). LCMS (ESI) m/z: 226 (M+1).

Example 39

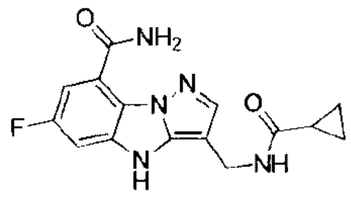
3-(aminomethyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



To a mixture of EXAMPLE 37D (100 mg, 0.4 mmol) in DCM (20 mL) and MeOH (50 mL) was added $NiCl_2$-$6H_2O$ (200 mg, 0.8 mmol) and $NaBH_4$ (47 mg, 1.2 mmol) in protions. After being stirred at 0℃ for 5 min, the reaction mixture was evaporated to give the residue which was purified by prep-HPLC to provide the title compound (45 mg, 45%). ^{1}H NMR (400 MHz, D2O) ppm 4.2 (S, 2 H), 7.269-7.318 (t, 2 H), 7.796 (S, 1 H), 8.399(S, 1 H). LCMS (ESI) m/z: 248 (M+1).

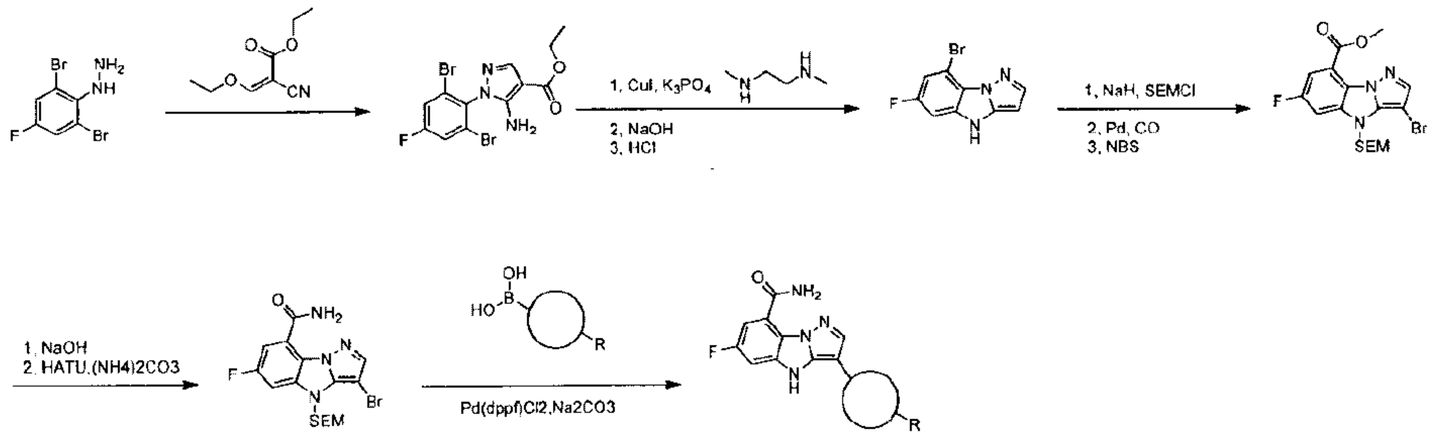
Example 40

3-(cyclopropanecarboxamidomethyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



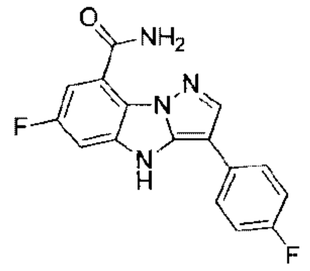
A mixture of EXAMPLE 39 (20 mg, 0.081 mmol), cyclopropanecarboxylic acid (8.36 mg, 0.098 mmol), HOBt (13.12 mg, 0.0979 mmol), EDCI (18.61 mg, 0.097 mmol) and Et_3N (25 mg, 0.242 mmol) in DMF (5 mL) was stirred at 30℃ for 6h. After removal of solution in vacuum, the residue was purified by prep-HPLC to provide the title compound (11.9mg, 48%). ^{1}H NMR (400 MHz, DMSO-d6) ppm 0.64-0.72 (m, 4 H), 1.52-1.57 (m, 1 H), 4.25-2.50 (d, 2 H), 7.57-7.61 (m, 2 H), 7.82 (s, 1 H), 8.13 (s, 1 H), 8.44-8.46 (t, 1 H), 10.46 (s, 1 H), 11.93(br, 1 H). LCMS (ESI) m/z: 316 (M+1).

Scheme B



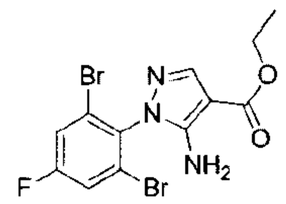
Example 41

6-fluoro-3-(4-fluorophenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 41A

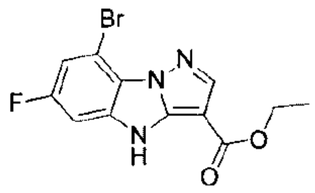
ethyl 5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazole-4-carboxylate



A mixture of EXAMPLE 1D (5 g, 17.61 mmol) and ethyl 2-cyano-3-ethoxyacrylate (2.98 g, 17.61 mmol) in EtOH (100 mL) was stirred at 78℃ for 16h. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (2.7 g, yield: 38%) which could be used directly in the next step without further purification.

Example 41B

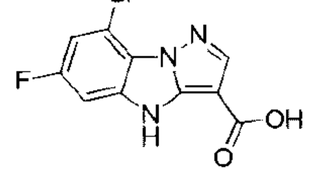
ethyl 8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carboxylate



A mixture of EXAMPLE 41A (2.7 g, 6.63 mmol), CuI (252 mg, 1.33 mmol), N^1,N^2-dimethylethane-1,2-diamine (233.9 mg, 2.65 mmol) and K_3PO_4 (4.22 g, 19.9 mmol) in DMF (60 mL) was stirred at 70℃ for 16 hours under N_2 atmosphere. After being cooled to room temperature, the mixture was filtered and the solvent was evaporated off under vacuum. The resultant residue (2.16 g) could be used directly in the next step without further purification.

Example 41C

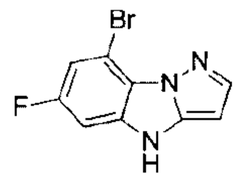
8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carboxylic acid



A mixture of EXAMPLE 41B (2.16 g, 6.62 mmol) and NaOH (1.06 g, 26.49 mmol) in MeOH (40 mL) and H_2O (10 mL) was stirred at 70℃ for 16h. After evaporation off solvent, the resultant residue could be used directly in the next step without further purification.

Example 41D

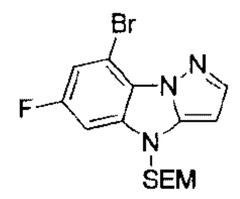
8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole



A solution of EXAMPLE 41C (1.97 g, 6.61 mmol) in a mixture of concentrate HCl (20 mL) and H_2O (20 mL) was stirred at 80℃ for 16h. After neutralized with concentrate NH_4OH, the resultant mixture was filtered. The cake was washed with MeOH and dried under vacuum. The obtained solid (1.58 g) could be used directly in the next step without further purification.

Example 41E

8-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole

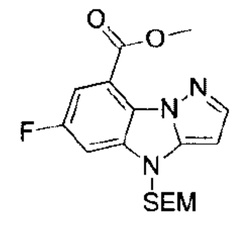


To a solution of NaH (0.746 g, 18.66 mmol) in THF (10 mL) was added a solution of EXAMPLE 41D (1.58 g, 6.22 mmol) in THF (20 mL) at 0℃ under N_2 atmosphere. The mixture was stirred at 0℃ for 0.5h, and thereafter SEMCl (1.56 g, 9.33 mmol) was added thereto. The mixture was stirred at 0℃ for another 1h and then quenched with water (20 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (0.43 g, yield: 17% for 4 steps). LCMS (ESI) m/z: 384, 386 (M, M+2).

Example 41F

methyl

6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxylate

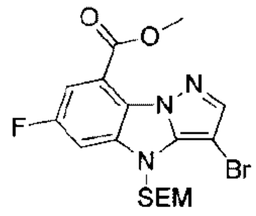


A mixture of EXAMPLE 41E (0.43 g, 1.12 mmol), $Pd(OAc)_2$ (50 mg, 0.233 mmol), $Pd(dppf)Cl_2$ (164 mg, 0.233 mmol), Xantphos (194 mg, 0.335 mmol), DPPP (138 mg, 0.335 mmol), PPh_3 (88 mg, 0.335 mmol) and Et_3N (566 mg, 5.59 mmol) in DMF (10 mL) and MeOH (10 mL) was stirred at 80℃ for 24h under CO atmosphere (3 atms). After being cooled to room temperature, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatograph to provide the title compound (0.265 g, yield: 63%). LCMS (ESI) m/z: 364 (M+1).

Example 41G

methyl

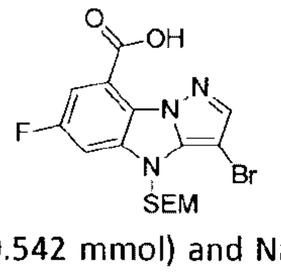
3-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxylate



A mixture of EXAMPLE 41F (0.265 g, 729 mmol) and NBS (117 mg, 656 mmol) in DCM (20 mL) was stirred at 10℃ for 20 min. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (0.24 g, yield: 75%). LCMS (ESI) m/z: 442, 444 (M, M+2).

Example 41H

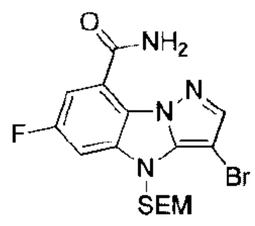
3-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxylic acid



A mixture of EXAMPLE 41G (240 mg, 0.542 mmol) and NaOH (108 mg, 2.71 mmol) in MeOH (6 mL) and H_2O (1.5 mL) was stirred at 60℃ for 0.5h. After being cooled to room temperature, the mixture was adjusted to pH 4 with 1 *N* HCl and the aqueouos phase was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to provide the title compound (196 mg, yield: 84%) which was used directly in the next step without further purification.

Example 41I

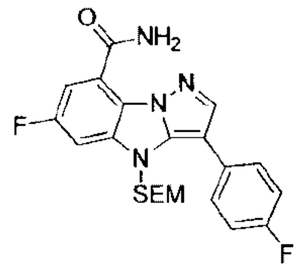
3-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 41H (0.196 g, 0.46 mmol), HATU (0.226 mg, 0.595 mmol), $(NH_4)_2CO_3$ (0.439 g, 4.6 mmol) and Et_3N (0.138 g, 1.37 mmol) in DMF (8 mL) was stirred at 40℃ for 16h under N_2 atmosphere. After removal of solution in vacuum, the residue was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatograph to provide the title compound (0.125 g, yield: 64%). LCMS (ESI) m/z: 427, 429 (M, M+2).

Example 41J

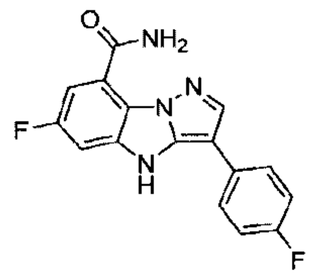
6-fluoro-3-(4-fluorophenyl)-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 41I (50 mg, 0.117 mmol), Pd (dppf)Cl_2 (17 mg, 0.023 mmol), Na_2CO_3 (31 mg, 0.292 mmol) and (4-fluorophenyl)boronic acid (24 mg, 0.175 mmol) in DMF (3 mL) and H_2O (0.5 mL) was stirred at 100℃ for 16h under N_2 atmosphere. After removal of solution in vacuum, the residue was diluted with water (10mL). The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by prep-TLC to provide the title compound (40 mg, yield: 77%). LCMS (ESI) m/z: 443 (M+1).

Example 41K

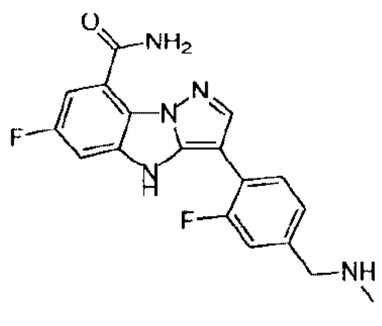
6-fluoro-3-(4-fluorophenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 41J (40 mg, 0.090 mmol) in TFA (0.5 mL) and DCM (0.5 mL) was stirred at 10℃ for 5h. After removal of the solution in vacuum, to the residue were added MeOH (3 mL) and K_2CO_3 (0.037 g, 0.271 mmol). The mixture was stirred at 10℃ for 2h. The mixture was filtered and the solvent was evaporated off under vacuum. The residue was purified by prep-HPLC to provide the title compound (6.3 mg, yield: 24%). ^{1}H NMR (400 MHz, DMSO-d6) δ: 8.32 (s, 1 H), 7.67-7.71 (m, 2 H), 7.59-7.61 (d, 1 H), 7.55-7.57 (d, 1 H), 7.22-7.27 (t, 2H). LCMS (ESI) m/z: 313 (M+1).

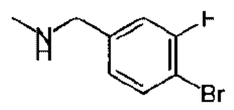
Example 42

6-fluoro-3-(2-fluoro-4-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 42A

1-(4-bromo-3-fluorophenyl)-N-methylmethanamine

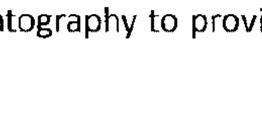


A mixture of 4-bromo-3-fluorobenzaldehyde (2 g, 9.8 mmol) and methanamine (30-40% in EtOH) (10 mL, 16.7 mmol) in EtOH (10 mL) was stirred at 75℃ for 15h. The mixture was cooled to

room temperature, and then added thereto $NaBH_4$ (745 mg, 19.6 mmol) in one portion and stirred for another 30 min. After removal of solution in vacuum, the residue was diluted with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound (1.47 g, yield: 74%). LCMS (ESI) m/z: 218, 220 (M, M+2).

Example 42B

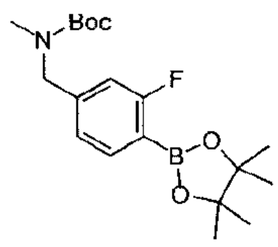
tert-butyl (4-bromo-3-fluorobenzyl)(methyl)carbamate



A mixture of EXAMPLE 42A (1.47 g, 6.77 mmol), Boc_2O (1.77 g, 8.12 mmol) and Et_3N (1.37 g, 13.54 mmol) in DCM (15 mL) was stirred at 18℃ for 2h. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (1.83 g, yield: 85%). LCMS (ESI) m/z: 319 (M+1).

Example 42C

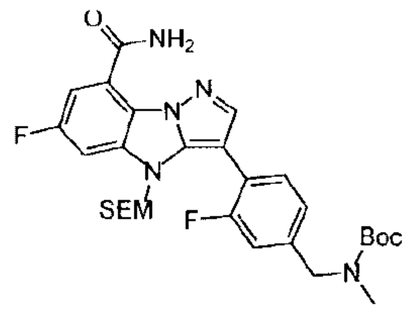
tert-butyl (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)(methyl)carbamate



A mixture of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.76 g, 6.92 mmol), EXAMPLE 42B (1.83 g, 5.77 mmol), KOAc (1.13 g, 11.54 mmol) and $Pd(dppf)Cl_2$ (422 mg, 0.577 mmol) in DMSO (15 mL) was stirred at 80℃ for 15h under N_2 atmosphere. After being cooled to room temperature, the mixture was filtered and the filtrate was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound (2 g, yield: 95%) as colorless oils.

Example 42D

tert-butyl (4-(8-carbamoyl-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-3-fluorobenzyl)(methyl)carbamate

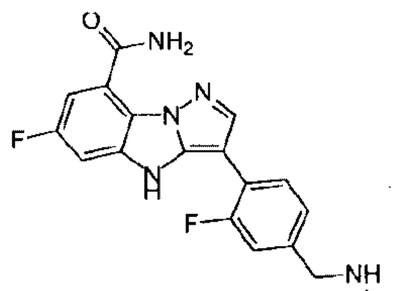


A mixture of EXAMPLE 41I (100 mg, 0.23 mmol), EXAMPLE 42C (85.7 mg, 0.23 mmol), Na_2CO_3 (50 mg, 0.47 mmol) and $Pd(dppf)Cl_2$ (17.1 mg, 0.023 mmol) in DMF (5 mL) and H_2O (1 mL) was stirred

at 80℃ for 15h under N_2 atmosphere. After being cooled to room temperature, the mixture was filtered and the filtrate was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by prep-TLC to provide the title compound (110 mg, yield: 97%). LCMS (ESI) m/z: 586 (M+1).

Example 42E

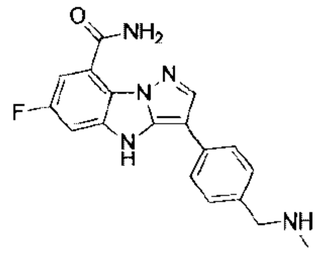
6-fluoro-3-(2-fluoro-4-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 42D (110 mg, 0.19 mmol) in TFA (5 mL) and DCM (5 mL) was stirred at 10℃ for 15h. After removal of solution in vacuum, to the residue were added MeOH (15 mL) and K_2CO_3 (53 mg, 0.38 mmol). The mixture was stirred at 18℃ for 15 h. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc /THF=3/1 (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by prep-HPLC to provide the title compound (22.45 mg, yield: 34%) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) □ ppm 2.79 (s, 3 H), 4.24 (s, 2 H), 4.48 - 5.29 (m, 27 H), 7.37 - 7.43 (m, 2 H), 7.52 (d, *J*=7.78 Hz, 1 H), 7.72 (d, *J*=9.79 Hz, 1 H), 7.78 (t, *J*=7.78 Hz, 1 H), 8.23 (s, 1 H), 8.49 (br. s., 1 H). LCMS (ESI) m/z: 356 (M+1).

Example 43

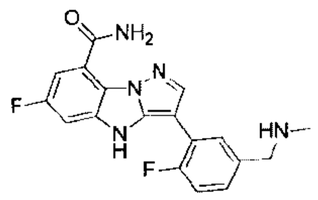
6-fluoro-3-(4-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 42. ^{1}H-NMR (400 MHz, MethanoL-d_4+D_2O) 2.77 (s, 3 H), 4.21 (s, 2 H), 7.46 - 7.62 (m, 3 H), 7.75 (d, *J*=8.16 Hz, 3 H), 8.26 (s, 1 H), 8.53 (br. s., 1 H). LCMS (ESI) m/z: 338 (M+1).

Example 44

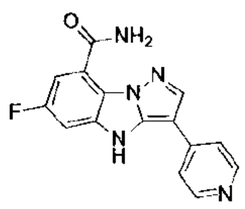
6-fluoro-3-(2-fluoro-5-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 42. ^{1}H-NMR (400 MHz, DMSO-d_6+D_2O) 2.59 (br. s., 3 H), 4.13 (br. s., 2 H), 7.15 - 7.41 (m, 2 H), 7.47 - 7.68 (m, 2 H), 7.95 - 8.09 (m, 1 H), 8.16 - 8.27 (m, 1 H), 8.36 (br. s., 1 H). LCMS (ESI) m/z: 356 (M+1).

Example 45

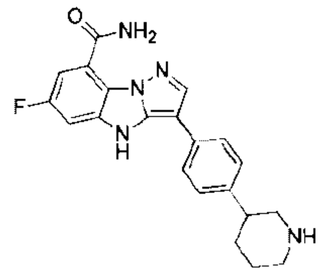
6-fluoro-3-(pyridin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 42. ^{1}H-NMR (MeOD, 400 MHz) δ: 7.55-7.63 (m, 2 H), 7.73-7.79 (m, 1 H), 8.11-8.14 (m, 1 H), 8.15-8.19 (m, 1 H), 8.48-8.54 (m, 2 H), 8.55-8.59 (m, 1 H), 10.28-10.36 (m, 1 H). LCMS (ESI) m/z: 296 (M+1).

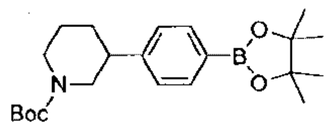
Example 46

6-fluoro-3-(4-(piperidin-3-yl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 46A

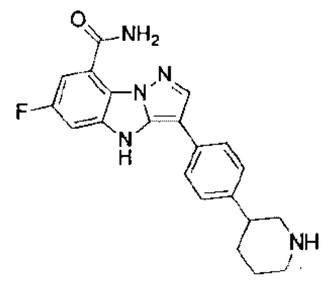
tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate



A mixture of tert-butyl 3-(4-aminophenyl)piperidine-1-carboxylate (0.1 g, 0.362 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.101 g, 0.398 mmol), BPO (1.75 g, 0.00724 mmol) and t-BuONO (0.056 g, 0.542 mmol) in acetonitrile (3 mL) was stirred at 10℃ for 16h under N_2 atmosphere. The solvent was evaporated off under vacuum and the residue was purified by prep-TLC to provide the title compound (0.095 g, yield: 68%).

Example 46B

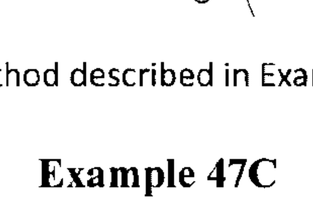
6-fluoro-3-(4-(piperidin-3-yl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 42. ^{1}H NMR (300 MHz, METHANOL-d4) δ ppm 1.189 (m, 2 H), 2.10-2.01 (m, 2 H), 3.03-3.14 (m, 3 H), 3.45 - 3.49 (m, 2 H), 7.37 – 7.40 (d, 2 H), 7.44 - 7.47 (dd, 1 H), 7.66 - 7.68 (d, 2 H), 7.74 - 7.79 (dd, 1 H), 8.22 (s, 1 H), 8.53 (s, 1 H). LCMS (ESI) m/z: 378 (M+1).

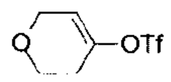
Example 47

6-fluoro-3-(tetrahydro-2H-pyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 47A

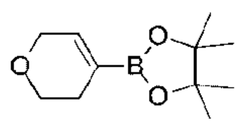
3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate



To a solution of dihydro-2H-pyran-4(3H)-one (1.8 g, 18.0 mol) in THF (20 ml) was added LiHMDS (1 M, 21.6 ml, 21.6 mmol) at -78℃ under N_2 atmosphere. After stirring for 1h at -78 °C, $(CF_3SO_2)_2NPh$ (6.4 g, 18.0 mmol) was added in portions. The mixture was stirred at 15 °C for 16h and quenched with aq NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatograph to provide the title compound as a colorless oil (1.5 g, yield: 35.7%). LCMS (ESI) m/z: 233 (M+1).

Example 47B

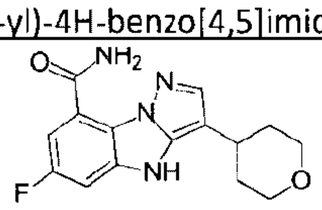
2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



This example was prepared as the method described in Example 42C.

Example 47C

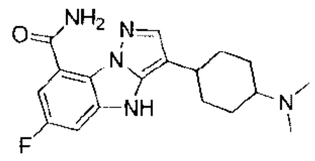
6-fluoro-3-(tetrahydro-2H-pyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 46B. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.82-2.03 (m, 4 H), 2.93-3.04 (m, 1 H), 3.62 (td, J=11.70, 2.45 Hz, 2 H), 4.04-4.11 (m, 2 H), 7.32-7.39 (m, 1 H), 7.66-7.75 (m, 2 H), 8.51-8.55 (m, 1 H). LCMS (ESI) m/z: 303 (M+1).

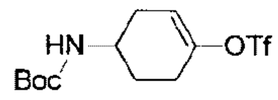
Example 48

3-(4-(dimethylamino)cyclohexyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 48A

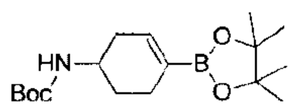
4-((tert-butoxycarbonyl)amino)cyclohex-1-en-1-yl trifluoromethanesulfonate



To a solution of tert-butyl (4-oxocyclohexyl)carbamate (1 g, 4.689 mol) in THF (20 mL) was added dropwise LiHMDS (1 M, 9.4 ml, 9.378 mmol) at -78℃ under N_2 atmosphere. After stirring at -78 °C for 1h, a solution of $(CF_3SO_2)_2NPh$ (1.84 g, 5.158 mmol) in THF (5 mL) was added. The mixture was stirred at 15 °C for 16h, and then quenched with aq NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph on silica gel to provide the title compound as a white solid (1.16 g, yield: 71.60%). LCMS (ESI) m/z: 347 (M+1).

Example 48B

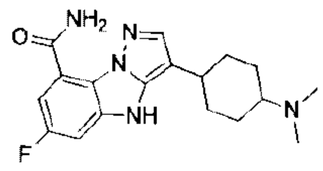
tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)carbamate



This example was prepared as the method described in Example 47B

Example 48C

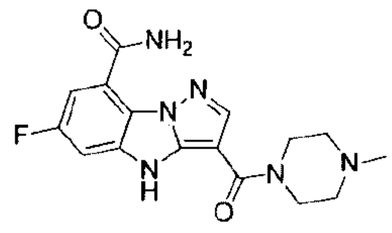
3-(4-(dimethylamino)cyclohexyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the methods described in Example 47C and Example 2. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.63-1.87 (m, 3H), 1.91-2.10 (m, 2H), 2.20-2.46 (m, 3H), 2.81 (s, 4H), 2.90 (s, 3H), 3.19-3.30 (m, 1H), 7.34-7.44 (m, 1H), 7.64-7.75 (m, 2H), 7.78-7.85 (m, 1H), 8.38-8.73 (m, 3H). LCMS (ESI) m/z: 344 (M+1).

Example 49

6-fluoro-3-(4-methylpiperazine-1-carbonyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

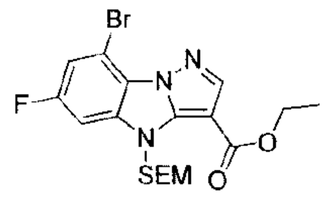


Example 49A

ethyl

8-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-car

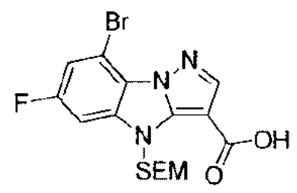
boxylate



To a solution of EXAMPLE 41B (3.2 g, 9.812 mol) in THF (50 mL) was added NaH (785 mg, 19.625 mmol) in portions at 0℃ under N_2 atmosphere. After stirring at 15℃ for 0.5h and cooling to 0℃, SEMCl (3.3 g, 19.625 mmol) was added dropwise thereto. The mixture was stirred at 15 °C for another 16h and then quenched with aq NH_4Cl saturated solution (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatograph to provide the title compound as a yellow solid (2.16 g, yield: 48.21%). LCMS (ESI) m/z: 456, 458 (M, M+2).

Example 49B

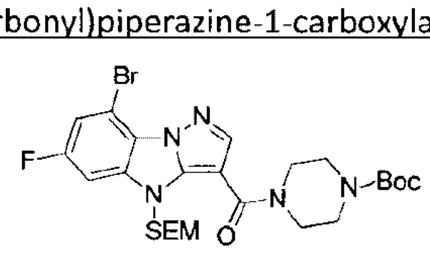
8-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carboxylic acid



A mixture of EXAMPLE 49A (2.16 g, 4.726 mmol) and NaOH (950 mg, 23.632 mmol) in a mixed solvent of MeOH/H_2O (2:1) (30 mL) was stirred at 80 °C for 16h. The resultant mixture was adjusted to pH 3 – 4 with 1N HCl. The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated to provide the title compound (1.73 g, yield: 85.22%) which could be used in the next step without further purification.

Example 49C

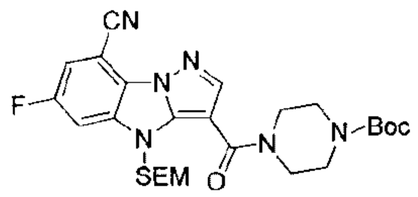
tert-butyl 4-(8-bromo-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carbonyl)piperazine-1-carboxylate



A mixture of tert-butyl piperazine-1-carboxylate (415 mg, 2.241 mmol), EXAMPLE 49B (800 mg, 1.868 mmol), HATU (1.42 g, 3.735 mmol) and Et_3N (567 mg, 5.603 mmol) in DMF (15 mL) was stirred at 15 °C for 16h under N_2 atmosphere. The mixture was quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatograph to provide the title compound (1 g, yield: 90%). LCMS (ESI) m/z: 596, 598 (M, M+2).

Example 49D

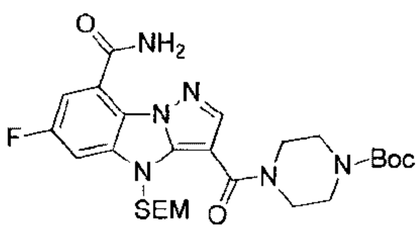
tert-butyl 4-(8-cyano-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carbonyl)piperazine-1-carboxylate



A mixture of EXAMPLE 49C (400 mg, 0.671 mmol), Zn (87 mg, 1.341 mmol), $Zn(CN)_2$ (158 mg, 1.341 mmol), DPPF (75 mg, 0.134 mmol) and $Pd_2(DBA)_3$ (61 mg, 0.0671 mmol) in DMF (10 mL) was stirred at 120℃ under N_2 atmosphere for 10 hours. After being cooled to room temperature, the resultant mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (350 mg, yield: 96.15%). LCMS (ESI) m/z: 543 (M+1).

Example 49E

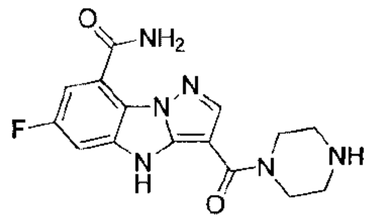
tert-butyl 4-(8-carbamoyl-6-fluoro-4-((2-(trimethylsilyl)ethoxy)methyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-3-carbonyl)piperazine-1-carboxylate



To a mixture of EXAMPLE 49D (400 mg, 0.737 mmol) and K_2CO_3 (510 mg, 3.685 mmol) in DMSO (10 mL) was added H_2O_2 (5 mL) at 0-5℃. After the dropwise addition was completed, the mixture was stirred at 15℃ for 1h, and quenched with aq Na_2SO_3 solution (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatograph to provide the title compound (400 mg, yield: 96.85%). LCMS (ESI) m/z: 561 (M+1).

Example 49F

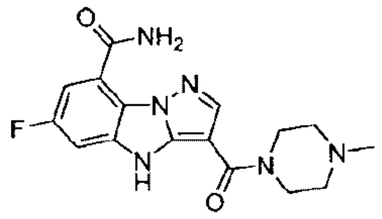
6-fluoro-3-(piperazine-1-carbonyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 49E (100 mg, 0.178 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at 15℃ for 16h. After removal of solution in vacuum, to the residue were added K_2CO_3 (123 mg, 0.892 mmol) and MeOH (2 mL). The mixture was stirred at 15℃ for 2h. The mixture was filtered and the filtrate was evaporated to provide the title compound which could be used directly in the next step without further purification.

Example 49G

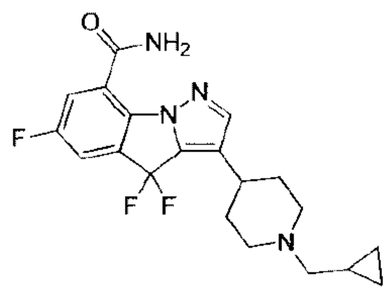
6-fluoro-3-(4-methylpiperazine-1-carbonyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 49F (59 mg, 0.179 mmol), formaldehyde (40 mg, 0.358 mmol) and $Na(CN)BH_3$ (56 mg, 0.894 mmol) in MeOH (2 mL) was stirred at 15℃ for 16h. After evaporation off solvent in vacuum, the residue was purified by prep-HPLC to provide the title compound (8.14 mg, yield: 13.23%) as a white solid. ^{1}H-NMR (MeOD, 400 MHz) δ: 2.68 (s, 3 H), 2.99 (d, J=4.64 Hz, 4 H), 4.00 (br.s., 4 H), 7.46-7.54 (m, 1 H), 7.74-7.84 (m, 1 H), 8.12-8.20 (m, 1 H), 8.24-8.35 (m, 2 H). LCMS (ESI) m/z: 345 (M+1).

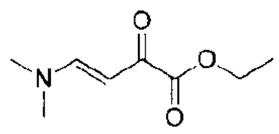
Example 50

3-(1-(cyclopropylmethyl)piperidin-4-yl)-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxamide



Example 50A

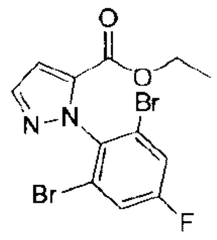
ethyl (E)-4-(dimethylamino)-2-oxobut-3-enoate



A solution of ethyl 2-oxopropanoate (5.0 g, 43.1 mmol) in DMF-DMA (5.0 g, 42.0 mmol) was stirred at 20℃ for 16h. The resultant mixture was evaporated to provide the title compound (7.0 g, crude) as brown oil which could be used directly in the next step without further purification.

Example 50B

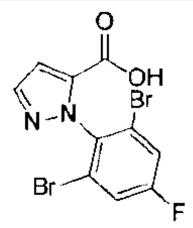
ethyl 1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazole-5-carboxylate



A mixture of EXAMPLE 1D (5.0 g, 17.6 mmol), EXAMPLE 50A (6.0 g, 35.2 mmol) in EtOH (100 ml) and conc HCl (2.4 mL) was stirred at 80℃ for 16h. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (3.6 g, yield: 46.8%) as a yellow solid.

Example 50C

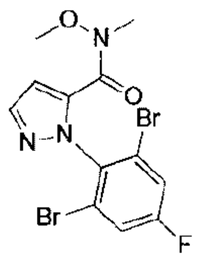
1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid



A mixture of EXAMPLE 50B (3.6 g, 9.18 mmol) and NaOH (2.2 g, 55.1 mmol) in MeOH (20 mL) and water (2 mL) was stirred at 20℃ for 1 h. After removal of solution in vacuum, the residue was diluted with water (50 mL) and adjusted to pH 3 with 2 N HCl. The aqueous layer was extracted with dichloromethane (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound (3.2 g, 97.0%) which could be used directly in the next step without further purification.

Example 50D

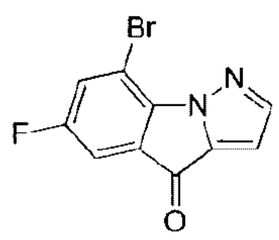
1-(2,6-dibromo-4-fluorophenyl)-N-methoxy-N-methyl-1H-pyrazole-5-carboxamide



A mixture of EXAMPLE 50C (3.2 g, 8.82 mmol), O,N-Dimethyl-hydroxylamine (1.7 g, 17.6 mmol), HATU (4.0 g, 10.6 mmol) and Et_3N (3.6 g, 35.3 mmol) in dry DMF (2 mL) was stirred at 20℃ for 16h under N_2 atmosphere. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (3.4 g, yield: 94.4%) as a yellow solid.

Example 50E

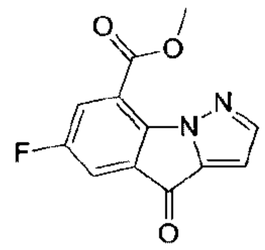
8-bromo-6-fluoro-4H-pyrazolo[1,5-α]indol-4-one



To a mixture of EXAMPLE 50D (3.2 g, 7.90 mmol) in dry THF (5 mL) was added dropwise n-BuLi (2.8 mL, 7.11 mmol) at -78℃ under N_2 atmosphere. After being stirred at -78℃ for 0.5h, the mixture was quenched with sat aq NH_4Cl solution (30 mL). The aqueous layer was extracted with DCM (50 mL x 2). The combined organic layers were evaporated. The residue was washed with MeOH (30 mL) to provide the title compound (1.5 g, yield: 71.4%) as a bright yellow solid. LCMS (ESI) m/z: 267, 269 (M, M+2).

Example 50F

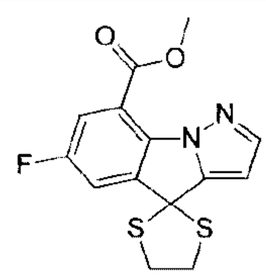
methyl 6-fluoro-4-oxo-4H-pyrazolo[1,5-α]indole-8-carboxylate



A mixture of EXAMPLE 50E (1.3 g, 4.89 mmol), $Pd(dppf)Cl_2$ (0.71 g, 0.98 mmol), $Pd(OAc)_2$ (0.22 g, 0.98 mmol), DPPP (0.81 g, 1.96 mmol), PPh_3 (0.51 g, 1.96 mmol), Xantphos (1.13 g, 1.96 mmol) and Et_3N (3 mL) in MeOH (20 mL) and DMF (60 mL) was stirred at 80℃ for 16h under CO atmosphere (3 atms). After being cooled to 20℃, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatograph to provide the title compound (0.9 g, yield: 75.0%) as a yellow solid. LCMS (ESI) m/z: 247 (M+1).

Example 50G

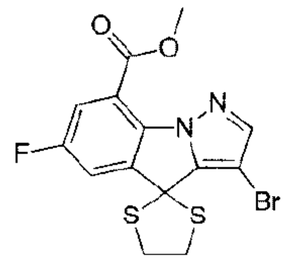
methyl 6-fluorospiro[pyrazolo[1,5-α]indole-4,2'-[1,3]dithiolane]-8-carboxylate



A mixture of EXAMPLE 50F (0.9 g, 3.66 mmol), 2-ethanedithiol (0.69 g, 7.32 mmol) and BF_3-Et_2O (1.0 g, 7.32 mmol) in dry DCM (30 mL) was stirred at 50℃ for 24 h under N_2 atmosphere. After cooled to room temperature, the mixture was diluted with DCM (30 mL). The combined organic layers were washed with 10% NaOH (30 mL), dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by column chromatograph on silica gel (PE: EtOAc= 10:1) to provide the title compound (0.5 g, yield: 42.4%) as a yellow solid. LCMS (ESI) m/z: 323 (M+1).

Example 50H

methyl 3-bromo-6-fluorospiro[pyrazolo[1,5-α]indole-4,2'-[1,3]dithiolane]-8-carboxylate

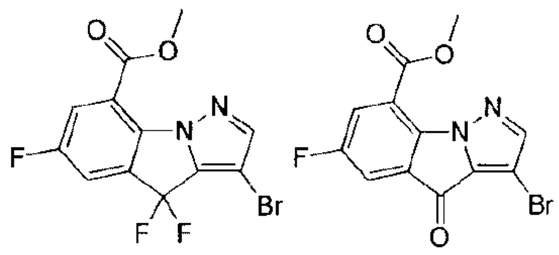


A mixture of EXAMPLE 50G (500 mg, 1.55 mmol) and NBS (276 mg, 1.55 mmol) in THF (20 mL) was stirred at 40℃ for 16h. After being cooled to 20℃, the mixture was evaporated and the residue was purified by column chromatograph to provide the title compound (470 mg, yield:75.7%) as a light yellow solid. LCMS (ESI) m/z: 401, 403 (M, M+2).

Example 50I

methyl 3-bromo-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxylate

methyl 3-bromo-6-fluoro-4-oxo-4H-pyrazolo[1,5-α]indole-8-carboxylate

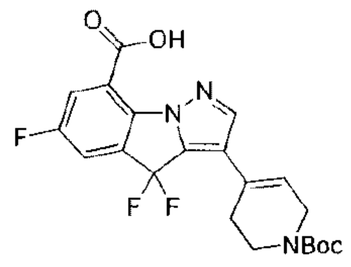


50IA 50IB

To a solution of NIS (2.1 g, 9.38 mmol) in DCM (20 mL) was added HF.Py (3.5 mL) dropwise at -78℃ under N_2 atmosphere. After stirring at -78℃ for 10 min, EXAMPLE 50H (470 mg, 1.17 mmol) was added. The resultant mixture was stirred at -78℃ for 16 h and then quenched with sat aq $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with sat aq Na_2SO_3 solution (30 mL) and evaporated off solvent under vacuum. The residue was purified by column chromatograph to provide EXAMPLE 50IA as a yellow solid (250 mg, yield: 61.6%) and provide EXAMPLE 50IB (110 mg, yield: 27.2%) as a white solid.

Example 50J

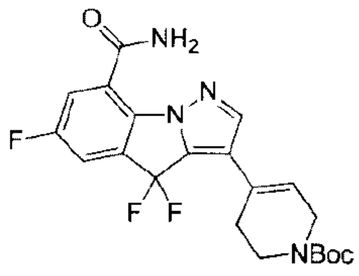
3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxylic acid



A mixture of EXAMPLE 50IA (200 mg, 0.499 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (185 mg, 0.598 mmol), $Pd(dppf)Cl_2$ (37 mg, 0.050 mmol) and K_2CO_3 (138 mg, 0.997 mmol) in DMF (9 mL) and H_2O (3 mL) was stirred at 90℃ for 16h under N_2 atmosphere. After the mixture was cooled to room temperature and concentrated in vacuum, the residue was dissolved in water (20 mL) and adjusted to pH 3 with 1 N HCl. The aqueous layer was extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound (220 mg, crude) without further purification.

Example 50K

tert-butyl 4-(8-carbamoyl-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indol-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate

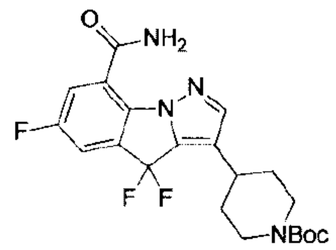


A mixture of EXAMPLE 50J (220 mg, 0.51 mmol), $(NH_4)_2CO_3$ (97 mg, 1.01 mmol), Et_3N (0.2 mL, 1.53 mmol) and HATU (252 mg, 0.66 mmol) in DMF (8 mL) was stirred at 20℃ for 16h. The reaction mixture was concentrated under vacuum and the residue was purified by column

chromatograph to provide the title compound as a yellow solid (70 mg, yield: 32.0%). LCMS (ESI) m/z: 435 (M+1).

Example 50L

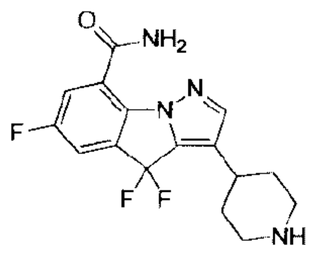
tert-butyl 4-(8-carbamoyl-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indol-3-yl)piperidine-1-carboxylate



A mixture of EXAMPLE 50K (35 mg, 0.08 mmol) and 10% Pd/C (20 mg) in dry DCM (20 mL) and MeOH (10 mL) was hydrogenated at 50℃ for 16h under H_2 (1 atm). The mixture was filtered and the filtrate was evaporated to provide the title compound (30 mg, yield: 85.7%) which could be used directly in the next step without further purification. LCMS (ESI) m/z: 437 (M+1).

Example 50M

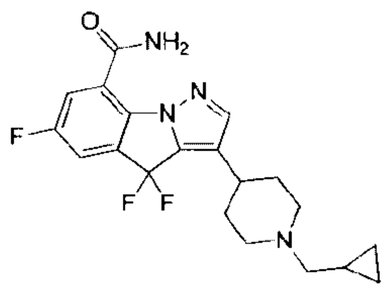
4,4,6-trifluoro-3-(piperidin-4-yl)-4H-pyrazolo[1,5-α]indole-8-carboxamide



A mixture of EXAMPLE 50L (200 mg, 0.466 mmol) in TFA (2 mL) and DCM (6 mL) was stirred at 20℃ for 2h. The resultant mixture was evaporated to provide the title compound which could be used directly in the next step without further purification (30 mg, crude).

Example 50N

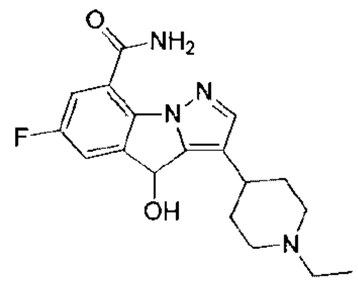
3-(1-(cyclopropylmethyl)piperidin-4-yl)-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxamide



A mixture of EXAMPLE 50M (30 mg, 0.069 mmol), cyclopropanecarbaldehyde (10 mg, 0.138 mmol), $Ti(O\text{-}ipr)_4$ (39 mg, 0.138 mmol) and $Na(CN)BH_3$ (13 mg, 0.207 mmol) in MeOH (8 mL) was stirred at 60℃ for 16h under N_2 atmosphere. The resultant mixture was quenched with water (10 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were evaporated and the residue was purified by prep-HPLC to provide the title compound as a white solid (5 mg, yield: 18.5%). ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.41 (d, *J*=4.89 Hz, 2 H), 0.72 - 0.81 (m, 2 H), 1.13 (br. s., 1 H), 1.93 - 2.13 (m, 2 H), 2.31 (d, *J*=13.93 Hz, 2 H), 2.87 - 3.12 (m, 5 H), 3.66 (d, *J*=11.17 Hz, 2 H), 7.78 - 7.82 (m, 1 H), 7.85 (s, 1 H), 7.97 (dd, *J*=9.91, 2.64 Hz, 1 H), 8.07 (s, 1 H). LCMS (ESI) m/z: 391 (M+1).

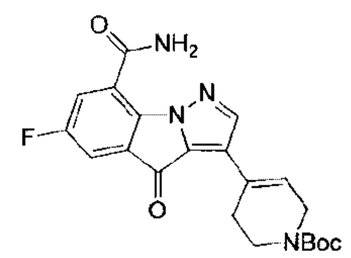
Example 51

3-(1-ethylpiperidin-4-yl)-6-fluoro-4-hydroxy-4H-pyrazolo[1,5-α]indole-8-carboxamide



Example 51A

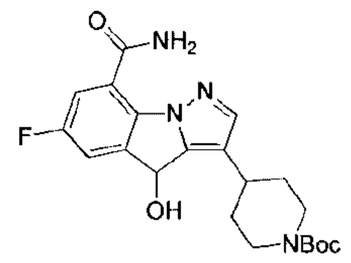
tert-butyl
4-(8-carbamoyl-6-fluoro-4-oxo-4H-pyrazolo[1,5-α]indol-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate



This example was prepared as described in Example 50K. LCMS (ESI) m/z: 413 (M+1).

Example 51B

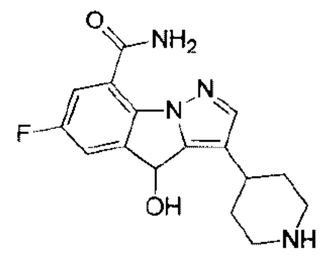
tert-butyl
4-(8-carbamoyl-6-fluoro-4-hydroxy-4H-pyrazolo[1,5-α]indol-3-yl)piperidine-1-carboxylate



A mixture of EXAMPLE 51A (50 mg, 0.121 mmol) and 10% Pd/C (10 mg) in dry MeOH (10 mL) was hydrogenated at 50℃for 16 h under H_2 (1 atm). The mixture was filtered and the filtrate was evaporated to provide the title compound (40 mg, yield: 80.0%) which could be used directly in the next step without further purification. LCMS (ESI) m/z: 417 (M+1).

Example 51C

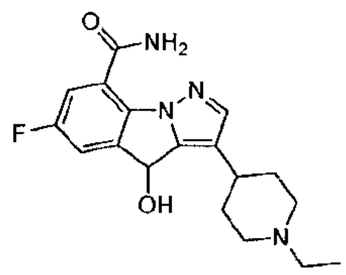
6-fluoro-4-hydroxy-3-(piperidin-4-yl)-4H-pyrazolo[1,5-α]indole-8-carboxamide



This example was prepared as described in Example 50M.

Example 51D

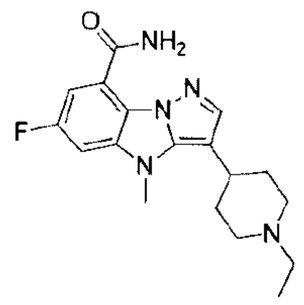
3-(1-ethylpiperidin-4-yl)-6-fluoro-4-hydroxy-4H-pyrazolo[1,5-α]indole-8-carboxamide



A mixture of EXAMPLE 51C (25 mg, 0.079 mmol), 40 % acetaldehyde (0.1 mL) and $Na(CN)BH_3$ (20 mg, 0.316 mmol) in MeOH (5 ml) was stirred at 10℃ for 16 h. The resultant mixture was diluted with water (10 mL). The aqueous layer was extracted with DCM (20 mL × 3). The combined organic layers were evaporated to give the residue which was purified by prep-HPLC to provide the title compound (9.40 mg, yield: 34.8%) as a white solid. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.11 - 1.18 (m, 3 H), 1.77 - 1.96 (m, 2 H), 2.01 - 2.16 (m, 2 H), 2.61 (br. s., 2 H), 2.81 (br. s., 3 H), 3.27 (br. s., 2 H), 5.72 (s, 1 H), 7.59 (dd, *J*=7.22, 2.45 Hz, 1 H), 7.70 (d, *J*=10.42 Hz, 1 H), 7.76 (s, 1 H), 7.99 (br. s., 1 H), 8.32 (br. s., 1 H), 10.09 (br. s., 1 H). LCMS (ESI) m/z: 345 (M+1).

Example 52

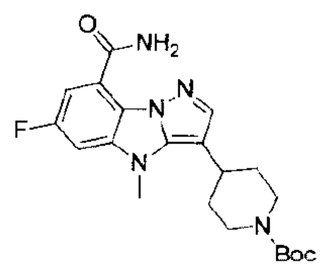
3-(1-ethylpiperidin-4-yl)-6-fluoro-4-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 52A

tert-butyl

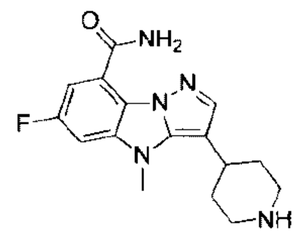
4-(8-carbamoyl-6-fluoro-4-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)piperidine-1-carboxylate



A mixture of EXAMPLE 1I (30 mg, 0.075 mmol), K_2CO_3 (31 mg, 0.224 mmol) and CH_3I (32 mg, 0.224 mmol) in DMF (3 mL) was stirred at 10℃ for 1h. The reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound which could be used directly in the next step without further purification.

Example 52B

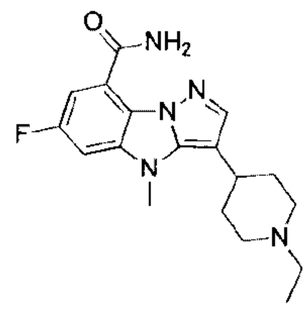
6-fluoro-4-methyl-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 52A (31 mg, 0.074 mmol) in DCM (1 mL) and TFA (0.2 mL) was stirred at 10℃ for 2h. The mixture was evaporated to provide the title compound which could be used directly in the next step without further purification.

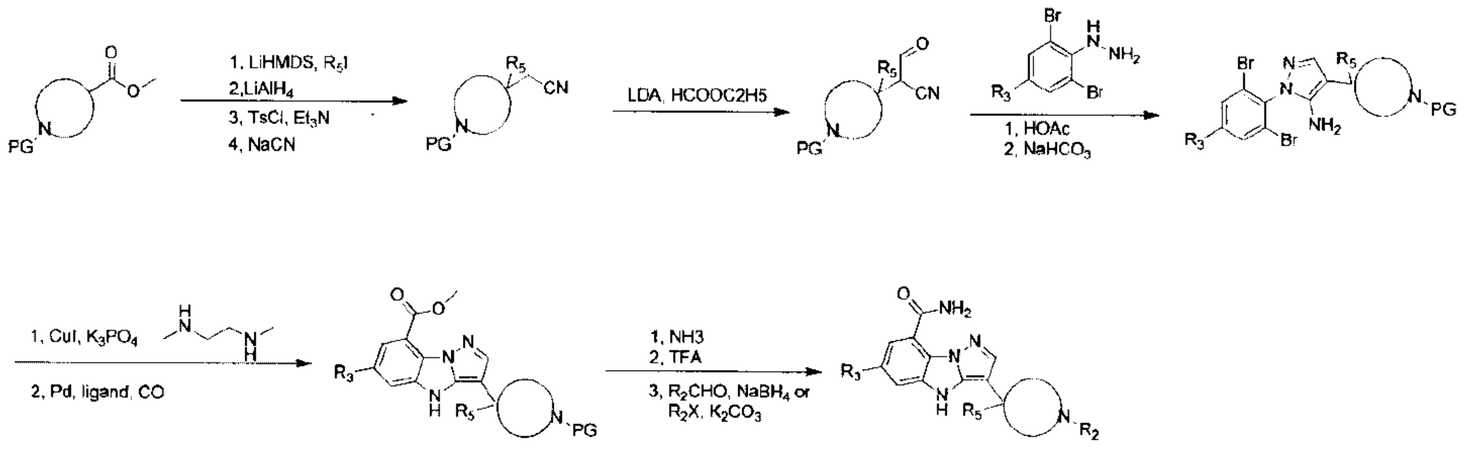
Example 52C

3-(1-ethylpiperidin-4-yl)-6-fluoro-4-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



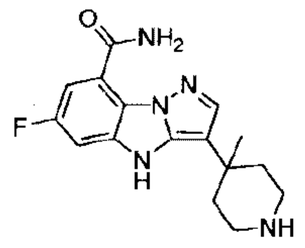
This example was prepared as the method described in Example 51D. ^{1}H-NMR (400 MHz, METHANOL-d4) δ ppm 1.23-1.26 (t, 3 H), 1.91-1.97 (m, 2 H), 2.11-2.14 (d, 2 H), 2.55 (t, 2 H), 2.78-2.80 (m, 2H), 3.04-3.07 (m, 2 H), 3.32 (2 H), 3.87 (s,2 H), 7.48-8.50 (m, 1 H), 7.64-7.67 (m, 1 H), 7.73 (s, 1 H), 8.54 (s, 1 H). LCMS (ESI) m/z: 344 (M+1).

Scheme C



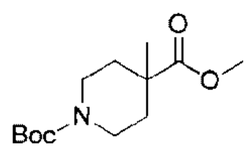
Example 53

6-fluoro-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 53A

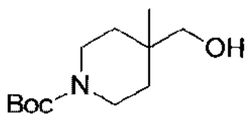
1-(tert-butyl) 4-methyl 4-methylpiperidine-1,4-dicarboxylate



To a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (36.5 g, 0.15 mol) in anhydrous THF (400 mL) was added dropwise LiHMDS (1 M, 300 mL) at -78℃ under N_2 atmosphere. After stirring at -78℃ for 30min, a solution of MeI (42.6 g, 0.3 mol) in THF (100 mL) was added dropwise thereto. The reaction mixture was stirred at -78℃ for 2 hours and warmed to 15℃ and stirred for further 20 hours. After completion of the reaction, the mixture was quenched with sat aq NH_4Cl solution (500 mL). The aqueous layer was extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (30 g, yield: 78%). LCMS (ESI) m/z: 258 (M+1).

Example 53B

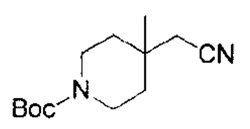
tert-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate



To a solution of $LiAlH_4$ (3.7 g, 97.5 mmol) in anhydrous THF (40 mL) was added dropwise a solution of EXAMPLE 53A (10 g, 39 mmol) in anhydrous THF (80 mL) at 0℃ under N_2 atmosphere. After the dropwise addition was completed, the reaction mixture was stirred at 0℃ for 2.5 hours, and then quenched with water (4 mL), 15% aq NaOH solution (4 mL) and water (12 mL). The resultant mixture was stirred at 0℃ for further 20 minutes. The mixture was filtered and the solid was washed with EtOAc (50 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound (9 g, crude) which could be used directly in the next step without further purification.

Example 53C

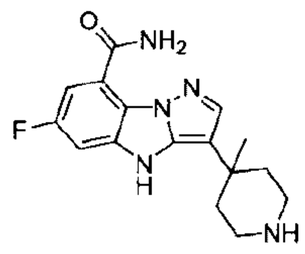
tert-butyl 4-(cyanomethyl)-4-methylpiperidine-1-carboxylate



This example was prepared as the method described in Examples 1A-1B.

Example 53D

6-fluoro-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

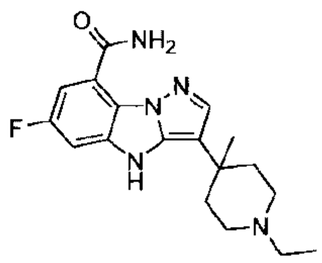


This example was prepared as described in Examples 1E-1J. ^{1}H NMR (400 MHz, MeOD) δ: 8.51 (s, 1 H), 7.81 (s, 1 H), 7.69 (dd, *J*=2.4 Hz / *J*=10.2 Hz, 1 H), 7.45 (dd, *J*=2.4 Hz / *J*=8.0 Hz, 1 H), 3.33-3.39 (m, 2H), 3.12-3.32(m, 2H), 2.42-2.46 (m, 2H), 2.03-2.08 (m, 2H), 1.46 (s, 3 H). LCMS (ESI)

m/z: 316 (M+1).

Example 54

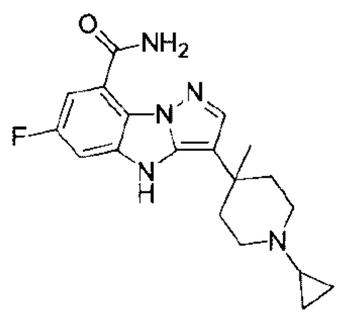
3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 52C (10 mg, yield: 38%). ^{1}H NMR (400 MHz, DMSO) δ: 10.58 (s, 1 H), 8.28 (s, 1 H), 8.13 (s, 1 H), 7.80 (s, 1 H), 7.61 (dd, *J*=2.8 Hz / *J*=7.2 Hz, 1 H), 7.49 (t, *J*=2.4 Hz, 1 H), 2.75-2.78 (m, 2H), 2.50-2.54 (m, 4H), 2.18-2.20 (m, 2H), 1.73-1.78 (m, 2H), 1.30 (s, 3H), 1.05 (t, *J*=7.2 Hz, 3 H). LCMS (ESI) m/z: 344 (M+1).

Example 55

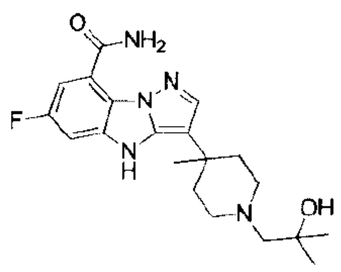
3-(1-cyclopropyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 4. ^{1}H-NMR (400 MHz, MethanoL-d_4) 0.77 (d, *J*=5.40 Hz, 4 H), 1.41 - 1.45 (m, 3 H), 1.90 - 2.01 (m, 2 H), 2.28 - 2.44 (m, 3 H), 3.03 (br. s., 2 H), 3.27 (br. s., 2 H), 7.39 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.73 (dd, *J*=10.92, 2.38 Hz, 1 H), 7.79 (s, 1 H), 8.41 (br. s., 1 H). LCMS (ESI) m/z: 356 (M+1).

Example 56

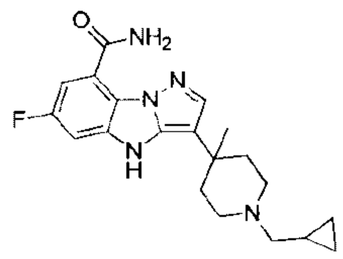
6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 6. ^{1}H-NMR (400 MHz, DMSO-d_4) δ ppm 1.13 (s, 6 H), 1.28 (s, 3 H), 1.86 (t, *J*=10.23 Hz, 2 H), 2.20 (d, *J*=15.43 Hz, 2 H), 2.62 (s, 2 H), 2.76 (br. s., 2 H), 3.04 (d, *J*=4.02 Hz, 2 H), 7.48 (dd, *J*=8.34, 2.57 Hz, 1 H), 7.56 (dd, *J*=10.92, 2.64 Hz, 1 H), 7.79 (s, 1 H), 8.31 (s, 1 H). LCMS (ESI) m/z: 388 (M+1).

Example 57

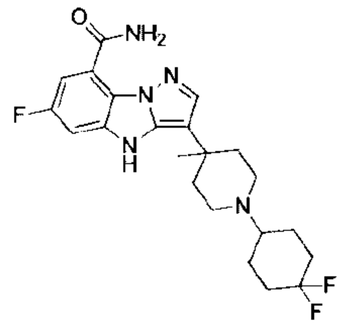
3-(1-(cyclopropylmethyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.37 (d, *J*=3.89 Hz, 2 H), 0.73 (d, *J*=7.53 Hz, 2 H), 1.02 - 1.14 (m, 1 H), 1.44 (br. s., 3 H), 2.08 (d, *J*=11.29 Hz, 2 H), 2.37 - 2.66 (m, 2 H), 2.94 (br. s., 3 H), 3.34 - 3.63 (m, 3 H), 7.38 (dd, *J*=8.09, 2.57 Hz, 1 H), 7.71 (dd, *J*=10.92, 2.51 Hz, 1 H), 7.79 (s, 1 H), 7.77 - 7.81 (m, 1 H), 8.51 (s, 1 H). LCMS (ESI) m/z: 370 (M+1).

Example 58

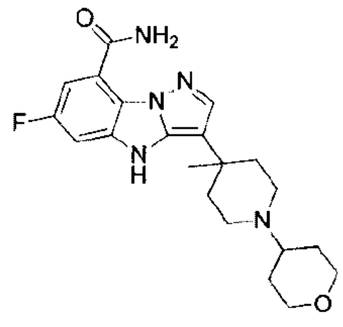
3-(1-(4,4-difluorocyclohexyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H-NMR (400 MHz, DMSO-d_4) δ ppm 1.22 (s, 3 H), 1.33 - 1.49 (m, 1 H), 1.70 (br. s., 6 H), 1.92 - 2.12 (m, 1 H), 2.31 - 2.38 (m, 1 H), 2.59 - 2.64 (m, 1 H), 7.40 - 7.62 (m, 2 H), 7.74 (s, 1 H). LCMS (ESI) m/z: 434 (M+1).

Example 59

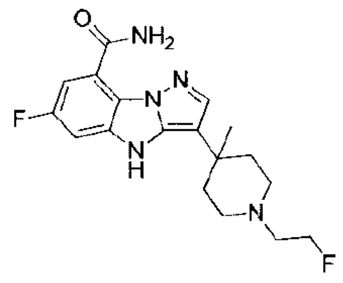
6-fluoro-3-(4-methyl-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.05 (t, *J*=7.22 Hz, 1 H), 1.36 (s, 3 H), 1.50 - 1.60 (m, 1 H), 1.82 (d, *J*=11.92 Hz, 3 H), 2.21 - 2.27 (m, 1 H), 2.44 - 2.56 (m, 1 H), 2.79 (br. s., 2 H), 3.35 - 3.42 (m, 1 H), 3.90 - 4.05 (m, 1 H), 7.32 - 7.38 (m, 1 H), 7.71 (s, 1 H). LCMS (ESI) m/z: 400 (M+1).

Example 60

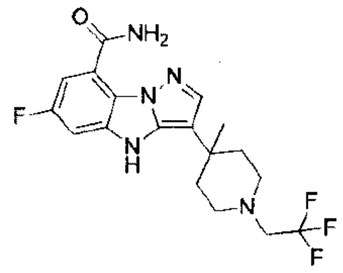
6-fluoro-3-(1-(2-fluoroethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.45 (s, 3 H), 2.01-2.05(m, 2 H), 2.24-2.47 (m, 2 H), 3.05 (m, 2 H), 3.24-3.25 (m, 1 H), 3.26-3.27 (m, 1 H), 3 .33-3.34 (m, 1 H), 4.70-4.72 (m, 1 H), 4.82-4.93 (m, 1H), 7.37-7.39 (m, 1 H), 7.68-7.79 (d ,1 H), 7.81(s, 1H), 8.45 (br. s., 1 H). LCMS (ESI) m/z: 362 (M+1).

Example 61

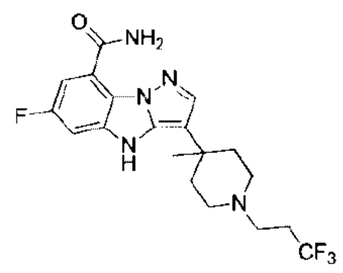
6-fluoro-3-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.37 (s, 3 H), 1.79 - 1.91 (m, 2 H), 2.16 - 2.27 (m, 2 H), 2.58 - 2.69 (m, 2 H), 2.79 - 2.89 (m, 2 H), 2.98 - 3.10 (m, 2 H), 7.33 - 7.39 (m, 1 H), 7.66 - 7.75 (m, 2 H). LCMS (ESI) m/z: 398 (M+1).

Example 62

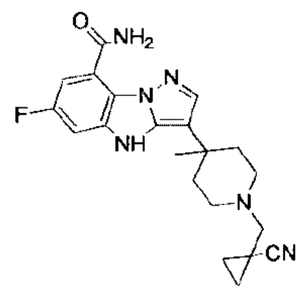
6-fluoro-3-(4-methyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.42 (s, 3 H), 1.92 - 2.05 (m, 2 H), 2.38 (d, *J*=14.93 Hz, 2 H), 2.54 - 2.71 (m, 2 H), 2.86 (d, *J*=9.79 Hz, 2 H), 2.93 - 3.07 (m, 2 H), 3.14 (d, *J*=11.17 Hz, 2 H), 7.37 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.70 (dd, *J*=10.92, 2.51 Hz, 1 H), 7.76 (s, 1 H), 8.37 (br. s., 1 H). LCMS (ESI) m/z: 412 (M+1).

Example 63

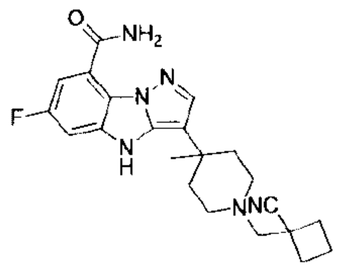
3-(1-((1-cyanocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.05 (d, *J*=2.26 Hz, 2 H), 1.32 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.89 - 2.05 (m, 2 H), 2.33 (d, *J*=15.69 Hz, 2 H), 2.69 (s, 4 H), 3.02 (br. s., 2 H), 7.38 (dd, *J*=8.09, 2.57 Hz, 1 H), 7.68 - 7.83 (m, 2 H), 8.28 (br. s., 1 H). LCMS (ESI) m/z: 395 (M+1).

Example 64

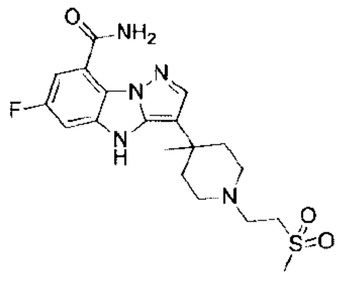
3-(1-((1-cyanocyclobutyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.38 (s, 3 H), 1.85 - 1.94 (m, 2 H), 2.00 - 2.09 (m, 1 H), 2.18 - 2.31 (m, 5 H), 2.42 - 2.52 (m, 2 H), 2.63 (t, *J*=9.22 Hz, 2 H), 2.81 (s, 2 H), 2.88 (d, *J*=5.65 Hz, 2 H), 7.36 (dd, *J*=8.03, 2.26 Hz, 1 H), 7.69 (d, *J*=2.26 Hz, 1 H), 7.73 (s, 1 H), 8.30 (br. s., 1 H). LCMS (ESI) m/z: 409 (M+1).

Example 65

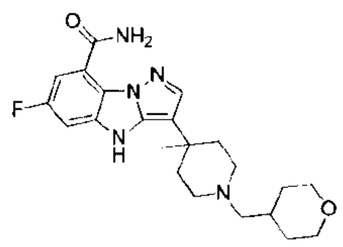
6-fluoro-3-(4-methyl-1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.40 (s, 3 H), 1.87 - 1.98 (m, 2 H), 2.28 - 2.38 (m, 2 H), 2.63 - 2.80 (m, 2 H), 2.95 - 3.05 (m, 2 H), 3.07 (s, 3 H), 3.07 - 3.14 (m, 2 H), 3.38 - 3.47 (m, 2 H), 7.33 - 7.40 (m, 1 H), 7.66 - 7.73 (m, 1 H), 7.73 - 7.77 (m, 1 H), 8.20 - 8.37 (m, 1 H). LCMS (ESI) m/z: 422 (M+1).

Example 66

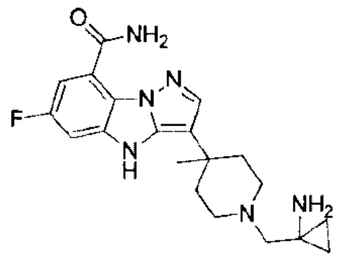
6-fluoro-3-(4-methyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.25 - 1.33 (m, 2 H), 1.37 (s, 3 H), 1.70 (d, *J*=13.30 Hz, 2 H), 1.80 - 1.89 (m, 3 H), 2.22 (br. s., 2 H), 2.23 (br. s., 2 H), 2.38 (br. s., 2 H), 2.67 (br. s., 2 H), 3.40 - 3.47 (m, 2 H), 3.94 (dd, *J*=11.67, 2.89 Hz, 2 H), 7.36 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.69 (d, *J*=2.51 Hz, 1 H), 7.72 (br. s., 1 H). LCMS (ESI) m/z: 414 (M+1).

Example 67

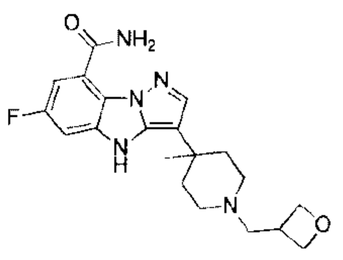
3-(1-((1-aminocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 0.72 - 0.82 (m, 2 H), 0.93 - 1.00 (m, 2 H), 1.40 (s, 3 H), 1.91 - 2.03 (m, 2 H), 2.26 - 2.37 (m, 2 H), 2.66 (s, 4 H), 2.94 - 3.06 (m, 2 H), 7.33 - 7.41 (m, 1 H), 7.67 - 7.73 (m, 1 H), 7.73 - 7.77 (m, 1 H), 8.22 - 8.48 (m, 2 H). LCMS (ESI) m/z: 385 (M+1).

Example 68

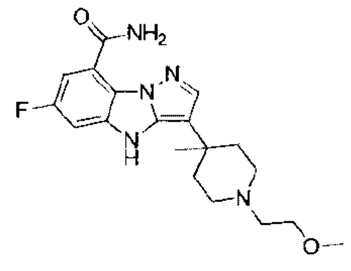
6-fluoro-3-(4-methyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) ppm 1.36 (s, 3 H), 1.78 - 1.88 (m, 2 H), 2.17 - 2.25 (m, 2 H), 2.36 (br. s., 2 H), 2.57 - 2.68 (m, 2 H), 2.72 (d, *J*=7.03 Hz, 2 H), 4.38 - 4.47 (m, 2 H), 4.60 - 4.63 (m, 1 H), 4.80 - 4.82 (m, 2 H), 7.33 - 7.39 (m, 1 H), 7.68 - 7.76 (m, 2 H). LCMS (ESI) m/z: 386 (M+1).

Example 69

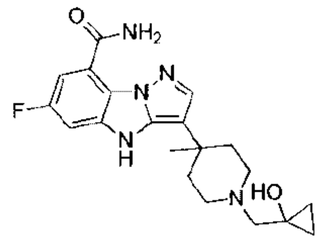
6-fluoro-3-(1-(2-methoxyethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.45 (s, 3 H), 2.07 (ddd, *J*=14.68, 10.85, 3.58 Hz, 2 H), 2.46 (d, *J*=14.81 Hz, 2 H), 3.12 (br. s., 2 H), 3.23 (t, *J*=4.83 Hz, 2 H), 3.41 (s, 5 H), 3.66 - 3.73 (m, 2 H), 7.39 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.71 (dd, *J*=10.92, 2.51 Hz, 1 H), 7.80 (s, 1 H), 8.52 (s, 1 H). LCMS (ESI) m/z: 374 (M+1).

Example 70

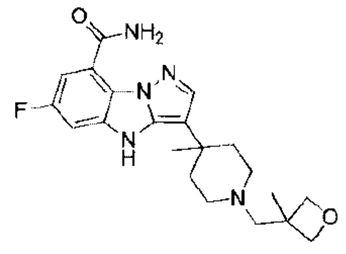
6-fluoro-3-(1-((1-hydroxycyclopropyl)methyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.64 - 0.74 (m, 2 H), 0.84 - 0.93 (m, 2 H), 1.46 (s, 3 H), 2.04 - 2.18 (m, 2 H), 2.50 (d, *J*=15.18 Hz, 2 H), 3.16 (br. s., 4 H), 3.47 - 3.68 (m, 2 H), 7.36 - 7.43 (m, 1 H), 7.68 - 7.75 (m, 1 H), 7.79 - 7.84 (m, 1 H), 8.48 - 8.65 (m, 1 H). LCMS (ESI) m/z: 386 (M+1).

Example 71

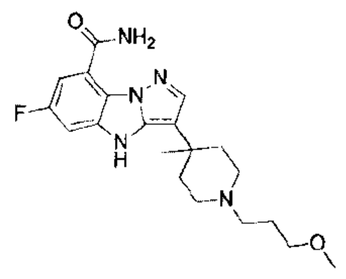
6-fluoro-3-(4-methyl-1-((3-methyloxetan-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.38 (s, 3 H), 1.46 (s, 3 H), 1.81 - 1.93 (m, 2 H), 2.18 - 2.29 (m, 2 H), 2.33 - 2.54 (m, 2 H), 2.54 - 2.84 (m, 4 H), 4.31 - 4.35 (m, 2 H), 4.49 - 4.54 (m, 2 H), 7.34 - 7.39 (m, 1 H), 7.68 - 7.75 (m, 2 H). LCMS (ESI) m/z: 400 (M+1).

Example 72

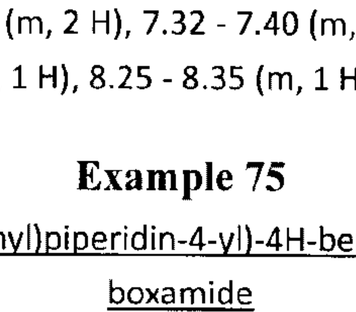
6-fluoro-3-(1-(3-methoxypropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.45 (s, 3 H), 1.94 - 2.01 (m, 2 H), 2.02 - 2.12 (m, 2 H), 2.47 (d, *J*=13.05 Hz, 2 H), 2.89 - 3.20 (m, 4 H), 3.34 (s, 3 H), 3.39 (br. s., 2 H), 3.45 - 3.52 (m, 2 H), 7.38 (dd, *J*=8.09, 2.57 Hz, 1 H), 7.71 (dd, *J*=10.92, 2.51 Hz, 1 H), 7.79 (s, 1 H), 8.55 (s, 1 H). LCMS (ESI) m/z: 434 (M+1).

Example 73

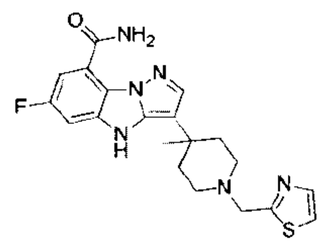
6-fluoro-3-(4-methyl-1-((1-(methylsulfonyl)cyclopropyl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 0.95 - 1.01 (m, 2 H), 1.38 (s, 3 H), 1.41 - 1.49 (m, 2 H), 1.83 - 1.96 (m, 2 H), 2.27 (d, *J*=13.30 Hz, 2 H), 2.55 (br. s., 2 H), 2.86 (s, 2 H), 2.92 (br. s., 2 H), 3.24 (s, 3 H), 7.36 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.67 - 7.78 (m, 2 H). LCMS (ESI) m/z: 448 (M+1).

Example 74

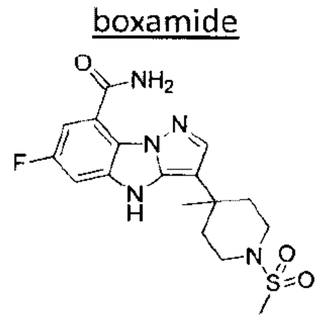
6-fluoro-3-(4-methyl-1-(thiazol-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.36 - 1.42 (m, 3 H), 1.86 - 1.97 (m, 2 H), 2.23 - 2.33 (m, 2 H), 2.63 - 2.73 (m, 2 H), 2.89 - 2.98 (m, 2 H), 4.02 - 4.07 (m, 2 H), 7.32 - 7.40 (m, 1 H), 7.58 - 7.63 (m, 1 H), 7.68 - 7.73 (m, 1 H), 7.74 (s, 1 H), 7.75 - 7.79 (m, 1 H), 8.25 - 8.35 (m, 1 H). LCMS (ESI) m/z: 413 (M+1).

Example 75

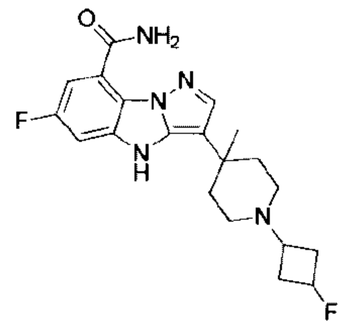
6-fluoro-3-(4-methyl-1-(methylsulfonyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.38-1.46 (m, 3H), 1.88 (ddd, J=13.68, 9.66, 3.76 Hz, 2H), 2.32 (d, J=15.06 Hz, 2H), 2.78 (s, 3H), 3.00-3.17 (m, 2H), 3.46-3.53 (m, 2H), 7.35-7.41 (m, 1H), 7.69-7.75 (m, 1H), 7.77-7.79 (m, 1H), 8.46-8.53(m, 1H). LCMS (ESI) m/z: 394 (M+1).

Example 76

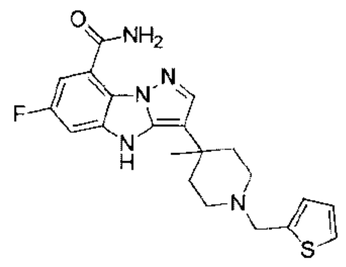
6-fluoro-3-(1-(3-fluorocyclobutyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.45 (s, 3 H), 1.96 - 2.18 (m, 2 H), 2.38 - 2.74 (m, 6 H), 2.94 (br. s., 4 H), 3.74 - 3.93 (m, 1 H), 5.12 - 5.32 (m, 1 H), 7.41 (dd, *J*=8.16, 2.38 Hz, 1 H), 7.67 (dd, *J*=10.79, 2.26 Hz, 1 H), 7.79 (s, 1 H), 8.52 (br. s., 1 H). LCMS (ESI) m/z: 388 (M+1).

Example 77

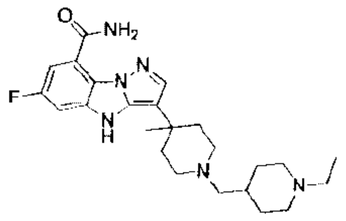
6-fluoro-3-(4-methyl-1-(thiophen-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.34 (s, 3 H), 1.82 (ddd, *J*=13.36, 9.41, 3.45 Hz, 2 H), 2.13 - 2.27 (m, 1 H), 2.32 - 2.53 (m, 1 H), 2.69 (br. s., 2 H), 3.72 (s, 2 H), 6.87 - 7.01 (m, 2 H), 7.25 - 7.39 (m, 2 H), 7.62 - 7.75 (m, 2 H). LCMS (ESI) m/z: 412 (M+1).

Example 78

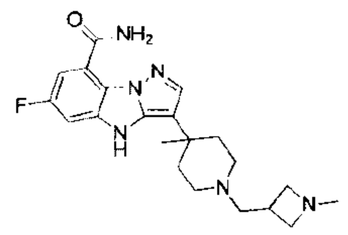
3-(1-((1-ethylpiperidin-4-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, METHANOL-d4) δ ppm 1.32-1.35 (t, 3 H), 1.42 (s, 3 H), 1.47-1.51 (d, 2 H), 1.99-2.08 (m, 5 H), 2.35-2.38 (d, 2 H), 2.64-2.65 (d, 2H), 2.89 (m, 2 H), 3.06 (t, 2 H), 3.11-3.15 (m, 4 H), 3.51-3.54 (d, 2 H), 7.37-7.39 (m, 1 H), 7.70-7.74 (m, 1 H), 7.77 (s, 1 H), 8.446 (s, 2 H). LCMS (ESI) m/z: 441 (M+1).

Example 79

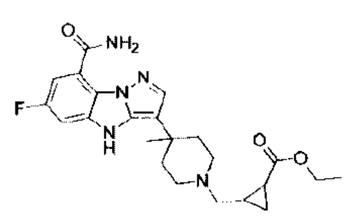
6-fluoro-3-(4-methyl-1-((1-methylazetidin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, METHANOL-d4) δ ppm 1.32 (s, 3 H), 1.89-1.95 (m, 2 H), 2.29-2.33 (d, 2 H), 2.60 (d, 2 H), 2.86-2.91, 2.64-2.65 (m, 7 H), 3.18 (m, 1 H), 3.84-3.88 (t, 2 H), 4.15-4.20 (t, 2 H), 7.36- 7.39 (m, 1 H), 7.70-7.73 (m, 1 H), 7.77 (s, 1 H), 8.41 (s, 2 H). LCMS (ESI) m/z: 399 (M+1).

Example 80

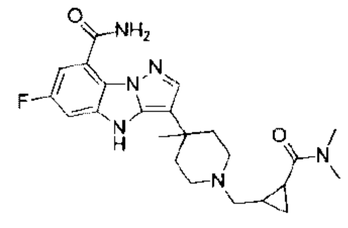
ethyl 2-((4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidin-1-yl)methyl)cyclopropanecarboxylate



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) 0.86-1.34 (m, 6 H), 1.35-1.49 (m, 2 H), 1.57-2.01 (m, 4 H), 2.09-2.28 (m, 2 H), 2.44-2.70 (m, 2 H), 2.99-3.27 (m, 2 H), 3.36-3.47 (m, 2 H), 3.53-3.75 (m, 2 H), 4.06-4.26 (m, 3 H), 7.50-7.65 (m, 1 H), 7.74-7.85 (m, 1 H), 8.05 (br. s., 1 H). LCMS (ESI) m/z: 442 (M+1).

Example 81

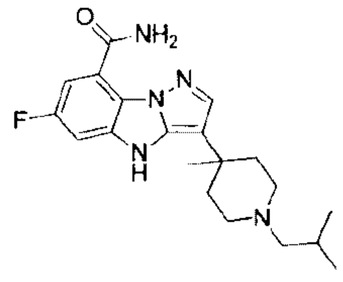
ethyl 3-(1-((2-(dimethylcarbamoyl)cyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400MHz, METHANOL-d_4) 0.97-1.29 (m, 2H), 1.47 (s, 2H), 1.65 (s, 1H), 2.08-2.30 (m, 3H), 2.63 (d, *J*=15.3 Hz, 1H), 2.85 (s, 1H), 2.92-3.01(m, 3H), 3.01-3.12 (m, 2H), 3.12-3.27 (m, 2H), 3.29 (s, 2H), 3.34-3.47 (m, 2H), 3.55-3.77 (m, 2H), 7.56-7.70 (m, 1H), 7.78-7.85 (m, 1H), 8.12 (d, *J*=6.5 Hz, 1H). LCMS (ESI) m/z: 441 (M+1).

Example 82

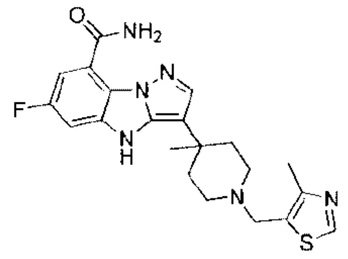
6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.00-1.02 (d, 6H), 1.43 (s, 3H), 2.03-2.07 (m, 3H), 2.10-2.11 (d, 2H), 2.81-2.83 (d, 2H), 3.03 (bs, 2H), 3.31 (bs, 2H), 7.35-7.38 (dd, 1H), 7.67-7.71 (s, 1H), 7.77 (s, 1H), 8.53 (bs, 1H). LCMS (ESI) m/z: 372 (M+1).

Example 83

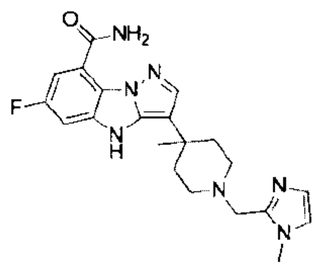
6-fluoro-3-(4-methyl-1-((4-methylthiazol-5-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.41 (s, 3 H), 1.89 - 2.01 (m, 2 H), 2.30 - 2.39 (m, 2 H), 2.43 (s, 3 H), 2.73 - 2.86 (m, 2 H), 2.97 - 3.15 (m, 2 H), 4.01 - 4.20 (m, 2 H), 7.30 - 7.47 (m, 1 H), 7.65 - 7.86 (m, 2 H), 8.90 - 9.04 (m, 1 H). LCMS (ESI) m/z: 427 (M+1).

Example 84

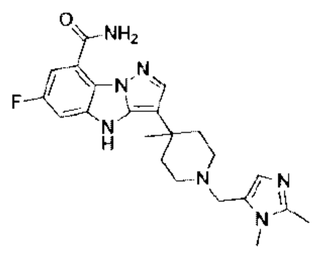
6-fluoro-3-(4-methyl-1-((1-methyl-1H-imidazol-2-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.32 - 1.44 (m, 3 H), 1.78 - 1.96 (m, 2 H), 2.18 - 2.33 (m, 2 H), 2.46 - 2.62 (m, 2 H), 2.71 - 2.88 (m, 2 H), 3.73 - 3.77 (m, 2 H), 3.81 (s, 3 H), 7.01 - 7.11 (m, 1 H), 7.18 - 7.23 (m, 1 H), 7.33 - 7.40 (m, 1 H), 7.73 (s, 2 H), 8.28 - 8.44 (m, 1 H). LCMS (ESI) m/z: 410 (M+1).

Example 85

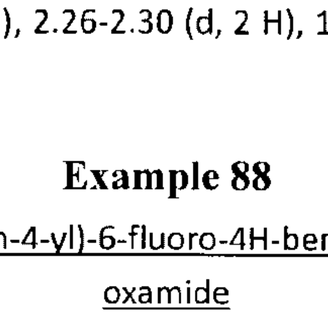
3-(1-((1,2-dimethyl-1H-imidazol-5-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.38 (s, 3 H), 1.83 - 1.92 (m, 2 H), 2.27 (d, *J*=13.80 Hz, 2 H), 2.54 (s, 5 H), 2.86 (d, *J*=10.92 Hz, 2 H), 3.70 (s, 2 H), 3.75 (s, 3 H), 7.17 (s, 1 H), 7.36 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.66 - 7.80 (m, 2 H), 8.38 (br. s., 1 H). LCMS (ESI) m/z: 424 (M+1).

Example 86

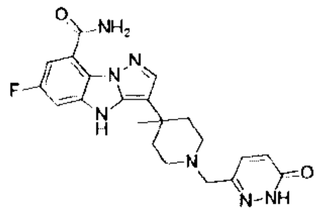
3-(1'-ethyl-4-methyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H-NMR (400 MHz, MethanoL-d_4) 1.09 (t, *J*=7.09 Hz, 3 H), 1.27 (s, 3 H), 1.50 - 1.70 (m, 2 H), 1.72 - 1.85 (m, 2 H), 1.92 (d, *J*=11.54 Hz, 2 H), 2.34 (br. s., 2 H), 2.75 (d, *J*=7.40 Hz, 7 H), 2.86 (br. s., 2 H), 3.23 (d, *J*=10.42 Hz, 2 H), 7.49 (d, *J*=8.41 Hz, 1 H), 7.58 (dd, *J*=10.85, 2.20 Hz, 1 H), 7.79 (s, 1 H), 8.28 (s, 2 H). LCMS (ESI) m/z: 427 (M+1).

Example 87

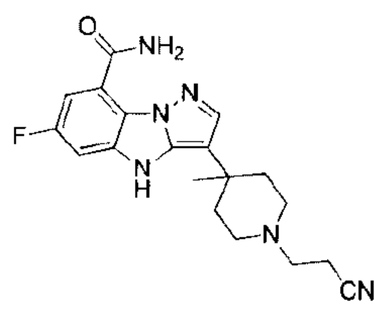
6-fluoro-3-(4-methyl-1-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 2. ^{1}H NMR (400 MHz, MeOD) δ: 8.35 (s, 1 H), 7.70-7.74 (m, 2 H), 7.57-7.60 (d, 1 H), 7.36-7.38 (t, 1 H), 6.98-7.00 (d, 1 H), 3.63 (s, 2 H), 2.86 (m, 2 H), 2.61-2.63 (m, 2 H), 2.26-2.30 (d, 2 H), 1.87-1.94 (m, 2 H), 1.39 (s, 3 H). LCMS (ESI) m/z: 424 (M+1).

Example 88

3-(1-(2-cyanoethyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

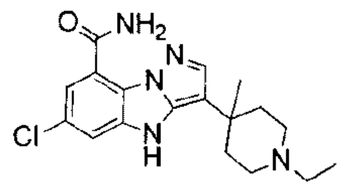


A mixture of EXAMPLE 53D (52 mg, 0.125 mmol), acrylonitrile (66 mg, 1.25 mmol) and potassium carbonate (172 mg, 1.25 mmol) in DMF (18 mL) was stirred at 28℃ for 1 hour. After completion, the reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and

evaporated. The residue was purified by prep-HPLC to provide the title compound (31 mg, yield 66.0%). ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.39 (s, 3 H), 1.86 - 1.97 (m, 2 H), 2.25 - 2.36 (m, 2 H), 2.60 - 2.70 (m, 2 H), 2.74 (s, 2 H), 2.84 - 2.98 (m, 4 H), 7.33 - 7.41 (m, 1 H), 7.68 - 7.73 (m, 1 H), 7.74 (s, 1 H), 8.21 - 8.32 (m, 1 H). LCMS (ESI) m/z: 369 (M+1).

Example 89

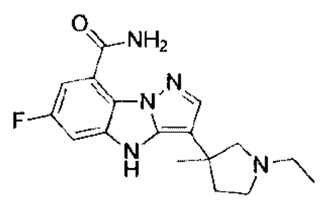
6-chloro-3-(1-ethyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 53, substituting (2,6-dibromo-4-chlorophenyl)hydrazine for (2,6-dibromo-4-fluorophenyl)hydrazine. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.32-1.39 (t, 3 H), 1.46 (m, 1 H), 2.52-2.55 (s, 3 H), 2.06-2.08 (m, 2 H), 2.47-2.48 (m, 2 H), 3.09-3.11 (m, 3 H), 3.34-3.41 (m, 3 H), 7.63 (s, 1 H), 7.83 (s, 1 H), 7.97-7.97 (d, 1 H), 8.54 (bs, 1 H). LCMS (ESI) m/z: 360 (M+1).

Example 90

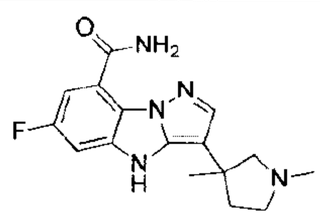
3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 53, substituting tert-butyl 3-(hydroxymethyl)-3-methylpyrrolidine-1-carboxylate for tert-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.38 (s, 3 H), 1.64 (s, 3 H), 2.25 - 2.42 (m, 1 H), 2.59 - 2.76 (m, 1 H), 3.27 - 3.32 (m, 2 H), 3.39 - 3.53 (m, 1 H), 3.54 - 3.71 (m, 2 H), 3.71 - 3.88 (m, 1 H), 7.33 - 7.39 (m, 1 H), 7.57 - 7.70 (m, 1 H), 7.76 - 7.90 (m, 1 H), 8.28 - 8.80 (m, 1 H). LCMS (ESI) m/z: 330 (M+1).

Example 91

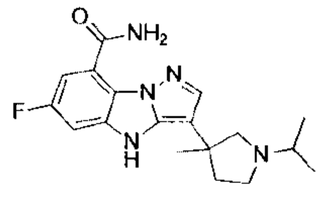
3-(1,3-dimethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 90. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 8.52 (br. s., 1 H), 7.84 (s, 1 H), 7.67 (dd, *J*=2.5, 10.9 Hz, 1 H), 7.38 (dd, *J*=2.5, 8.0 Hz, 1 H), 3.74 (d, *J*=11.3 Hz, 1 H), 3.67 - 3.49 (m, 2 H), 3.40 (d, *J*=11.3 Hz, 1 H), 2.96 (s, 3 H), 2.73 - 2.60 (m, 1 H), 2.34 (td, *J*=7.8, 13.4 Hz, 1 H), 1.64 (s, 3 H). LCMS (ESI) m/z: 316 (M+1).

Example 92

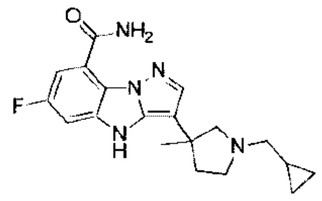
6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 90. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.38 - 1.52 (m, 6 H), 1.71 (d, J=2.26 Hz, 3 H), 2.32 - 2.46 (m, 1 H), 2.63 - 2.82 (m, 1 H), 3.38 - 3.70 (m, 3 H), 3.76 - 4.11 (m, 2 H), 7.58 - 7.70 (m, 1 H), 7.76 - 7.86 (m, 1 H), 8.15 - 8.29 (m, 1 H). LCMS (ESI) m/z: 344 (M+1).

Example 93

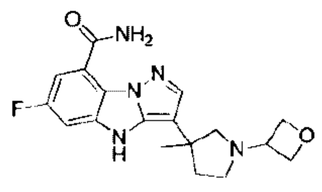
3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 0.41 - 0.52 (m, 2 H), 0.70 - 0.82 (m, 2 H), 1.10 - 1.26 (m, 1 H), 1.66 (s, 3 H), 2.27 - 2.39 (m, 1 H), 2.63 - 2.75 (m, 1 H), 3.17 (d, J=7.15 Hz, 2 H), 3.44 - 3.58 (m, 1 H), 3.59 - 3.78 (m, 2 H), 3.79 - 3.94 (m, 1 H), 7.27 - 7.40 (m, 1 H), 7.55 - 7.67 (m, 1 H), 7.77 - 7.89 (m, 1 H), 8.43 - 8.69 (m, 1 H). LCMS (ESI) m/z: 356 (M+1).

Example 94

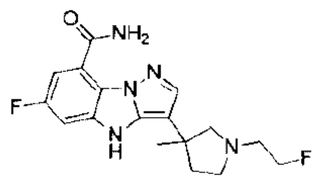
6-fluoro-3-(3-methyl-1-(oxetan-3-yl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.58 (s, 3 H), 2.01 - 2.10 (m, 1 H), 2.26 - 2.35 (m, 1 H), 2.68 - 2.74 (m, 1 H), 2.79 - 2.87 (m, 1 H), 2.87 - 2.96 (m, 1 H), 2.96 - 3.03 (m, 1 H), 3.78 - 3.85 (m, 1 H), 4.62 - 4.72 (m, 1 H), 4.74 - 4.81 (m, 1 H), 7.31 - 7.40 (m, 1 H), 7.64 - 7.71 (m, 1 H), 7.72 - 7.77 (m, 1 H). LCMS (ESI) m/z: 358 (M+1).

Example 95

6-fluoro-3-(1-(2-fluoroethyl)-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

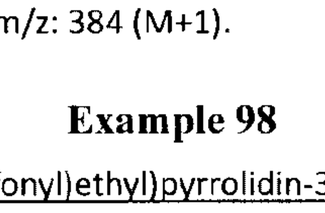


This example was prepared as the method described in Example 3. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.635 (s, 1H), 2.243-2.263 (m, 1H), 2.522-2.554 (m, 1H), 3.288-3.321 (d, 1H), 3.325 (s, 2H),

3.329-3.337 (m, 1H), 3.391-3.414 (m, 1H), 3.632-3.659 (d, 1H), 4.730-4.860 (dt, 2H), 7.291-7.317 (dd, 1H), 7.586-7.619 (dd, 1H), 7.788 (s, 1H), 8.445 (bs, 1H), LCMS (ESI) m/z: 348 (M+1).

Example 96

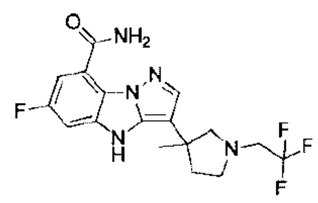
3-(1-((2,2-difluorocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.34 - 1.46 (m, 1 H) 1.64 (s, 3 H) 1.67 - 1.79 (m, 1 H) 2.03 - 2.11 (m, 1 H) 2.20 - 2.31 (m, 1 H) 2.52 - 2.63 (m, 1 H) 3.13 - 3.24 (m, 1 H) 3.24 - 3.31 (m, 2 H) 3.37 - 3.48 (m, 1 H) 3.48 - 3.58 (m, 1 H) 3.59 - 3.67 (m, 1 H) 7.29 - 7.39 (m, 1 H) 7.57 - 7.67 (m, 1 H) 7.76 - 7.84 (m, 1 H) 8.35 - 8.54 (m, 1 H) LCMS (ESI) m/z: 392 (M+1).

Example 97

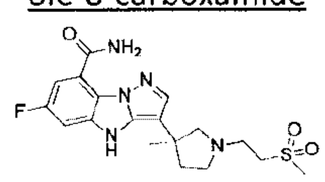
6-fluoro-3-(3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.74 (s, 3 H), 2.39 - 2.54 (m, 1 H), 2.74 - 2.88 (m, 1 H), 3.69 - 3.82 (m, 1 H), 3.82 - 3.95 (m, 2 H), 3.97 - 4.14 (m, 1 H), 4.36 - 4.50 (m, 2 H), 7.55 - 7.64 (m, 1 H), 7.73 - 7.83 (m, 1 H), 8.12 - 8.20 (m, 1 H). LCMS (ESI) m/z: 384 (M+1).

Example 98

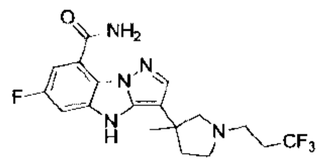
6-fluoro-3-(3-methyl-1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.60 (s, 3 H), 2.05 - 2.15 (m, 1 H), 2.18 - 2.28 (m, 1 H), 2.63 - 2.69 (m, 1 H), 2.69 - 2.78 (m, 1 H), 3.01 - 3.10 (m, 1 H), 3.11 (s, 3 H), 3.26 - 3.31 (m, 1 H), 3.34 - 3.41 (m, 2 H), 3.41 - 3.50 (m, 1 H), 3.50 - 3.60 (m, 1 H), 7.35 - 7.45 (m, 1 H), 7.63 - 7.70 (m, 1 H), 7.72 (s, 1 H), 8.22 (s, 1 H). LCMS (ESI) m/z: 408 (M+1).

Example 99

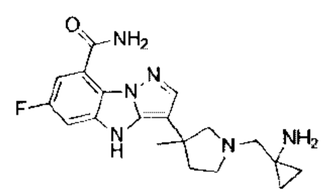
6-fluoro-3-(3-methyl-1-(3,3,3-trifluoropropyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.62 (s, 3 H), 2.16 - 2.25 (m, 1 H), 2.43 - 2.53 (m, 1 H), 2.58 - 2.72 (m, 1 H), 3.08 - 3.14 (m, 1 H), 3.16 - 3.29 (m, 1 H), 3.34 - 3.39 (m, 1 H), 3.41 - 3.47 (m, 1 H), 7.32 - 7.41 (m, 1 H), 7.63 - 7.71 (m, 1 H), 7.74 - 7.83 (m, 1 H), 8.24 - 8.34 (m, 1 H). LCMS (ESI) m/z: 398 (M+1).

Example 100

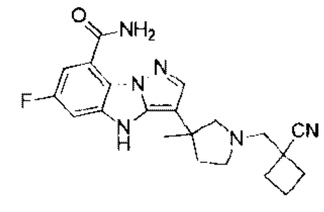
3-(1-((1-aminocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 0.85 (s, 1 H), 1.00 (s, 1 H), 1.62 (s, 3 H), 2.07 - 2.17 (m, 1 H), 2.34 - 2.44 (m, 1 H), 2.85 (s, 1 H), 2.94 - 3.01 (m, 1 H), 3.04 - 3.12 (m, 1 H), 3.20 (d, J=9.41 Hz, 1 H), 7.33 - 7.39 (m, 1 H), 7.64 - 7.70 (m, 1 H), 7.75 - 7.80 (m, 1 H), 7.83 - 7.85 (m, 1 H), 8.02 - 8.05 (m, 1 H), 8.34 - 8.47 (m, 1 H). LCMS (ESI) m/z: 371 (M+1).

Example 101

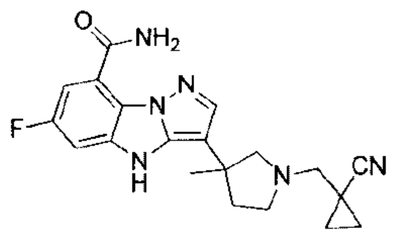
3-(1-((1-cyanocyclobutyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, METHANOL-d_4) 1.60 (s, 3 H), 2.00 - 2.11 (m, 2 H), 2.13 - 2.23 (m, 1 H), 2.25 - 2.40 (m, 3 H), 2.45 - 2.58 (m, 2 H), 2.65 - 2.70 (m, 1 H), 2.72 - 2.80 (m, 1 H), 2.93 (s, 1 H), 2.99 - 3.06 (m, 1 H), 3.14 - 3.23 (m, 2 H), 7.38 - 7.44 (m, 1 H), 7.69 (dd, J=10.85, 2.57 Hz, 1 H), 7.74 (s, 1 H), 8.33 (br. s., 1 H). LCMS (ESI) m/z: 395 (M+1).

Example 102

3-(1-((1-cyanocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide

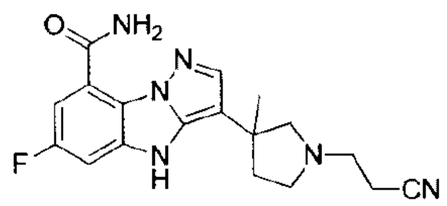


This example was prepared as the method described in Example 3. ^{1}H NMR (400 MHz, DMSO-d_6) ppm 0.92 (d, J=2.26 Hz, 2 H), 1.16 - 1.24 (m, 2 H), 1.48 (s, 3 H), 1.87 - 1.97 (m, 1 H), 2.05 (s, 1 H),

2.55 (d, *J*=7.53 Hz, 4 H), 2.91 (s, 2 H), 7.43 - 7.50 (m, 1 H), 7.51 - 7.61 (m, 1 H), 7.79 (s, 1 H). LCMS (ESI) m/z: 381 (M+1).

Example 103

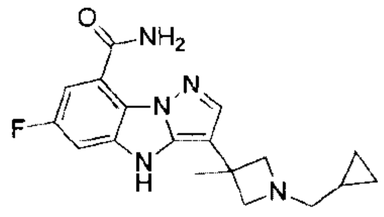
3-(1-(2-cyanoethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 88. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 1.61 (s, 3 H), 2.06 - 2.16 (m, 1 H), 2.23 - 2.33 (m, 1 H), 2.80 (d, *J*=6.40 Hz, 1 H), 2.83 - 2.91 (m, 1 H), 2.93 - 3.02 (m, 1 H), 3.03 - 3.12 (m, 1 H), 3.27 (d, *J*=9.29 Hz, 2 H), 7.37 - 7.44 (m, 1 H), 7.64 - 7.72 (m, 1 H), 7.76 (s, 1 H), 8.14 - 8.26 (m, 1 H). LCMS (ESI) m/z: 355 (M+1).

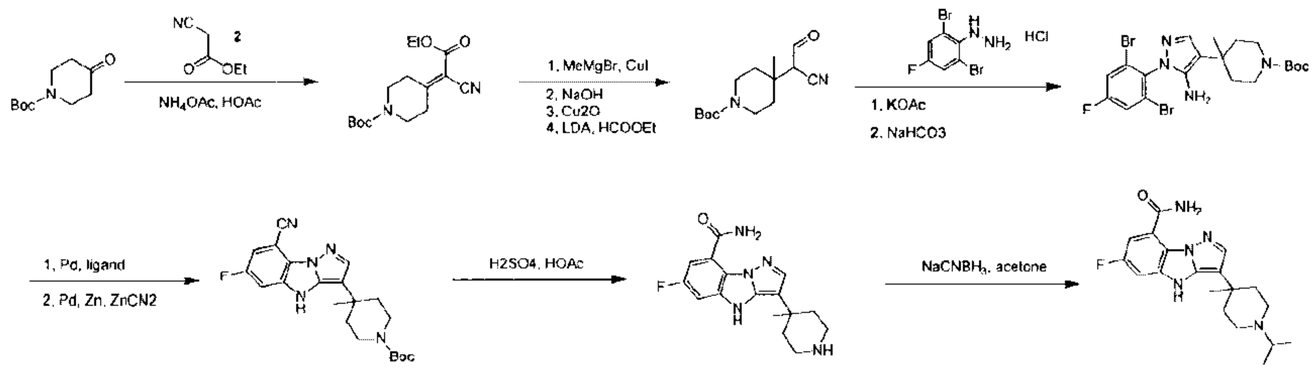
. Example 104

3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



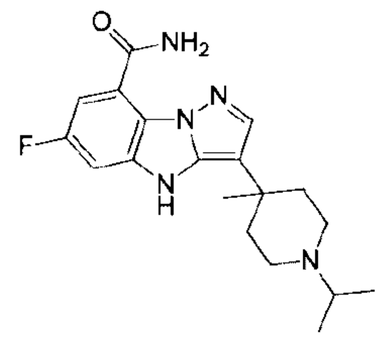
This example was prepared as the method described in Example 93. ^{1}H NMR (400 MHz, MeOD) δ: 8.51 (s, 1 H), 7.96 (s, 1 H), 7.70-7.73 (dd, 1 H), 7.39-7.41 (dd, 1 H), 4.39-4.32 (d, 2 H), 4.23-4.26 (d, 2 H), 3.15-3.17 (d, 2 H), 1.87 (s, 3 H), 1.06-1.08(m, 1 H), 0.69-0.74 (m, 2 H), 0.42-0.46 (m, 2 H). LCMS (ESI) m/z: 342 (M+1).

Scheme D



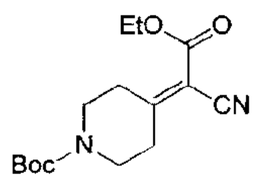
Example 105

6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 105A

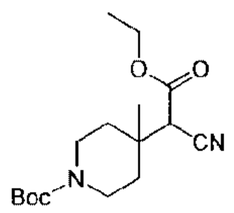
tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate



A mixture of tert-butyl 4-oxopiperidine-1-carboxylate (100 g, 0.5 mol), ethyl 2-cyanoacetate (56.5 g, 0.5 mol), NH_4OAc (19.2 g, 0.25 mol) and HOAc (15 g, 0.25 mol) in toluene (1 L) was stirred at 120℃ for 5-6 h to remove water by a Dean-Stark trap. After removal of solvent in vacuum, the residue was partitioned between EtOAc (500 mL) and water (500 mL), the aqueous layer was extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by pulping with PE/ EtOAc= 10/1 (300 mL). The white solid was collected by filtration to provide the title compound (90 g, 61% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.38 (t, *J*=7.15 Hz, 3 H), 1.50 (s, 9 H), 2.79 (t, *J*=5.90 Hz, 2 H), 3.15 (t, *J*=5.83 Hz, 2 H), 3.56 (t, *J*=5.71 Hz, 2 H), 3.63 (t, *J*=5.83 Hz, 2 H), 4.31 (q, *J*=7.15 Hz, 2 H). LCMS (ESI) m/z: 295 (M+1).

Example 105B

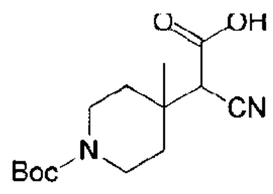
tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-methylpiperidine-1-carboxylate



To a mixture of CuI (86.3 g, 0.454 mol) in dry THF (1.7 L) was added dropwise 3M methylmagnesium bromide (378 mL, 1.13 mol) at -60-70℃ under N_2 atmosphere. After stirring at -10℃ – 0℃ for 1h and cooling to -60-70℃, a solution of EXAMPLE 105A (133.5 g, 0.454 mol) in THF (300 mL) was added. The mixture was stirred at 20℃ for 15h and then cooled to 0℃ and quenched with sat aq NH_4Cl solution (1.2 L). After filtration through a pad of celite, the aqueous layer was extracted with EtOAc (600mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and evaporated to provide the crude title compound (142 g) as a yellow oil which was used directly in the next step without further purification.

Example 105C

2-(1-(tert-butoxycarbonyl)-4-methylpiperidin-4-yl)-2-cyanoacetic acid

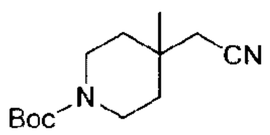


To a solution of EXAMPLE 105B (142 g, crude, 0.458 mol) in a mixture of THF/MeOH=10:1 (1.2 L) was added dropwise a solution of NaOH (73.3 g, 1.82 mol) in water (320 mL) at 0℃. After the dropwise addition was completed, the mixture was stirred at 20℃ for 2h, and then diluted by adding water (320 mL). The aqueous layer was extracted with EtOAc (500 mL x 3). The combined organic layers were washed with water (200 mL x 2). The combined aqueous layer

was adjusted to pH 3 – 4 by 1N HCl and extracted with DCM/MeOH= 10:1 (300 mL x 6). The combined DCM/MeOH organic layer was washed with brine (800 mL) and then dried over Na_2SO_4, filtered and evaporated to provide the crude title compound (111.5 g) as a yellow solid which was used directly in the next step without further purification.

Example 105D

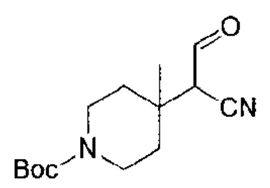
tert-butyl 4-(cyanomethyl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 105C (111.5 g, crude, 0.395 mol) and Cu_2O (11.4 g, 79.08 mmol) in acetonitrile (900 mL) was stirred at 80℃ for 2 h. After being cooled to room temperature, the mixture was evaporated and the residue was dissolved in EtOAc (1 L) and filtered through a pad of celite to remove insolubles. The filter residue was washed with EtOAc (250 mL × 2). To the filtrate was added THF (150mL) to dissolve the precipitates. The organic layer was washed withwater, water/brine= 1:1 (300 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by pulping with PE/ EtOAc= 10/1 (300 mL). The white solid was collected by filtration to provide the title compound (98 g). LCMS (ESI) m/z: 239 (M+1).

Example 105E

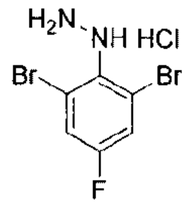
tert-butyl 4-(1-cyano-2-oxoethyl)-4-methylpiperidine-1-carboxylate



To a mixture of EXAMPLE 105D (50 g, 0.21 mol) in THF (400 mL) was added dropwise 2M LDA (160 mL, 0.32 mol) at -60-70℃ under N_2 atmosphere. After stirring at -60-70℃ for 1h, ethyl formate (32 g, 0.43 mol) was added dropwise till completion, followed by slowly warming up to 15℃ and stirring for another 4h. After completion, the reaction was quenched with aq NH_4Cl solution (500 mL). The aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with water (200 mL), 1N HCl (300 mL x 3), brine (200 mL), thereafter dried over Na_2SO_4, filtered and evaporated to give the residue which was purified by pulping with PE/ EtOAc= 10/1 (200 mL). The white solid was collected by filtration to provide the title compound (45 g, 80% yield). LCMS (ESI) m/z: 267 (M+1).

Example 105F

(2,6-dibromo-4-fluorophenyl)hydrazine hydrochloride



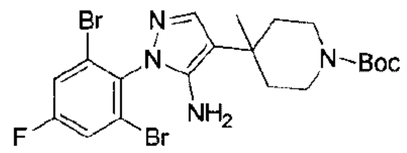
To a mixture of 2,6-dibromo-4-fluoroaniline (50 g, 0.186 mol) in conc HCl (190 mL) was added dropwise a solution of $NaNO_2$ (14.1 g, 0.205 mol) in water (70 mL) at-5-0℃. After being stirred at -5-0℃ for 40 min, the above reaction mixture was added dropwisein into a solution of

$SnCl_2$-$2H_2O$ (62.95 g, 0.279 mol) in conc HCl (240 mL) at -5-0℃. The resultant mixture was slowly warmed up to 20℃ and stirred for 12h. The solid was collected by filtration, washed with i-PrOH (200 mL) and thereafter dried in vacuum to provide the title compound (47 g, 78% yield) which could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 - 2.68 (m, 1 H), 6.94 - 7.28 (m, 1 H), 7.80 (d, J=8.03 Hz, 2 H), 10.13 (br. s., 3 H).

Example 105G

tert-butyl

4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazol-4-yl)-4-methylpiperidine-1-carboxylate

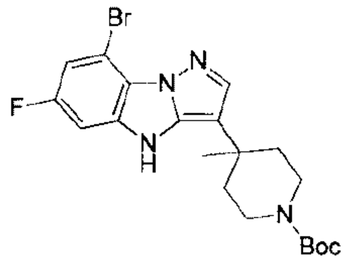


A mixture of EXAMPLE 105E (50 g, 187.73 mmol), KOAc (27.64 g, 281.73 mmol) and EXAMPLE 105F (72.17 g, 225.28 mmol) in ethanol (500 ml) was stirred at 60℃ for 5h. After the reaction was completed, to the mixture was added $NaHCO_3$ (31.57 g, 375.78 mmol) while stirring at 80℃ for another 15h. After being cooled to room temperature, the resultant mixture was evaporated and the residue was dissolved with EtOAc (200 mL) and water (200 mL). The aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by pulping with PE/ EtOAc= 10/1 (200 mL). The white solid was collected by filtration to provide the title compound (75 g, 75 %yield) which could be used directly in the next step without further purification.

Example 105H

tert-butyl

4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate

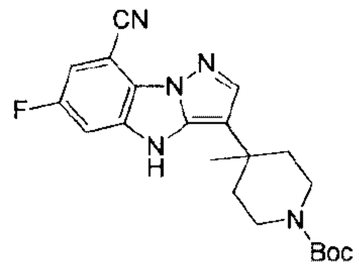


A mixture of EXAMPLE 105G (35 g, 65.78 mmol), $Pd_2(dba)_3$ (6.02 g, 6.57 mmol), Xantphos (7.61 g, 13.16 mmol) and Cs_2CO_3 (42.77 g, 131.58 mmol) in DMF (300 mL) was stirred at 130℃ for 9h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and the filtrate was evaporated. The residue was dissolved in EtOAc (500 mL). The organic layer was washed with water (200 mL x 2), brine (200 mL x 2), dried over Na_2SO_4, filtered and evaporated to provide the crude title compound as brown oil which could be used in the next step without further purification. LCMS (ESI) m/z: 451, 453 (M, M+2).

Example 105I

tert-butyl

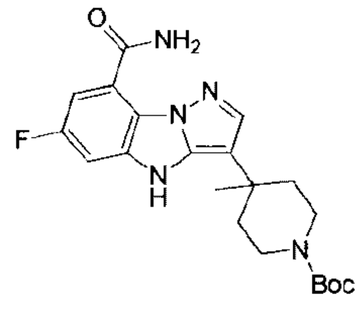
4-(8-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 105H (29.7g, crude, 65.8 mmol), $Zn(CN)_2$ (15.4 g, 131.71 mmol), $Pd_2(dba)_3$ (6.02 g, 6.58 mmol), DPPF (7.30 g, 13.17 mmol) and Zn (8.65 g, 131.71 mmol) in DMF (300 mL) was stirred at 120℃ for 5h under N_2 atmosphere. After being cooled to room temperature, the mixture was filtered and the filtrate was evaporated to give the residue which was purified by column chromatography to provide the crude title compound (35 g, crude) as yellow foam. LCMS (ESI) m/z: 398 (M+1).

Example 105J

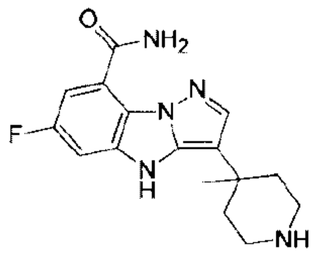
tert-butyl 4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



To a solution of EXAMPLE 105I (35 g, crude, 88.17 mmol) and 1N NaOH (140 mL, 140 mmol) in DMSO (100 mL) was added dropwise 30% H_2O_2 (40 mL) at 0℃. After the dropwise addition was completed, the reaction solution was warmed to 40-50℃ and stirredfor 2 hours, and thereafter diluted with water (200 mL) and extracted with EtOAc /THF= 3/1 (200 mL x 2). The combined organic layers were washed with water (150 mL × 2), brine (150 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound (12.2 g, yield: 45%) as yellow solids. LCMS (ESI) m/z: 416 (M+1).

Example 105K

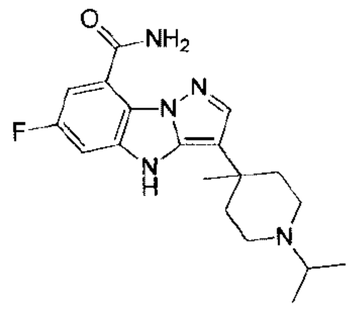
6-fluoro-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A solution of EXAMPLE 105J (5 g, 12 mmol) in a mixture of DCM/TFA (50 mL /10 mL) was stirred at 20℃ for 2h. The resultant mixture was evaporated to provide the title compound as yellow oil which could be used in the next step without further purification.

Example 105L

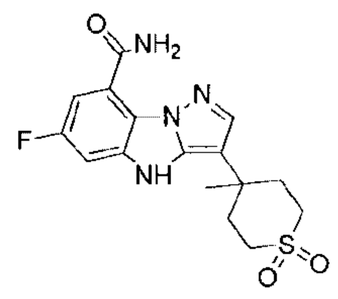
6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A solutionof EXAMPLE 105K (3.8 g, crude, 12 mmol), $Na(CN)BH_3$ (2.8, 60 mmol) in a mixture of acetone (2.0 g, 34 mmol) and methanol (50 mL) was stirred at 25℃ for 3h. After removal of solution in vacuum, the residue was dissolved in EtOAc/THF=5/1 (200 mL). The organic layers were washed with water (50 mL x 2), brine (50 mL), then dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (4 g, yield: 90%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 1.11 - 1.61 (m, 9 H), 1.89 - 2.29 (m, 2 H), 2.47 (br. s., 1 H), 2.55 (br. s., 1 H), 2.77 (d, *J*=12.05 Hz, 1 H), 3.09 - 3.66 (m, 4 H), 7.53 (dd, *J*=8.28, 2.51 Hz, 1 H), 7.63 (dt, *J*=10.92, 2.26 Hz, 1 H), 7.79 - 7.99 (m, 1 H), 8.17 (br. s., 1 H), 10.23 - 10.75 (m, 2 H), 12.49 - 12.93 (m, 1 H). LCMS (ESI) m/z: 358 (M+1).

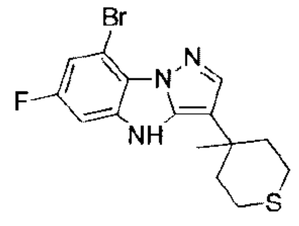
Example 106

6-fluoro-3-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 106A

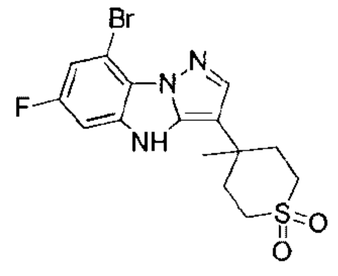
8-bromo-6-fluoro-3-(4-methyltetrahydro-2H-thiopyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole



This example was prepared as described in Examples 105A-105H, substituting dihydro-2H-thiopyran-4(3H)-one for tert-butyl 4-oxopiperidine-1-carboxylate. LCMS (ESI) m/z: 368, 370 (M, M+2).

Example 106B

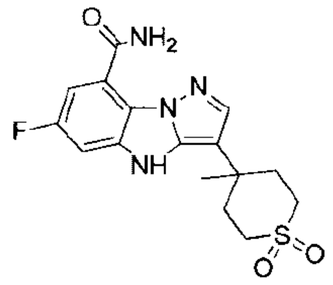
4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methyltetrahydro-2H-thiopyran 1,1-dioxide



A mixture of EXAMPLE 106A (0.1g, 0.271 mmol) and mCPBA (0.94 g, 0.542 mmol) in DCM (15 mL) and THF (3 mL) was stirred at 25℃ for 3h. The mixture was quenched with sat aq Na_2SO_3 solution (20 mL). The aqueous layer was extracted with DCM (15 mL × 3). The combined organic layers were washed with sat aq $NaHCO_3$ solution (20 mL), brine (15 mL), dried over Na_2SO_4, filtered and evaporated to provide the title compound which could be used directly in the next step without further purification.

Example 106C

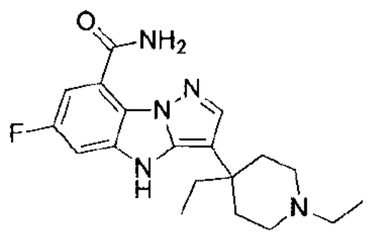
6-fluoro-3-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 105I and 105J. ^{1}H NMR (400 MHz, MeOD) δ: 7.8798 (s, 1 H), 7.56-7.59 (d, 1 H), 7.46-7.48 (d, 1 H), 3.11 (m, 2 H), 2.95-3.01 (m, 2 H), 2.52 (m, 2 H), 2.13-2.19 (m, 2 H), 1.35 (s, 3 H). LCMS (ESI) m/z: 365 (M+1).

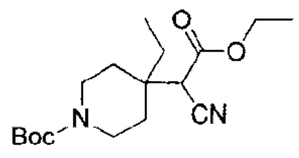
Example 107

3-(1,4-diethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 107A

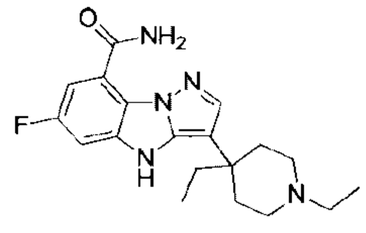
tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-ethylpiperidine-1-carboxylate



1,4-ethylpiperidin-4-yl To a mixture of EXAMPLE 105A (1.0 g, 3.4 mmol) in THF (20 mL) was added dropwise ethylmagnesium bromide (2.83 mL, 8.49 mmol) at -78℃ under N_2 atmosphere. After being stirred at -78℃ for 1h, the mixture was warmed to 32℃ and stirred for 15h and then quenched with sat NH_4Cl aq solution (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (0.8 g, yield: 73%) as a colorless oil. LCMS (ESI) m/z: 325 (M+1).

Example 107B

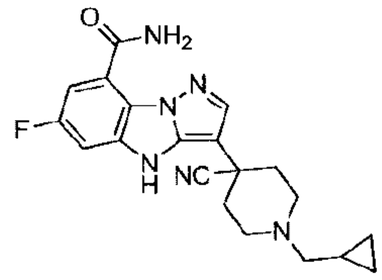
3-(1,4-diethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Example 105. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.80 (t, *J*=7.47 Hz, 3 H), 1.28 (t, *J*=7.34 Hz, 3 H), 1.72 (d, *J*=7.40 Hz, 1 H), 1.89 - 2.14 (m, 1 H), 2.41 - 2.61 (m, 1 H), 3.06 (d, *J*=7.28 Hz, 3 H), 3.37 - 3.58 (m, 1 H), 7.35 (dd, *J*=8.16, 2.51 Hz, 1 H), 7.69 (dd, *J*=10.92, 2.64 Hz, 1 H), 7.76 (s, 1 H), 8.52 (s, 1 H). LCMS (ESI) m/z: 358 (M+1).

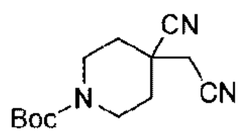
Example 108

3-(4-cyano-1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 108A

tert-butyl 4-cyano-4-(cyanomethyl)piperidine-1-carboxylate

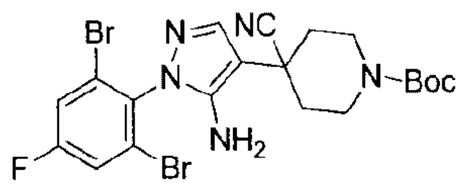


A solution of EXAMPLE 105A (2.0 g, 6.8 mmol) and KCN (1.71 g, 26.3 mmol) in a mixture of ethanol (20 mL)/Water (4 mL) was stirred at 70-80℃ for 15h. After removal of solution in vacuum, the residue was dissolved by adding water (100mL). The aqueous phase was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (1.3 g, yield: 79%) as a white solid. LCMS (ESI) m/z: 250 (M+1).

Example 108B

tert-butyl

4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazol-4-yl)-4-cyanopiperidine-1-carboxylate

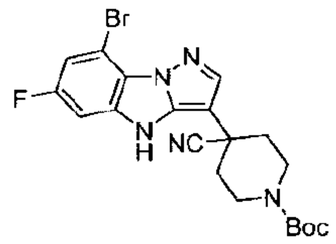


This example was prepared as described in Examples 105E-105G.

Example 108C

tert-butyl

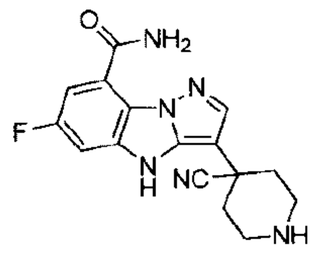
4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-cyanopiperidine-1-carboxylate



A mixture of EXAMPLE 108B (660 mg, 1.22 mmol), CuI (70 mg, 0.37 mmol), N^1,N^2-dimethylethane-1,2-diamine (65 mg, 0.74 mmol) and K_3PO_4 (780 mg, 3.68 mmol) in DMF (15mL) was stirred at 70℃ for 10 hours under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered through a pad of celite. The filtrate was evaporated and the residue was purified by column chromatography to provide the title compound (470 mg, yield: 78%) as white solids. LCMS (ESI) m/z: 462, 464 (M, M+2).

Example 108D

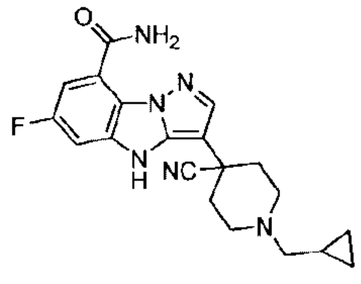
3-(4-cyanopiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 1G-1J. LCMS (ESI) m/z: 327 (M+1).

Example 108E

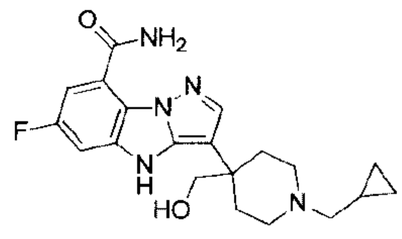
3-(4-cyano-1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 5. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.34 (d, *J*=5.90 Hz, 2 H), 0.67 - 0.75 (m, 2 H), 0.99 - 1.13 (m, 1 H), 2.37 (br. s., 2 H), 2.58 (br. s., 2 H), 2.75 (d, *J*=6.90 Hz, 2 H), 2.89 - 3.07 (m, 2 H), 3.39 - 3.61 (m, 2 H), 7.44 (dd, *J*=8.09, 2.57 Hz, 1 H), 7.75 (dd, *J*=10.85, 2.57 Hz, 1 H), 7.90 (s, 1 H), 8.34 - 8.47 (m, 1 H). LCMS (ESI) m/z: 381 (M+1).

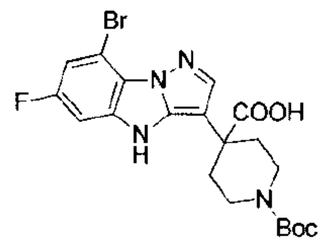
Example 109

3-(1-(cyclopropylmethyl)-4-(hydroxymethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 109A

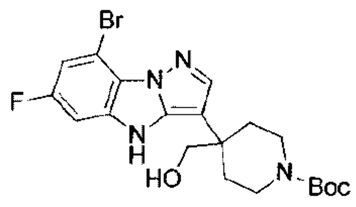
4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid



A mixture of EXAMPLE 108C (800 mg, 1.73 mmol) and 40% NaOH aq solution (5 mL) in ethanol (25 mL) was stirred at 80-90℃ for 15h. After being cooled to room temperature, the mixture was acidified to pH 3 –4 by 1N HCl and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (50 mL × 2), brine (50 mL × 2), dried over Na_2SO_4, filtered and evaporated to provide the title compoun (850 mg, purity: 79% yield: 98%) as a yellow solid which was used directly in the next step without further purification. LCMS (ESI) m/z: 481, 483 (M, M+2).

Example 109B

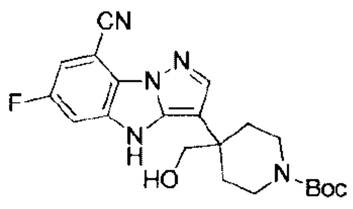
tert-butyl 4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-(hydroxymethyl)piperidine-1-carboxylate



To a mixture of EXAMPLE 109A (800 mg, 1.56 mmol) in THF (15 mL) was added 10 M BH_3-DMS (1 mL, 10 mmol) at 0℃ under N_2 atmosphere. After the dropwise addition was completed, the mixture was stirred at 0℃ for 2 hours, and then quenched with MeOH (20 mL) and evaporated off solvent in vacuum. The residue was purified by column chromatography to provide the title compound as white solids. (508 mg, yield: 70%). LCMS (ESI) m/z: 467, 469 (M, M+2).

Example 109C

tert-butyl 4-(8-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-(hydroxymethyl)piperidine-1-carboxylate

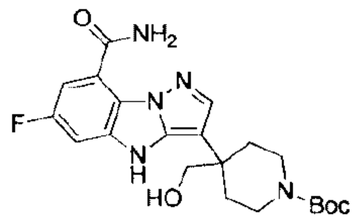


A mixture of EXAMPLE 109B (450 mg, 0.96 mmol), $Zn(CN)_2$ (225 mg, 1.92 mmol), $Pd_2(dba)_3$ (176 mg, 0.19 mmol), DPPF (215 mg, 0.38 mmol) and Zn (125 mg, 1.92 mmol) in DMF (5 mL) was stirred at 120℃ for 15h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to provide the title compound as brown solids (387 mg, yield:

87%). LCMS (ESI) m/z: 414 (M+1).

Example 109D

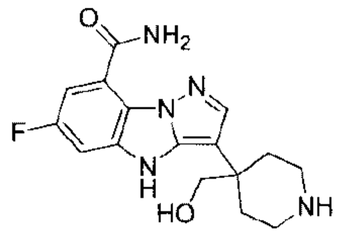
tert-butyl 4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-(hydroxymethyl)piperidine-1-carboxylate



To a mixture of EXAMPLE 109C (350 mg, 0.85 mmol) and K_2CO_3 (600 mg, 4.34 mmol) in DMSO (10 mL) was added dropwise 30% H_2O_2 (10 mL) at 0℃. After the dropwise addition was completed, the mixture was stirred at 25℃ for 10h, and then diluted with water (50 mL). The aqueous layer was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (50 mL × 2), brine (50 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound as yellow solids (270 mg, yield: 68%). LCMS (ESI) m/z: 432 (M+1).

Example 109E

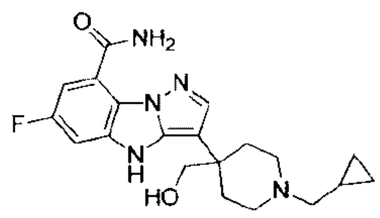
6-fluoro-3-(4-(hydroxymethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 109D (100 mg, 0.23 mmol) in DCM (10 mL) and TFA (3 mL) was stirred at 25℃ for 3h. The resultant mixture was evaporated to give the title compound as yellow oil which could be used directly in the next step without further purification. LCMS (ESI) m/z: 332 (M+1).

Example 109F

3-(1-(cyclopropylmethyl)-4-(hydroxymethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



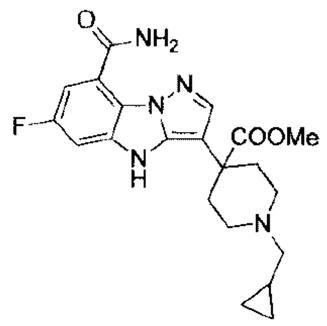
This example was prepared as the method described in Example 108E. ^{1}H-NMR (400 MHz, DMSO-d_6+D_2O) δ ppm 0.06 - 0.35 (m, 2 H), 0.44 - 0.70 (m, 2 H), 0.81 - 1.14 (m, 1 H), 1.57 - 2.01 (m, 1 H), 2.05 - 2.47 (m, 1 H), 2.57 - 2.98 (m, 1 H), 3.08 - 3.28 (m, 1 H), 3.32 - 3.52 (m, 1 H), 7.38 - 7.69 (m, 2 H), 7.80 (s, 1 H), 8.34 (s, 1 H). LCMS (ESI) m/z: 386 (M+1).

Example 110

methyl

101

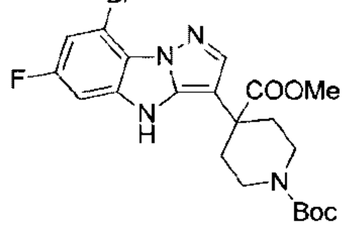
4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-1-(cyclopropylmethyl)piperidin e-4-carboxylate



Example 110A

1-(tert-butyl) 4-methyl

4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)piperidine-1,4-dicarboxylate

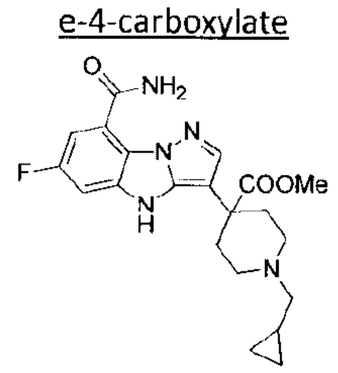


A solution of EXAMPLE 109A (250 mg, 0.52 mmol) in a mixture of MeOH/DCM= 10/1 (1 mL) was added dropwise $TMSCH_2N_2$ (0.52 mL, 1.04 mmol) at 0℃ under N_2 atmosphere. After being stirred at 0℃ for 5min, the reaction solution was quenched with $HOAc/H_2O$= 1/10 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (200 mg, yield: 78%). LCMS (ESI) m/z: 495, 497 (M, M+2).

Example 110B

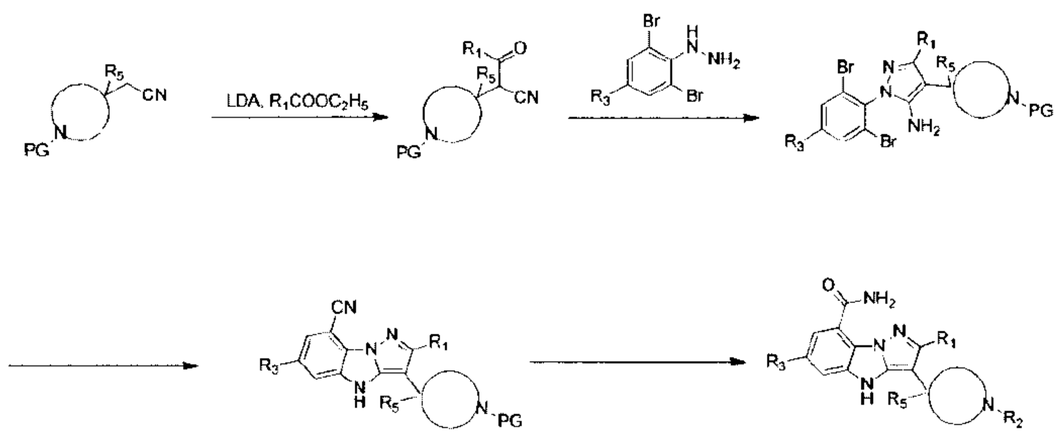
methyl

4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-1-(cyclopropylmethyl)piperidin e-4-carboxylate



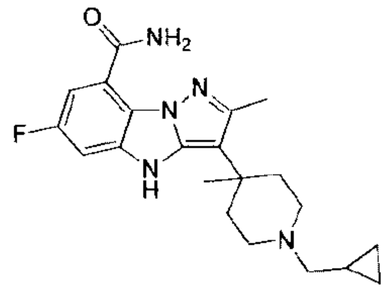
This example was prepared as the method described in Examples 109C-109F. (11 mg, yield: 37%). LCMS (ESI) m/z: 414 (M+1). ^{1}H-NMR (400 MHz, MethanoL-d4) δ ppm 0.34 (d, J=5.90 Hz, 2 H), 0.67 - 0.75 (m, 2 H), 0.99 - 1.13 (m, 1 H), 2.37 (br. s., 2 H), 2.58 (br. s., 2 H), 2.75 (d, J=6.90 Hz, 2 H), 2.89 - 3.07 (m, 2 H), 3.39 - 3.61 (m, 2 H), 7.44 (dd, J=8.09, 2.57 Hz, 1 H), 7.75 (dd, J=10.85, 2.57 Hz, 1 H), 7.90 (s, 1 H), 8.34 - 8.47 (m, 1 H). LCMS (ESI) m/z: 414 (M+1).

Scheme E



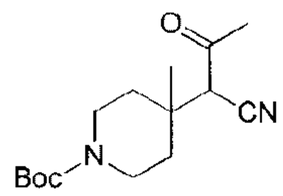
Example 111

3-(1-(cyclopropylmethyl)-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 111A

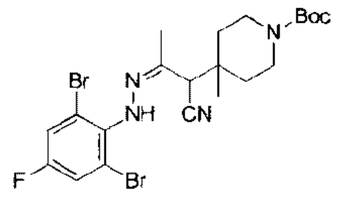
tert-butyl 4-(1-cyano-2-oxopropyl)-4-methylpiperidine-1-carboxylate



To a solution of EXAMPLE 53C (5.0 g, 21.0 mmol) in dry THF (60 mL) was added dropwise LDA (26 mL, 52.0 mmol) at -78℃ under N_2 atmosphere, followed by dropwise addition of Ac_2O (5.4 g, 52.0 mmol) after stirring at -78℃ for 1 h. The resultant mixture was slowly warmed to room temperature and stirred for 30 min. The mixture was quenched with sat aq NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (30 mL×2). The combined organic layers were evaporated and the residue was purified by column chromatograph to provide the title compound (4.5 g, yield: 76.5%) as yellow oil. LCMS (ESI) m/z: 281 (M+1).

Example 111B

tert-butyl-4-(1-cyano-2-(2-(2,6-dibromo-4-fluorophenyl)hydrazono)propyl)-4-methylpiperidine-1-carboxylate

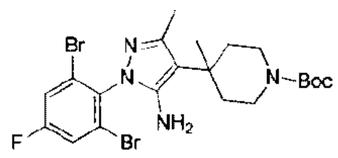


A mixture of EXAMPLE 111A (2.0 g, 7.14 mmol), HOAc (0.2 mL) and EXAMPLE 1D (2.4 g, 8.57 mmol) in EtOH (30 mL) was stirred at 70℃ for 16 h. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (2.1 g, yield: 53.8%) as a light yellow solid.

Example 111C

tert-butyl

4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl)-4-methylpiperidine-1-carboxylate

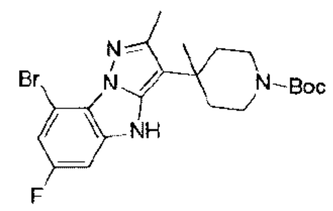


A mixture of EXAMPLE 111B (2.1 g, 3.84 mmol) and K_2CO_3 (2.1 g, 15.4 mmol) in EtOH (30 mL) was heated to 80℃ and stirred for 4h. After removal of solution in vacuum, the residue was purified by column chromatograph to provide the title compound (0.8 g, yield: 54.4%) as a light red solid.

Example 111D

tert-butyl

4-(8-bromo-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate

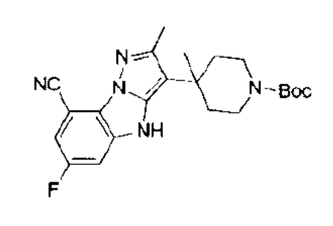


A mixture of EXAMPLE 111C (700 mg, 1.28 mmol), CuI (73 mg, 0.38 mmol), K_3PO_4 (814 mg, 3.84 mmol) and N, N-dimethyl-1,2-ethane-1,2-diamine (68 mg, 0.76 mmol) in DMF (15 mL) was stirred at 70℃ for 5h under N_2 atmosphere. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatograph to provide the title compound (400 mg, yield: 67.0%) as a yellow solid. LCMS (ESI) m/z: 465, 467 (M, M+2).

Example 111E

tert-butyl

4-(8-cyano-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate

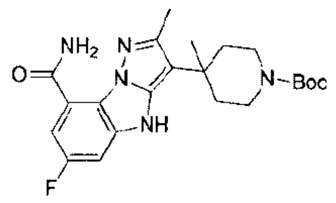


A mixture of EXAMPLE 111D (650 mg, 1.39 mmol), $Zn(CN)_2$ (326 mg, 2.78 mmol), $Pd_2(dba)_3$ (254 mg, 0.28 mmol), DPPF (309 mg, 0.56 mmol) and Zn (181 mg, 2.78 mmol) in DMF (8 mL) was stirred at 120℃ for 3h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and concentrated in vacuum. The residue was purified by column chromatography to provide the title compound (450 mg, yield: 78.5 %) as yellow solids. LCMS (ESI) m/z: 412 (M+1).

Example 111F

tert-butyl

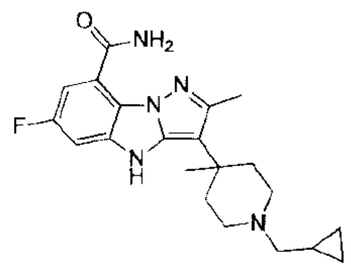
4-(8-carbamoyl-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



To a mixture of EXAMPLE 111E (450 mg, 1.09 mmol) and K_2CO_3 (906 mg, 6.56 mmol) in DMSO (10 mL) was added 30% H_2O_2 (6 mL) at 0℃. After the dropwise addition was completed, the mixture was stirred at 25℃ for 16h, and then diluted with water (50 mL). The aqueous phase was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with sat Na_2SO_3 aq solution (50 mL x 2), brine (100 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (450 mg, yield: 95.7%) as a white solids. LCMS (ESI) m/z: 430 (M+1).

Example 111G

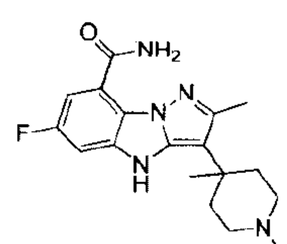
3-(1-(cyclopropylmethyl)-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as described in Examples 109E and 109F. (50 mg, yield: 56.2%). ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.41 (d, *J*=4.52 Hz, 2 H), 0.64 - 0.83 (m, 2 H), 1.12 (br. s., 1 H), 1.47 (br. s., 3 H), 2.09 (br. s., 2 H), 2.50 (s, 3 H), 2.54 - 2.71 (m, 2 H), 2.84 - 3.29 (m, 4 H), 3.52 (br. s., 2 H), 7.28 (d, *J*=8.03 Hz, 1 H), 7.48 - 7.69 (m, 1 H), 8.63 (br. s., 1 H). LCMS (ESI) m/z: 384 (M+1).

Example 112

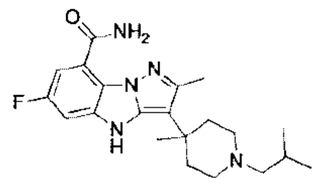
3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.20 - 1.61 (m, 6 H), 2.09 (br. s., 2 H), 2.49 (s, 3 H), 2.52 - 2.77 (m, 2 H), 3.17 (br. s., 4 H), 3.49 (br. s., 2 H), 7.16 - 7.34 (m, 1 H), 7.46 - 7.63 (m, 1 H), 8.46 (s, 1 H). LCMS (ESI) m/z: 358 (M+1).

Example 113

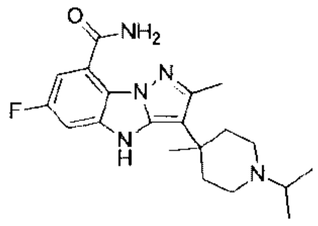
6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H NMR (400MHz, DMSO-d_6) 0.84 (d, *J*=6.5 Hz, 7 H), 1.26 (s, 3 H), 1.76 (d, *J*=6.8 Hz, 3 H), 2.00 (d, *J*=7.3 Hz, 2 H), 2.13-2.29 (m, 3 H), 2.34 (s, 1 H), 2.41 (s, 3 H), 2.68 (s, 1 H), 7.36 (dd, *J*=2.5, 8.3 Hz, 1 H), 7.55 (dd, *J*=2.5, 11.0 Hz, 1 H), 8.04 (s, 1 H), 8.29 (br, s, 1 H), 10.63 (s, 1 H). LCMS (ESI) m/z: 386 (M+1).

Example 114

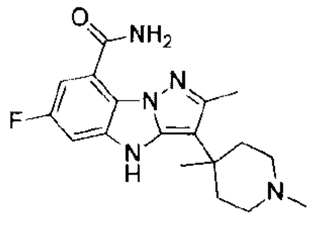
6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) d ppm 1.34 (d, *J*=5.52 Hz, 6 H), 1.47 (br. s., 3 H), 2.11 (br. s., 2 H), 2.51 (s, 3 H), 2.53 - 2.72 (m, 2 H), 3.11 (br. s., 2 H), 3.44 (br. s., 3 H), 7.20 - 7.38 (m, 1 H), 7.59 (dd, *J*=10.92, 2.64 Hz, 1 H), 8.66 (br. s., 1 H). LCMS (ESI) m/z: 372 (M+1).

Example 115

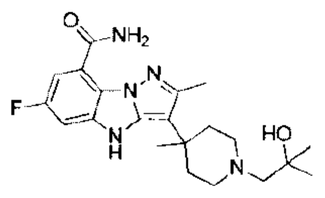
3-(1,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.46 (s, 3 H), 2.05 (br. s., 2 H), 2.50 (s, 3 H), 2.56 (d, *J*=11.67 Hz, 2 H), 2.79 (s, 3 H), 3.09 (br. s., 2 H), 3.34 - 3.41 (m, 2 H), 7.31 (dd, *J*=8.09, 2.32 Hz, 1 H), 7.63 (dd, *J*=10.98, 2.20 Hz, 1 H), 8.55 (s, 1 H). LCMS (ESI) m/z: 344 (M+1).

Example 116

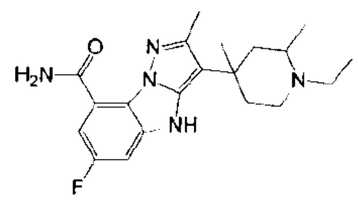
6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H NMR (400MHz, DMSO-d_6) 1.02-1.14 (m, 6H), 1.26 (s, 3H), 1.69-1.81 (m, 2H), 2.11-2.24 (m, 4H), 2.32-2.44 (m, 6H), 2.68 (br, s, 2H), 7.37 (dd, *J*=2.5, 8.3 Hz, 1H), 7.56 (dd, *J*=2.5, 11.0 Hz, 1H), 8.06 (s, 1H), 8.28 (s, 1H), 10.65 (s, 1H). LCMS (ESI) m/z: 402 (M+1).

Example 117

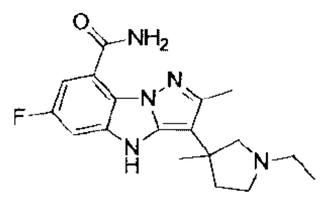
3-(1-ethyl-2,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H NMR (400 MHz, DMSO-d_6) 1.07 (t, *J*=7.0 Hz, 3H), 1.13 (d, *J*=6.0 Hz, 3H), 1.41 (s, 3H), 1.84 - 1.72 (m, 1H), 1.97 (d, *J*=10.8 Hz, 2H), 2.05 - 2.16 (m, 1H), 2.44 (s, 3H), 2.54 - 2.70 (m, 2H), 2.77 (br, s, 1H), 2.90 – 3.03 (m, 2H), 7.41 (dd, *J*=2.4, 8.4 Hz, 1H), 7.55 (dd, *J*=2.5, 11.0 Hz, 1H), 8.05 (s, 1H), 8.33 (s, 1H), 10.63 (s, 1H). LCMS (ESI) m/z: 372 (M+1).

Example 118

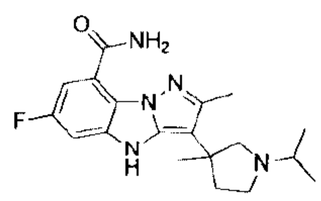
3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.37-1.41 (t, 3H), 1.58 (s, 3H), 2.47-2.49 (m, 1H), 2.51 (s, 3H), 2.67-2.74 (m, 1H), 3.29-3.30 (m, 2H), 3.34-3.67 (m, 4H), 7.33-7.35 (d, 1H), 7.66-7.69 (d, 1H), 8.52 (bs, 1H). LCMS (ESI) m/z: 344 (M+1).

Example 119

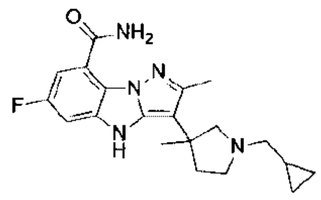
6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.36-1.45 (m, 6H), 1.52-1.59 (m, 3H), 2.48 (s, 4H), 2.61-2.73 (m, 1H), 3.45-3.53 (m, 1H), 3.55-3.82 (m, 4H), 7.24-7.33 (m, 1H), 7.56-7.68(m, 1H), 8.40-8.55 (bs, 1H). LCMS (ESI) m/z: 358 (M+1).

Example 120

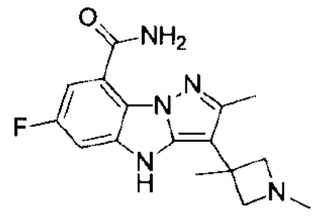
3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (MeOD, 400 MHz) δ: 0.59 (d, 2H), 0.96-1.06 (m, 1H), 1.53 (s, 3H), 2.12-2.22 (m, 1H), 2.48 (s, 5H), 2.83-2.94 (m, 1H), 2.98-3.08 (m, 2H), 3.11-3.20 (m, 1H), 7.33-7.36 (m, 1H), 7.61-7.74 (m, 1H). LCMS (ESI) m/z: 370 (M+1).

Example 121

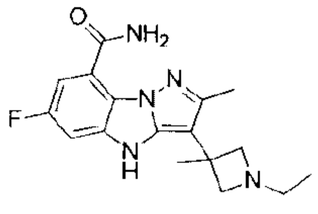
3-(1,3-dimethylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.74 (s, 3 H), 2.37 (s, 3 H), 2.94 (s, 3 H), 4.27 (d, *J*=9.79 Hz, 2 H), 4.43 (d, *J*=9.29 Hz, 2 H), 7.29 (d, *J*=8.28 Hz, 1 H), 7.62 (d, *J*=10.92 Hz, 1 H), 8.51 (br. s., 1 H). LCMS (ESI) m/z: 316 (M+1).

Example 122

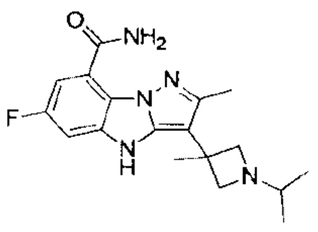
3-(1-ethyl-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.01-1.08 (m, 3H), 1.65-1.70 (m, 3H), 2.34 (s, 3H), 2.55-2.65 (m, 2H), 3.47-3.53 (m, 2H), 3.59-3.66 (m, 2H), 7.28-7.36 (dd, 1H), 7.63-7.73 (dd, 1H). LCMS (ESI) m/z: 330 (M+1).

Example 123

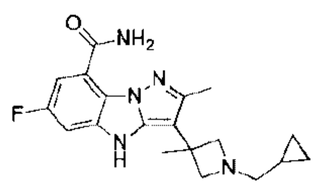
6-fluoro-3-(1-isopropyl-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (MeOD, 400 MHz) δ: 1.26 (d, J=6.53 Hz, 6H), 1.75 (s, 3H), 2.40 (s, 3H), 3.38 (d, J=5.90 Hz, 1H), 4.20-4.28 (m, 2H), 4.33-4.44 (m, 2H), 7.27-7.43 (dd, 1H), 7.62-7.76 (dd, 1H), 8.43-8.58 (bs, 1H). LCMS (ESI) m/z: 344 (M+1).

Example 124

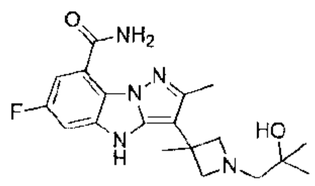
3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 0.46 (d, *J*=4.02 Hz, 2 H), 0.66 - 0.82 (m, 2 H), 1.09 (d, *J*=6.02 Hz, 1 H), 1.76 (s, 3 H), 2.37 (s, 3 H), 3.19 (br. s., 2 H), 4.19 - 4.40 (m, 2 H), 4.54 (d, *J*=9.16 Hz, 2 H), 7.24 (br. s., 1 H), 7.57 (br. s., 1 H), 8.53 (br. s., 1 H). LCMS (ESI) m/z: 356 (M+1).

Example 125

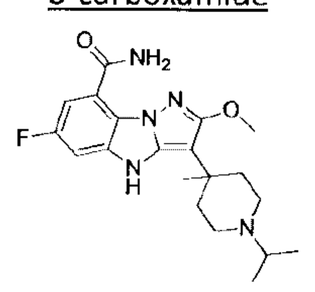
6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



This example was prepared as the method described in Example 111. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.32 (s, 6 H), 1.75 (s, 3 H), 2.30 - 2.43 (m, 3 H), 3.24 (s, 2 H), 4.35 (d, *J*=9.91 Hz, 2 H), 4.52 (d, *J*=9.29 Hz, 2 H), 7.26 (d, *J*=8.03 Hz, 1 H), 7.61 (d, *J*=11.04 Hz, 1 H), 8.50 (br. s., 1 H). LCMS (ESI) m/z: 374 (M+1).

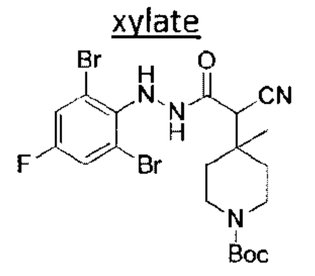
Example 126

6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 126A

tert-butyl 4-(1-cyano-2-(2-(2,6-dibromo-4-fluorophenyl)hydrazinyl)-2-oxoethyl)-4-methylpiperidine-1-carboxylate

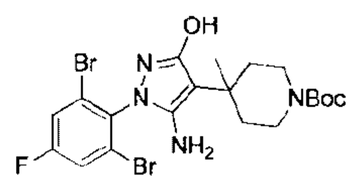


A mixture of EXAMPLE 105C (2.73 g, crude, 9.67 mmol), HATU (5.51 g, 0.26 mmol), EXAMPLE 1D (3.29 g, 11.60 mmol) and Et_3N (2.84 g, 29.01 mmol) in DMF (20 mL) was stirred at 25℃ for 10h under N_2 atmosphere. After completion the reaction mixture was quenched with water (100

mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (50 mL x 2) and brine (50 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (4.50 g, yield: 85%) as yellow solids.

Example 126B

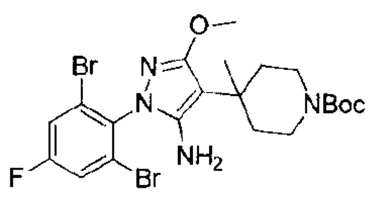
tert-butyl 4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-3-hydroxy-1H-pyrazol-4-yl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 126A (4.50 g, 8.21 mmol) and K_2CO_3 (2.27 g, 16.42 mmol) in ethanol (100 mL) was stirred at 80℃ for 15h. After removal of solution in vacuum, the residue was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (50 mL × 2) and brine (50 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (3.81 g, yield: 84%) as a yellow solid.

Example 126C

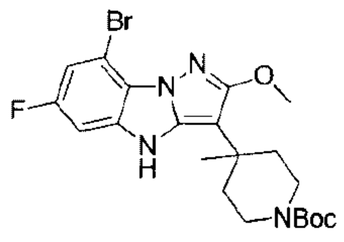
tert-butyl 4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-3-methoxy-1H-pyrazol-4-yl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 126B (2.3 g, 3.65 mmol), MeI (517.80 mg, 3.65 mmol) and K_2CO_3 (1.51 g, 10.94 mmol) in DMF (50 ml) was stirred at 25℃ for 15h. After removal of solution in vacuum, the residue was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (50 mL x 2), brine (50 mL x 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (590 mg, yield: 28.76%) as a yellow solid.

Example 126D

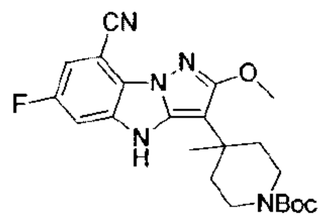
tert-butyl 4-(8-bromo-6-fluoro-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 126C (680 mg, 1.21 mmol), CuI (69 mg, 0.36 mmol), N^1,N^2-dimethylethane-1,2-diamine (64 mg, 0.73 mmol) and K_3PO_4 (770 mg, 3.63 mmol) in DMF (15mL) was stirred at 70℃ for 10h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography to provide the title compound (455 mg, yield: 78%) as white solids. LCMS (ESI) m/z: 481, 483 (M, M+2).

Example 126E

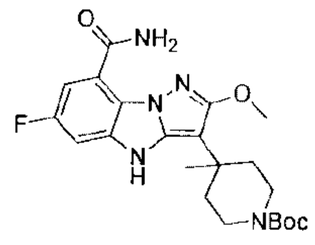
tert-butyl 4-(8-cyano-6-fluoro-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



A mixture of EXAMPLE 126D (400 mg, 0.83 mmol), $Zn(CN)_2$ (108 mg, 1.69 mmol), $Pd_2(dba)_3$ (152 mg, 0.16 mmol), DPPF (185 mg, 0.33 mmol) and Zn (108 mg, 1.66 mmol) in DMF (8 mL) was stirred at 120 ℃ for 15h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography to provide the title compound (330 mg, yield: 81%) as yellow solids. LCMS (ESI) m/z: 428 (M+1).

Example 126F

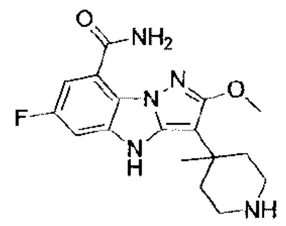
tert-butyl 4-(8-carbamoyl-6-fluoro-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidine-1-carboxylate



To a mixture of EXAMPLE 126E (200 mg, 0.47 mmol) and K_2CO_3 (300 mg, 2.17 mmol) in DMSO (5 mL) was added 30% H_2O_2 (5 mL) at 0℃. After being stirred at 25℃ for 15h, the mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to provide the title compound (195 mg, yield: 93%) as white solids. LCMS (ESI) m/z: 446 (M+1).

Example 126G

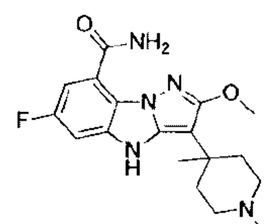
6-fluoro-2-methoxy-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A solution of EXAMPLE 126F (100 mg, 0.22 mmol) in a mixture of DCM/TFA (10 mL /3 mL) was stirred at 25℃ for 3h. After removal of solution in vacuum, the title compound was provided and used directly in the next step without further purification.

Example 126H

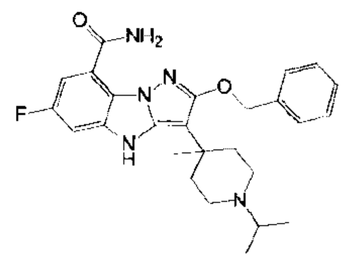
6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



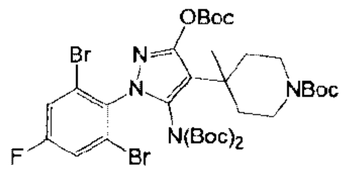
A mixture of EXAMPLE 126G (78 mg, crude, 0.22 mmol), acetone (70 mg, 1.2 mmol) and $Na(CN)BH_3$ (140 mg, 2.22 mmol) in a mixture of THF/MeOH (15 mL/5 mL) was stirred at 24℃ for 15h. The mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by prep-HPLC to provide the title compound (35 mg, yield: 41%) as a white solid. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.27 - 1.52 (m, 9 H), 1.77 - 2.19 (m, 2 H), 2.69 (br. s., 2 H), 2.84 - 3.28 (m, 2 H), 3.39 - 3.55 (m, 3 H), 4.06 (s, 3 H), 7.31 (dd, *J*=8.03, 2.51 Hz, 1 H), 7.66 (dd, *J*=10.98, 2.45 Hz, 1 H), 8.55 (br. s., 1 H). LCMS (ESI) m/z: 388 (M+1).

Example 127

2-(benzyloxy)-6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



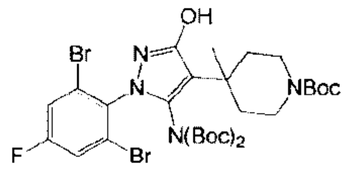
Example 127A



A mixture of EXAMPLE 126B (3.0 g, 5.48 mmol), Boc_2O (10.0 g, 45.8 mmol) and DMAP (670 mg, 5.48 mmol) was stirred at 80℃ for 3 hours. After being cooled to room temperature, the mixture was diluted with aq $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with DCM (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and

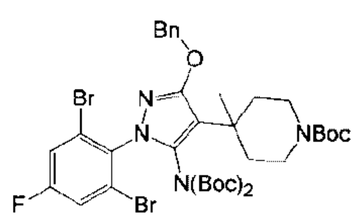
evaporated to provide the title compound (4.5 g crude) which could be used directly in the next step without further purification.

Example 127B



A mixture of EXAMPLE 127A (4.5 g, 5.31 mmol) and K_2CO_3 (1.46 g, 10.62 mmol) in MeOH (40 mL) was stirred at 20℃ for 4h. The mixture was filtered and the filtrate was evaporated. The residue was purified by chromatography to provide the title compound (3.1 g, yield: 80%) as a yellow solid.

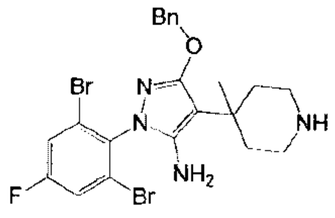
Example 127C



A mixture of EXAMPLE 127B (2.5 g, 3.35 mmol), K_2CO_3 (925 mg, 6.7 mmol) and BnBr (626 mg, 3.68 mmol) in MeOH (30 mL) was stirred at 60℃ for 8h. The mixture was filtered and the filtrate was evaporated. The residue was purified by chromatography to provide the title compound (1.4 g crude) as a white solid.

Example 127D

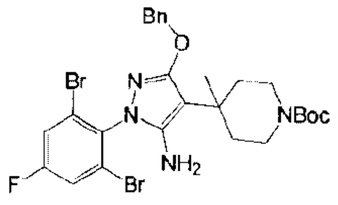
3-(benzyloxy)-1-(2,6-dibromo-4-fluorophenyl)-4-(4-methylpiperidin-4-yl)-1H-pyrazol-5-amine



A solution of EXAMPLE 127C (1.4 g, 1.63 mmol) in 4M HCl/EtOAc (20 mL) was stirred at 10℃ for 3 hours. After removal of solution in vacuum, the title compound was provided (1.0 g, yield: 100%) as a yellow solid and used directly in the next step without further purification.

Example 127E

tert-butyl 4-(5-amino-3-(benzyloxy)-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazol-4-yl)-4-methylpiperidine-1-carboxylate

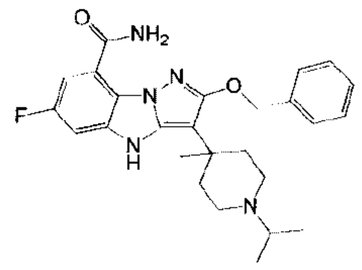


A mixture of EXAMPLE 127D (1.0 g, 1.78 mmol), Et_3N (362 mg, 3.56 mmol) and Boc_2O (776 mg, 3.56 mmol) in DCM (15 mL) was stirred at 10℃ for 4 hours. The mixture was diluted with H_2O (20 mL). The aqueous layer was extracted with DCM (15 mL x 2). The combined organic layers

were washed with water, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (1.0 g crude) as a white solid.

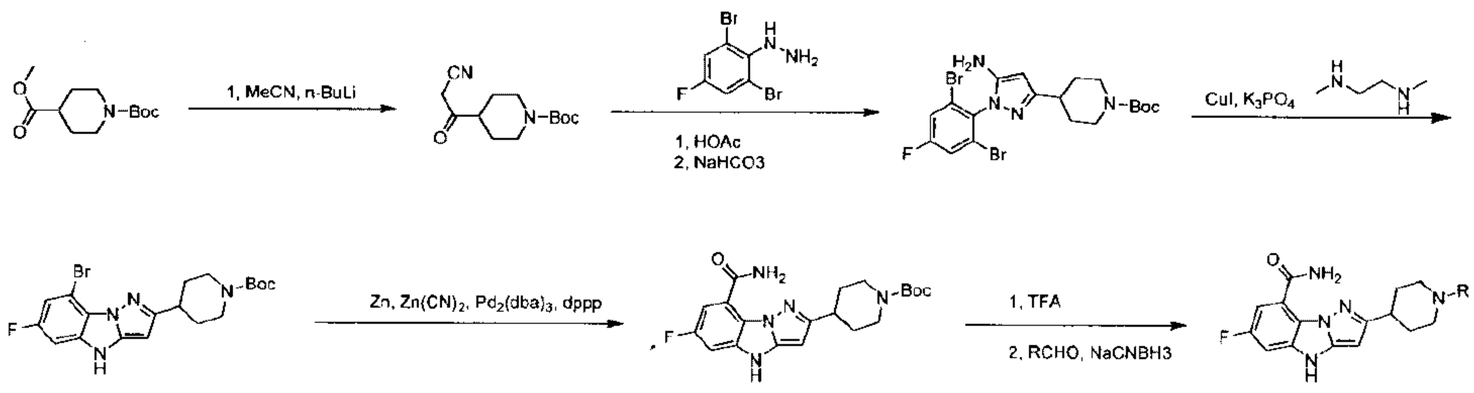
Example 127F

2-(benzyloxy)-6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



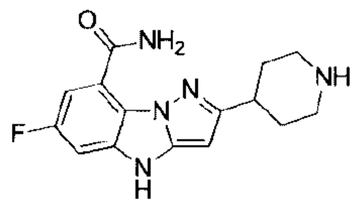
This example was prepared as described in Examples 126D-126H. ^{1}H NMR (400 MHz, DMSO-d_6) 0.95 (d, *J*=6.5 Hz, 6 H), 1.24 (s, 3 H), 1.60-1.72 (m, 2 H), 2.34 (br, s, 4 H), 2.66-2.77 (m, 3 H), 5.32 (s, 2 H), 7.29-7.55 (m, 7 H), 8.04 (s, 1 H), 8.34 (br, s, 1 H), 10.20 (s, 1 H). LCMS (ESI) m/z: 464 (M+1).

Scheme F



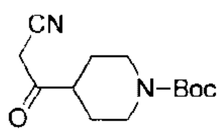
Example 128

6-fluoro-2-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



Example 128A

tert-butyl 4-(2-cyanoacetyl)piperidine-1-carboxylate

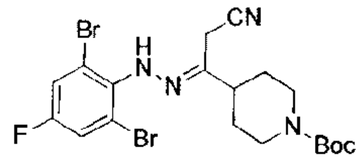


To a solution of acetonitrile (5.06 g, 123.4 mmol) in dry THF (200 mL) was added n-BuLi (39.5 mL, 98.6 mmol) dropwise at -78℃ under nitrogen atmosphere. The mixture was stirred at -78℃ for 2 h. Thereafter, a solution of 1-(tert-butyl) 4-methyl piperidine-1,4-dicarboxylate (20 g, 82.2 mmol) in tetrahydrofuran (100 mL) was added dropwise into the above mixture. After the dropwise addition was completed, the resultant mixture was warmed to 15℃ and stirred for 16h and subsequently quenched with sat aq NH_4Cl solution (100 mL). The aqueous phase was extracted with EtOAc (100 mL x 2). The combined organic layers were dried over Na_2SO_4,

filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (7.9 g, yield: 38.1%) as a yellow solid. LCMS (ESI) m/z: 253 (M+1).

Example 128B

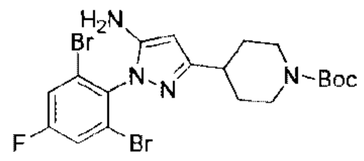
tert-butyl-4-(2-cyano-1-(2-(2,6-dibromo-4-fluorophenyl)hydrazono)ethyl)piperidine-1-carboxylate



A mixture of EXAMPLE 128A (6.35 g, 25.16 mmol) and EXAMPLE 1D (10 g, 35.2 mmol) in ethanol (80 mL) and HOAc (80 mL) was stirred at 85℃ for 16 h. After being cooled to room temperature, the mixture was evaporated to provide the title compound (15 g, crude) which could be used directly in the next stepwith out further purification.

Example 128C

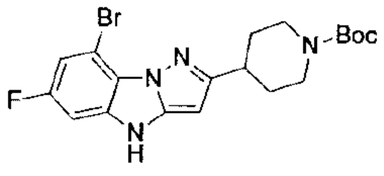
tert-butyl 4-(5-amino-1-(2,6-dibromo-4-fluorophenyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate



A mixture of EXAMPLE 128B (13 g, 25.1 mmol) and Et_3N (12.7 g, 125.5 mmol) in ethanol (100 mL) was heated to 80℃ for about 16h. After being cooled to room temperature, the mixture was evaporated. The residue was purified by column chromatograph to provide the title compound (11 g, yield: 84.6%) as a yellow solid.

Example 128D

tert-butyl 4-(8-bromo-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-2-yl)piperidine-1-carboxylate

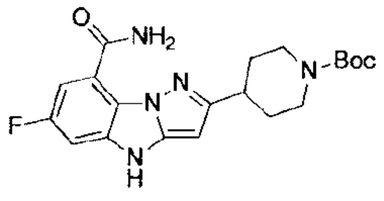


A mixture of EXAMPLE 128C (1.5 g, 2.9 mmol), CuI (166 mg, 0.87 mmol), K_3PO_4 (1.8 g, 8.7 mmol) and N^1,N^2-dimethylethane-1,2-diamine (153 mg, 1.74 mmol) in DMF (8 mL) was stirred at 55℃ for 18h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatograph to provide the title compound (350 mg, yield: 27.6%) as a yellow solid. LCMS (ESI) m/z: 437, 439 (M, M+2).

Example 128E

tert-butyl

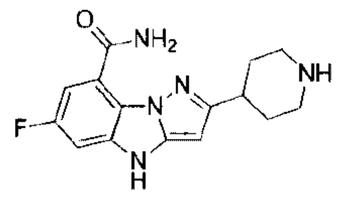
4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-2-yl)piperidine-1-carboxylate



A mixture of EXAMPLE 128D (350 mg, 0.8 mmol), $Zn(CN)_2$ (188 mg, 1.6 mmol), $Pd_2(dba)_3$ (110 mg, 0.12 mmol), DPPF (133 mg, 0.24 mmol), and Zn powder (104 mg, 1.6 mmol) in DMF (4 mL) was stirred at 120℃ for 2h under N_2 atmosphere. After being cooled to room temperature, the resultant mixture was filtered and the filtrate was evaporated. The residue was purified by prep-TLC to provide the title compound (50 mg, yield: 16.2%) as a yellow solid. LCMS (ESI) m/z: 402 (M+1).

Example 128F

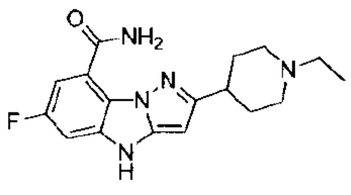
6-fluoro-2-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixed solution of EXAMPLE 128E (50 mg, 0.125 mmol) in TFA (1 mL) and DCM (6 mL) was stirred at 20℃ for 2h. The resultant mixture was evaporated. The residue was purified by prep-HPLC to provide the title compound (23 mg, yield: 59.0%) as a white solid. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.07 - 1.27 (m, 9 H), 2.51 (d, *J*=1.51 Hz, 2 H), 2.76 - 2.97 (m, 2 H), 3.34 (d, *J*=3.26 Hz, 2 H), 5.74 (br. s., 1 H), 7.36~7.39 (m, 1 H), 7.68~7.72 (m, 1 H). LCMS (ESI) m/z: 302 (M+1).

Example 129

2-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide



A mixture of EXAMPLE 128F (20 mg, 0.066 mmol), 40% acetaldehyde (0.2 mL) and $Na(CN)BH_3$ (17 mg, 0.264 mmol) in MeOH (5 mL) was stirred at 10℃ for 16h. After the reaction was complete, the resultant mixture was diluted with water (5 mL). The aqueous layer was extracted with DCM (20 mL x 2). The combined organic layers were evaporated. The residue was purified by prep-HPLC to provide the title compound (17.36 mg, yield: 78.9%) as a light yellow solid. ^{1}H-NMR (400 MHz, MethanoL-d_4) δ ppm 1.38 (t, *J*=7.28 Hz, 3 H), 1.98 - 2.23 (m, 2 H), 2.28 - 2.49 (m, 2 H), 2.92 - 3.25 (m, 5 H), 3.57 (d, *J*=11.54 Hz, 2 H), 5.83 (s, 1 H), 7.29 (dd, *J*=8.28, 2.51 Hz, 1 H), 7.61 (dd, *J*=10.92, 2.51 Hz, 1 H), 8.60 (br. s., 1 H). LCMS (ESI) m/z: 330 (M+1).

***In vitro* studies**

Cellular PARylation assay

HCC1937 cells were planted into 96 well plates at $4x10^4$ cells/well and incubated at 37℃ in an incubator overnight. After being treated with a test compound for 30 min, cells were then treated with 1 mM H_2O_2 for 10 min. The cells were washed with 200ul pre-chilled PBS twice and fixed with 100ul pre-chilled methanol/acetone (7:3) on ice for 30 min. After being air-dried, the plates were blocked using PBS-tween blocking solution (0.05%) with dissolved 5% nonfat dry milk for 30 min at room temperature. The cells were incubated with anti-PAR antibody 10H

(1:100) at room temperature for 1 hour followed by washing with PBS-tween20 for 3 times; and then added into a blocking solution including goat anti-mouse fluorescein isothiocyanate (FITC)-coupled secondary antibody and 1μg/mL DAPI to incubate away from light at room temperature for 1 hour. After being washed with PBS-tween20 for 3 times, the plate was analyzed with a fluorescence microplate counter (Flexstation III, Molecular Device).

PARP enzymatic assay (following the manual of HT Universal Colorimetric PARP1 Assay Kit).

Histone proteins were coated on a 96-well plate and incubated overnight at 4°C. After be washed 3 times with 200ul PBST solution, the plate was blocked with a blocking solution and incubated for 30 min at room temperature, and then washed with PBST solution 3 times. A compound to be tested was treated and added to the plate. Thereafter, 20 μl of diluted PARP1 (1nM) or 20 μl of PARP2 (3nM) solution was added into the reaction system and incubated for 1 or 2 hours. 50ul of streptavidin-HRP mixture (1:50) was added into the plate and incubated for 30 min at room temperature. The plate was then washed with three times with PBST buffer. 100μl of (HRP) (Chemiluminescent substrate A and substrate B (1:1)) was added into the plate, and the plate was immediately read on a microplate reader (Envision, PerkinElmer).

Anti-proliferation assay

MDA-MB-436 and MDA-MB-231 cells were seeded in 96-well plates at the density of 500 and 2000cells per well respectively and cultured overnight in a medium RPMI1640 supplemented with 10% (v/v) FBS and 1% (v/v) Penicillin-Streptomycin. After adding a compound to be tested, the cells were treated for 8 days. Cellular viabilities were measured by CCK8 kit following the specific method:adding 10ul CCK8 reagent each well and incubating for 3 hours at 37°C in 5% CO2 incubator. After shaking for 10 min, the optical density values(OD) were measured at 450 nm by Flexstation III (Molecular Device).

For the compound combination test (in combination with drugs for DNA damages), the PF50 value is calculated to measure a synergetic effect of a drug. PF50 = [IC50 of a tested compound] / [IC50 of the tested compound at a fixed conc. of a drug for DNA damages]. Temozolomide (TMZ) was used as the drug for DNA damages in this study.

The data of PARP-1 enzymatic inhibition IC_{50} and cellular PARylation EC_{50} of the compounds of this invention were provided in Table I below. Compounds with IC_{50} between 1 nM to 100 nM were designated as +++; compounds with IC_{50} between 101 nM to 1000 nM were designated as ++, and compounds with IC_{50} above 1000 nM were designated as +.

Table 1

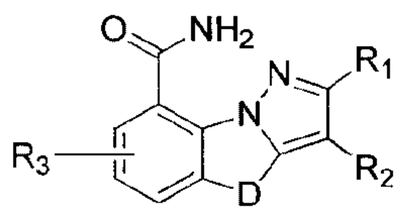
Tested/Example Title Compounds	IC_{50} (nM)	EC_{50} (nM)	Tested/Example Title Compounds	IC_{50} (nM)	EC_{50} (nM)
ABT-888	+++	+++	64	+++	++
MK-4827	+++	+++	65	+++	+++
BMN-673	+++	+++	66	+++	+++
1	+++	++	67	+++	+++
2	+++	+++	68	+++	+++
3	+++	+++	69	+++	+++

4	+++	+++	70	+++	+++
5	+++	+++	71	+++	+++
6	+++	+++	72	+++	+++
7	+++	+++	73	+++	+++
8	+++	++	74	+++	++
9	+++	+++	75	+++	++
10	+++	+++	76	+++	+++
11	+++	++	77	+++	+++
12	+++	+++	78	+++	+++
13	+++	++	79	+++	+++
14	+++	+++	80	+++	+++
15	+++	+++	81	+++	+++
16	+++	+++	82	+++	+++
17	+++	++	83	+++	+++
18	+++	+++	84	+++	+++
19	+++	+++	85	+++	+++
20	+++	+++	86	+++	+++
21	+++	+++	87	+++	++
22	+++	+++	88	+++	+++
23	+++	+++	89	+++	++
24	+++	++	90	+++	+++
25	+++	+++	91	+++	+++
26	+++	++	92	+++	+++
27	+++	+++	93	+++	+++
28	+++	+++	94	+++	++
29	+++	+++	95	+++	+++
30	+++	+++	96	+++	+++
31	+++	+++	97	+++	++
32	+++	+++	98	+++	++
33	+++	++	99	+++	+++
34	+++	++	100	+++	+++
35	+++	++	101	+++	++
36	+++	++	102	+++	++
37	+++	+	103	+++	++
38	++	+	104	+++	+++
39	+++	++	105	+++	+++
40	+++	+	106	+++	++
41	++	+	107	+++	+++
42	+++	++	108	+++	+++
43	+++	++	109	+++	++
44	++	++	110	+++	++
45	++	+	111	+++	+++

46	++	+	112	+++	+++
47	+++	+	113	+++	+++
48	+++	+++	114	+++	+++
49	+++	++	115	+++	+++
50	++	+	116	+++	+++

Claims

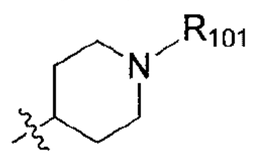
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

wherein,

D is $-C(R_{d1})(R_{d2})-$ or $-N(R_{d4})-$;

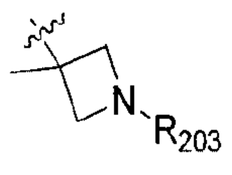
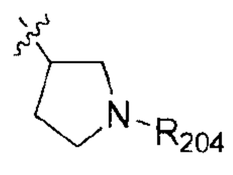
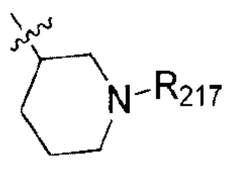
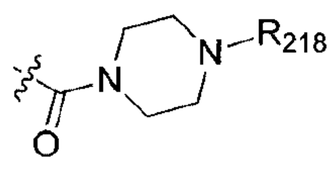
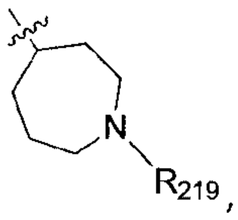
R_1 is selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, C_{1-3} alkyl, C_{1-3} alkyloxyl, benzyloxyl, and  , in which R_{101} is selected from the group consisting of H, methyl, ethyl, n-propyl or isopropyl;

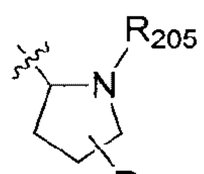
R_3 is selected from the group consisting of H, F, Cl, Br, CN, and methyl;

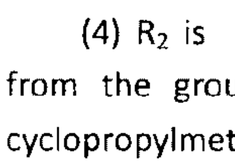
R_2 satisfies any one of following requirements (1) – (10):

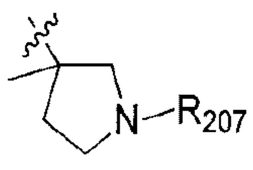
(1) R_2 is selected from H, F, Cl, Br, I, CN, OH, SH, and NH_2;

(2) R_2 is $-CH_2N(R_{201})(R_{202})$, in which R_{201} and R_{202} are separately and independently selected from the group consisting of H, C_{1-3} alkyl, C_{1-3} alkylacyl, C_{3-6} cycloalkylacyl or C_{3-6} cycloalkyl;

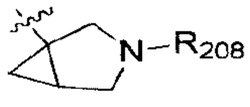
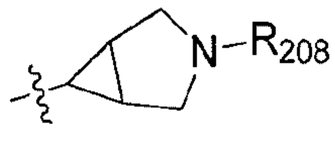
(3) R_2 is selected from the group consisting of  ,  ,  ,  , and  , in which R_{203}, R_{204}, R_{217}, and R_{218} are separately and independently selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl or cyclopropylmethylene, the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl or methyloxyl, and the number of substituents is 0, 1, 2 or 3; R_{219} is selected from the group consisting of methyl and ethyl;

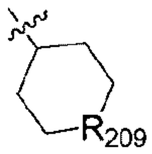


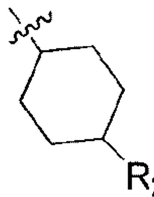
(4) R_2 is  , in which R_{205} and R_{206} are separately and independently selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl, and cyclopropylmethylene, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl or methyloxyl, and the number of substituents is 0, 1, 2 or 3; R_{206} is also selected from the group consisting of F, Cl, Br, I, CN, OH, and NH_2;

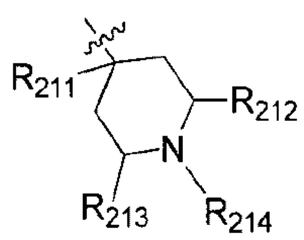
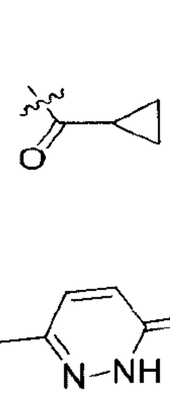
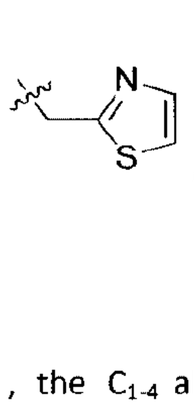
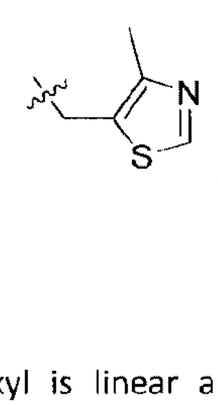
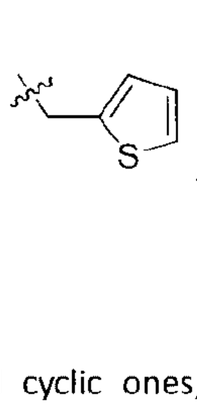
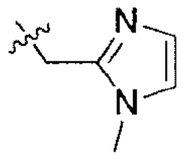
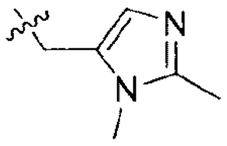
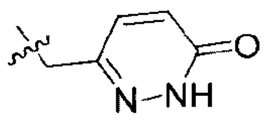
(5) R_2 is  , in which R_{207} is selected from the group consisting of H, substituted or unsubstituted C_{1-3} alkyl, cyclopropyl, cyclopropylmethylene, cyclobutyl,

cyclobutylmethylene, oxacyclobutyl or oxacyclobutylalkylene, where the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, CF_3, methyloxyl, and methylsulfonyl, and the number of substituents is 0, 1, 2 or 3;

(6) R_2 is  or  , in which R_{208} is selected from the group consisting of H, cyclopropylmethylene, substituted or unsubstituted C_{1-4} alkyl, in the R_{208}, the substituted or unsubstituted C_{1-4} alkyl is linear and cyclic ones, wherein the substituent is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, CF_3, methyloxyl, and methylsulfonyl, and the number of substituents is 0, 1, 2 or 3;

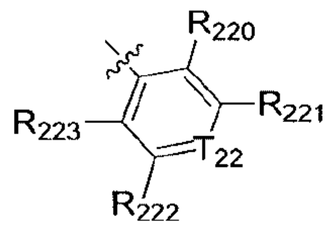
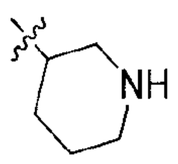
(7) R_2 is selected from  , in which R_{209} is selected from the group consisting of $-C(R_{d1})(R_{d2})-$, $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, $-C(=O)O-$, $-C(=O)-$, $-C(=S)-$, $-S(=O)-$ or $-S(=O)_2-$;

(8) R_2 is  , in which R_{210} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NH_2, N,N-di(C_{1-3} alkyl)amino, and C_{1-3} alkylamino;

(9) R_2 is selected from  , in which $R_{211-213}$ are selected from the group consisting of H or substituted or unsubstituted C_{1-4} alkyloxylcarbonyl, C_{1-4} alkyl, F, Cl, Br, I, CN, OH, and NH_2, R_{214} is selected from the group consisting of H or substituted or unsubstituted C_{1-4} alkyloxylcarbonyl, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethylene or unsaturated C_{5-6} heterocyclohydrocarbyl, $-S(=O)_2CH_3$,  ,  ,  ,  ,  ,  , and  , the C_{1-4} alkyl is linear and cyclic ones, wherein the substituent is R_{215}, the cycloalkyl or unsaturated heterocyclohydrocarbyl has O, S or NR_{216} with a number of 0, 1 or 2; R_{216} is selected from the group consisting of H and C_{1-4}alkyl substituted by R_{215}, R_{215} is selected from the group consisting of F, Cl, Br, I, CN, OH, NH_2, methyl, ethyl, methyloxyl, ethyloxyl, formyl, acetyl, methylsulfonyl, ethylsulfonyl, methyloxylcarbonyl, ethyloxylcarbonyl, dimethylamino, diethylamino, dimethylaminocarbonyl, diethylaminocarbonyl, oxo, the number of R_{215} is 1, 2 or 3,

or R_{212} and R_{213} join together to form a linker selected from the group consisting of $-CH_2-$,

$-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

(10) R_2 is selected from  , in which T22 is selected from the group consisting of N or $C(R_{224})$, $R_{220-224}$ are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, C_{1-3} alkylamino-C_{1-3} alkyl, and  ; R_{d1}, and R_{d2} are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, and NH_2, or selected from the group, optionally substituted by R_{01}, consisting of C_{1-10} alkyl, C_{1-10} heteroalkyl, C_{3-10} cyclohydrocarbyl, C_{3-10} heterocyclohydrocarbyl;

R_{01} is selected from the group consisting of F, Cl, Br, I, CN, OH, SH, NH_2, and R_{02};

R_{02} is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkylamino, N,N-di(C_{1-10} alkyl) amino, C_{1-10} alkyloxyl, C_{1-10} alkylacyl, C_{1-10} alkyloxylcarbonyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfinyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, C_{3-10} heterocycloalkylamino, C_{3-10} cycloalkyloxyl, C_{3-10} cycloalkylacyl, C_{3-10} cycloalkyloxylcarbonyl, C_{3-10} cycloalkylsulfonyl, and C_{3-10} cycloalkylsulfinyl;

heteroatom or heteroatomic group is separately and independently selected from the group consisting of $-C(=O)N(R_{d3})-$, $-N(R_{d4})-$, $-C(=NR_{d5})-$, $-S(=O)_2N(R_{d6})-$, $-S(=O)N(R_{d7})-$, -O-, -S-, $-C(=O)O-$, $-C(=O)-$, $-C(=S)-$, $-S(=O)-$, and $-S(=O)_2-$;

R_{d3-d7} are separately and independently selected from the group consisting of H, and R_{03};

R_{03} is C_{1-10} alkyl;

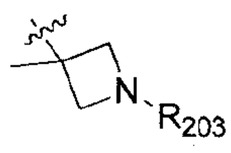
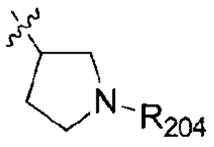
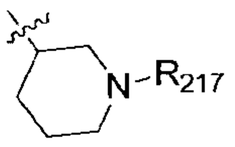
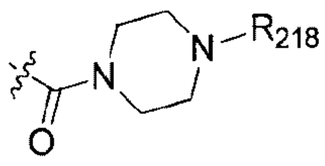
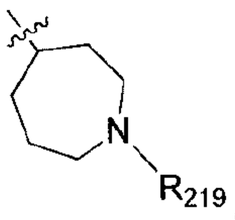
R_{02}, and R_{03} are optionally substituted by R_{001};

R_{001} is selected from the group consisting of F, Cl, Br, I, CN, OH, $N(CH_3)_2$, $NH(CH_3)$, NH_2, CF_3, $(NH_2)CH_2$, $(HO)CH_2$, CH_3, CH_3O, $CH_3C(=O)$, $CH_3O\,C(=O)$, $CH_3S(=O)_2$, and $CH_3S(=O)$; and

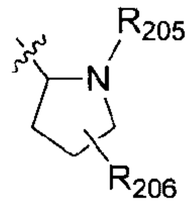
the number of R_{01}, R_{001}, the heteroatom, or heteroatomic group is separately and independently selected from 0, 1, 2, and 3.

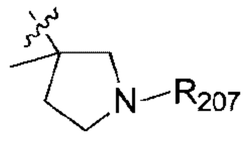
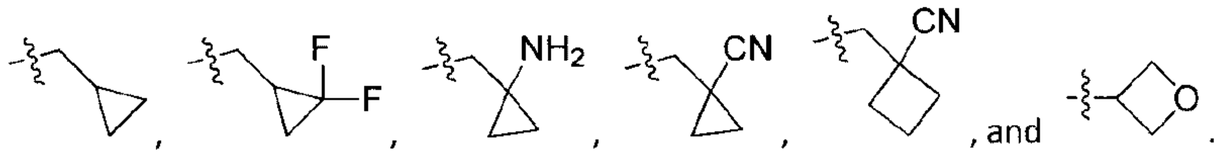
2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the D is selected from -NH-, $-N(CH_3)-$, $-C(F)_2-$, -C(H) (F)- and -C(H) (OH)-.

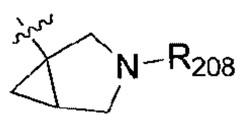
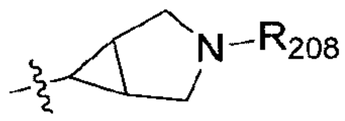
3.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from $-CH_2N(R_{201})(R_{202})$, R_{201} and R_{202} are separately and independently selected from the group consisting of H and cyclopropylacyl.

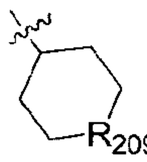
4.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from the group consisting of  ,  ,  ,  , and  , in which R_{203} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, $-CH_2C(CH_3)(CH_3)(OH)$, and cyclopropylmethylene, R_{204} is selected from the group consisting of methyl, ethyl, n-propyl, and isopropyl, $R_{217-219}$ are

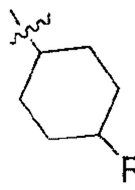
separately and independently selected from the group consisting of methyl and ethyl.

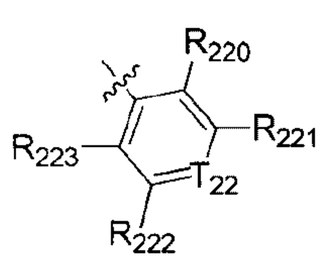
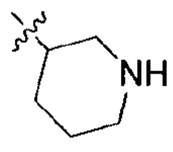
5.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which R_{205} and R_{206} are separately and independently selected from the group consisting of H, methyl, ethyl, n-propyl, and isopropyl, R_{206} is selected from the group consisting of F, Cl, Br, I, CN, OH, and NH_2.

6.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which R_{207} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2S(=O)_2CH_3$, $-CH_2CH_2CN$,  , and .

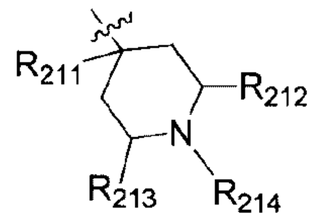
7.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from the group consisting of  or  , in which R_{208} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, cyclopropylmethylene, and cyclobutyl.

8.The compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which R_{209} is selected from the group consisting of O and $S(=O)_2$.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which R_{210} is selected from the group consisting of dimethylamino, methylamino, H, F, Cl, Br, I, CN, OH, and NH_2.

10. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which T22 is selected from the group consisting of N or $C(R_{224})$, $R_{220\text{-}224}$ are separately and independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, SH, NH_2, $C_{1\text{-}3}$ alkylamino-$C_{1\text{-}3}$ alkyl, and  ;

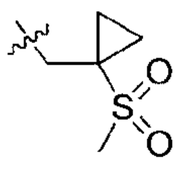
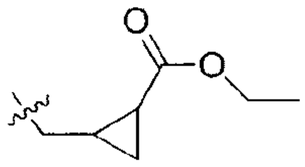
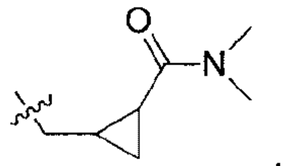
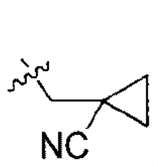
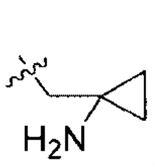
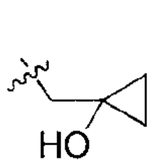
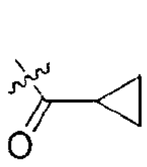
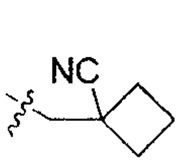
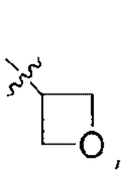
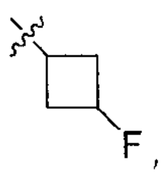
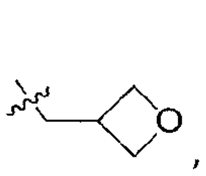
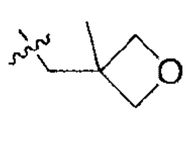
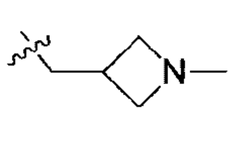
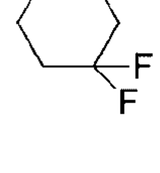
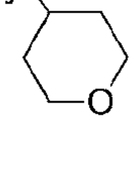
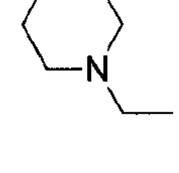
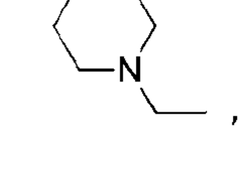
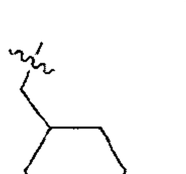
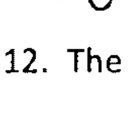
the $C_{1\text{-}3}$ alkylamino-$C_{1\text{-}3}$ alkyl is selected from methylaminomethylene.

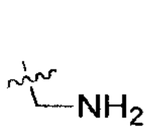
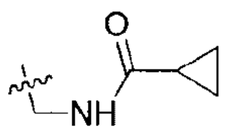
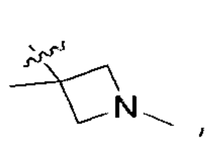
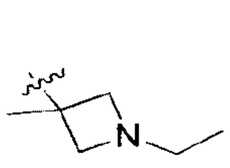
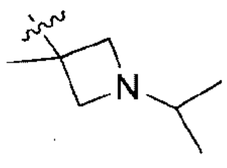
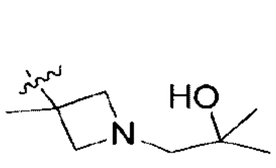
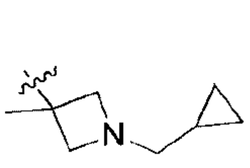
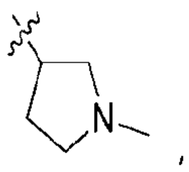
11.The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from  , in which

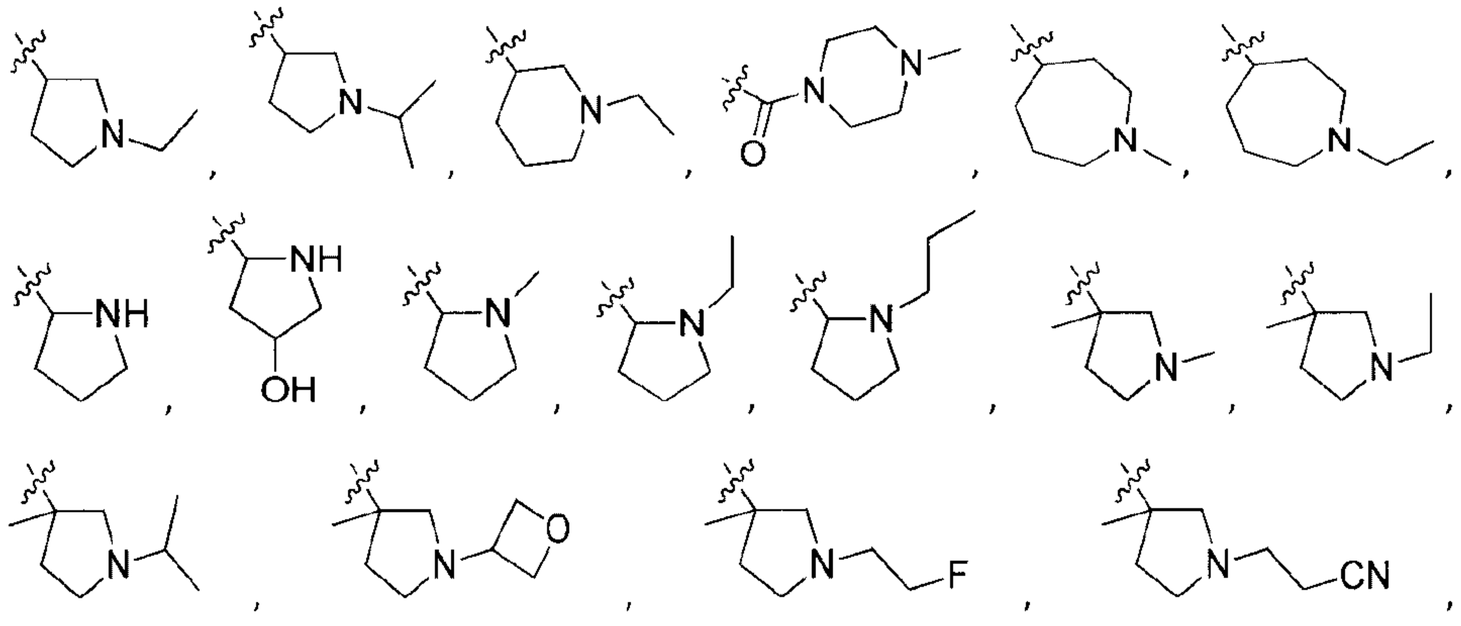
R_{211} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NH_2, methyl, ethyl, hydroxylmethyl, and methyloxylcarbonyl,

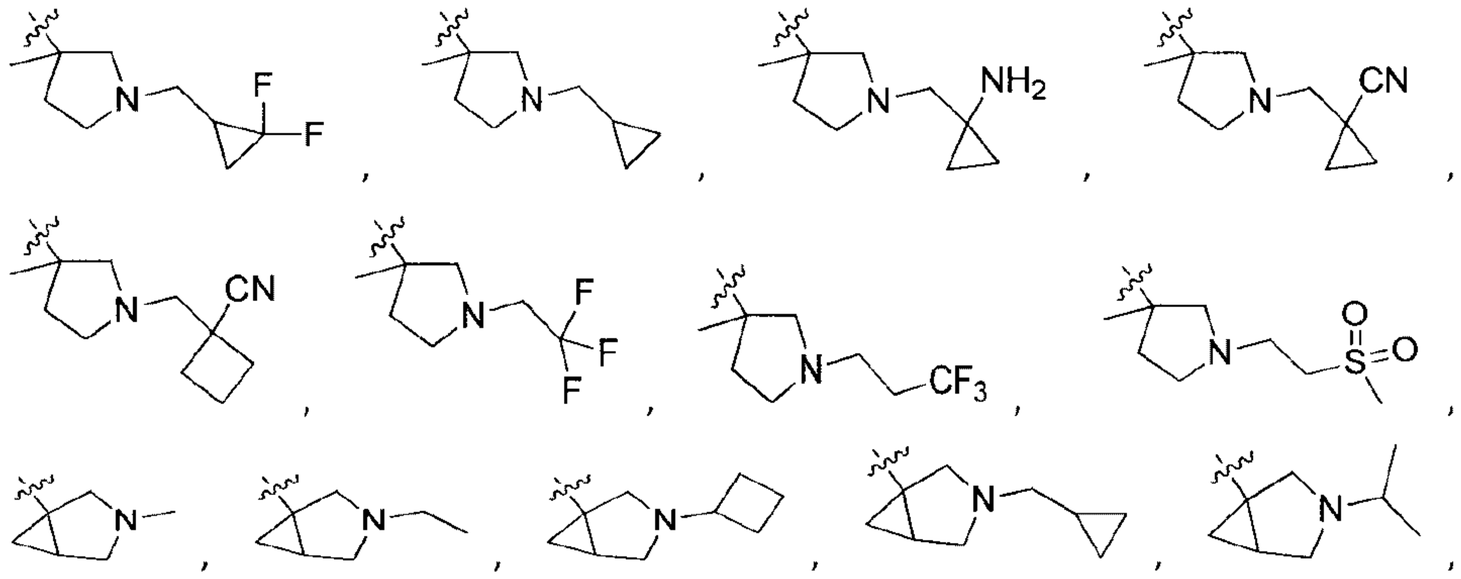
R_{212} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, NH_2, and methyl,

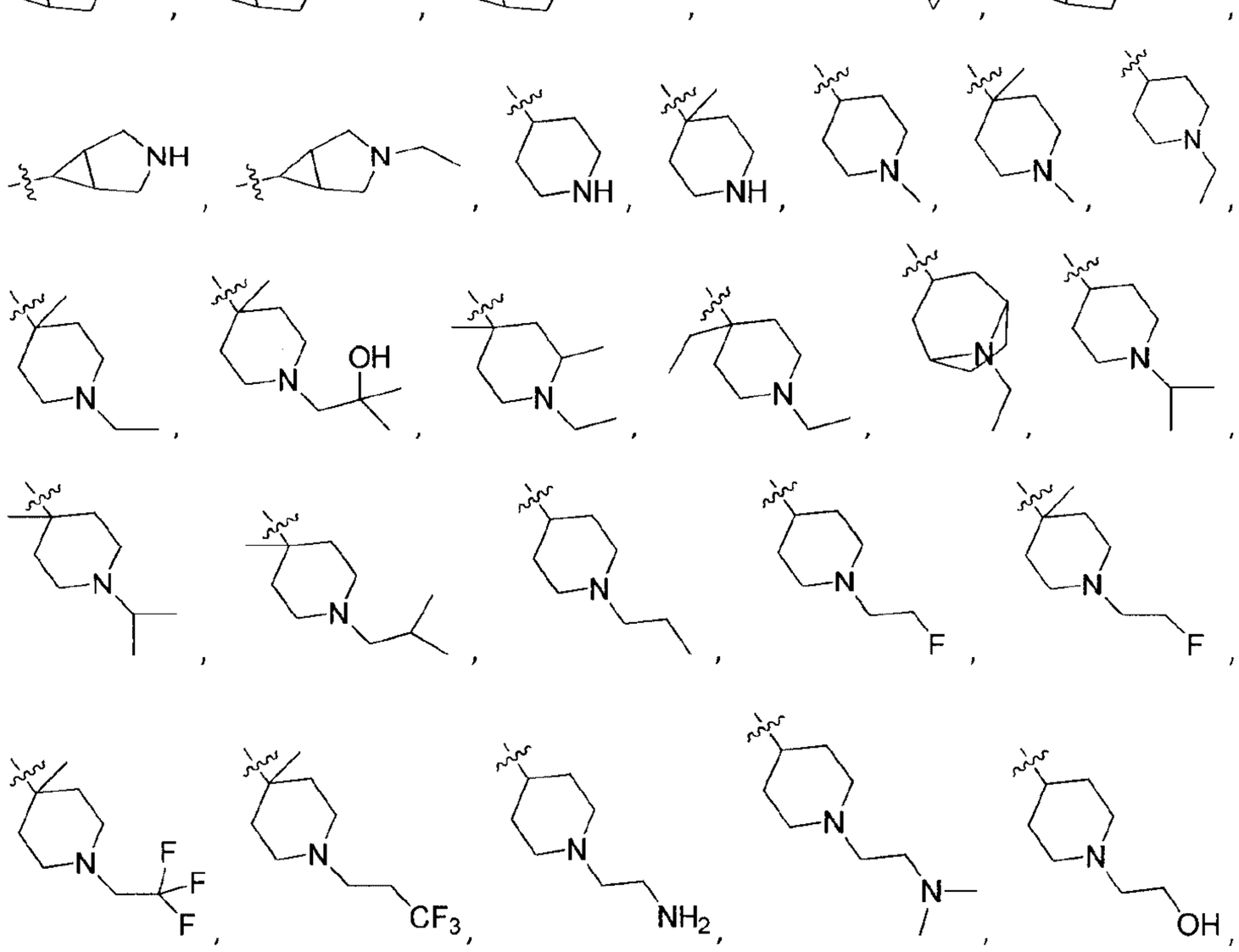
R_{213} is selected from the group consisting of H, F, Cl, Br, I, CN, OH, and NH_2,

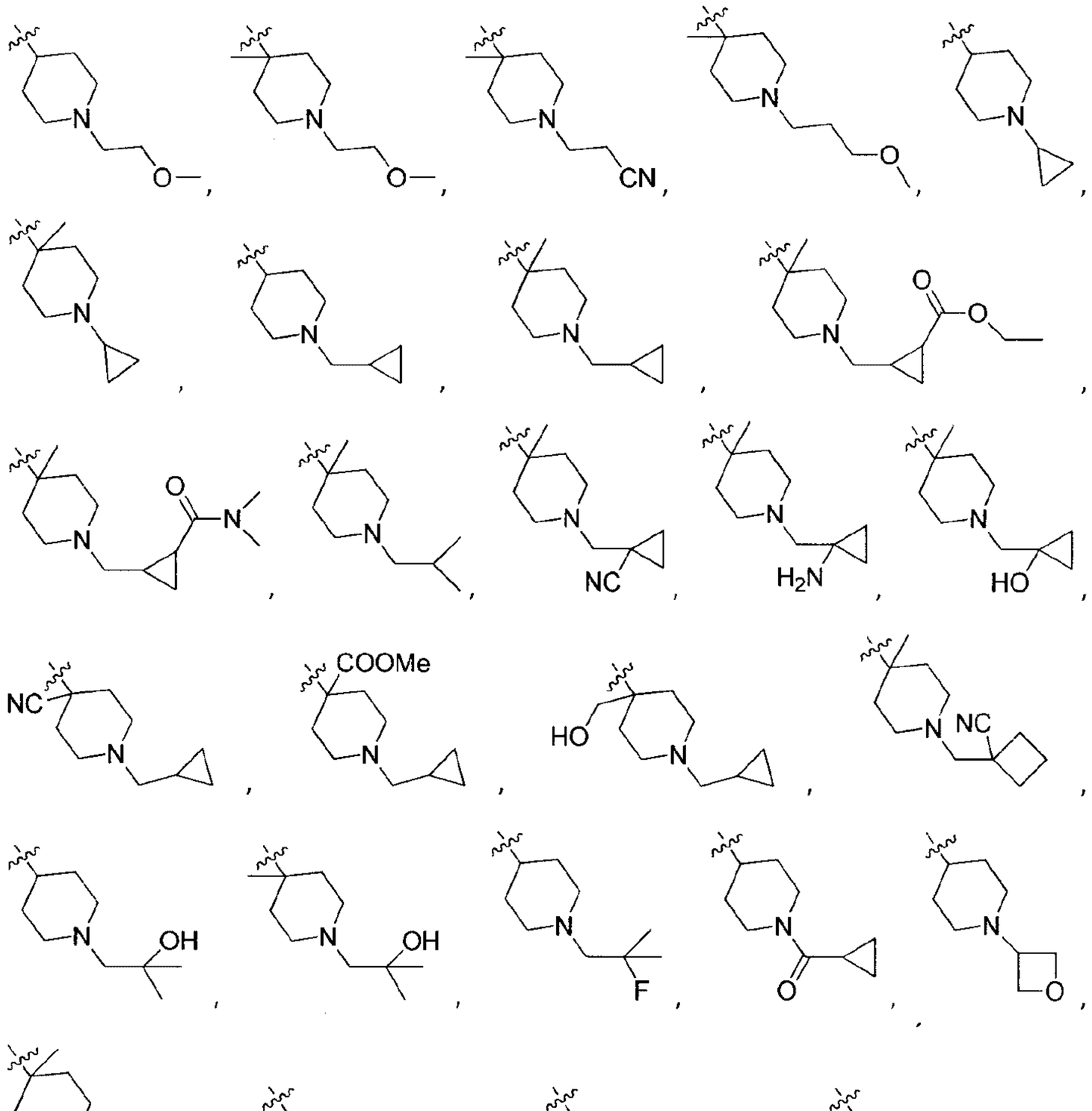
R_{214} is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, $-CH_2CH(OH)(CH_3)_2$, $-CH_2CH(F)(CH_3)_2$, $-CH_2CH_2F$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CH_2N(CH_3)_2$, $-S(=O)_2CH_3$, $-CH_2CH_2S(=O)_2CH_3$,  , cyclopropyl, cyclopropylmethylene,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , and  .

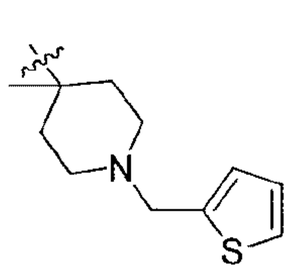
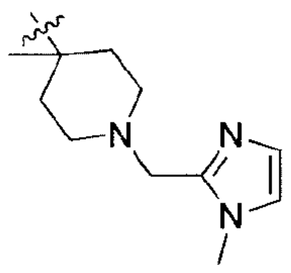
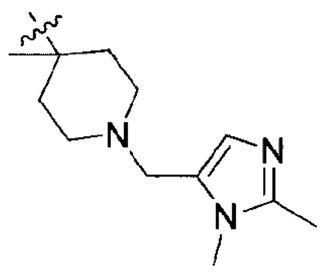
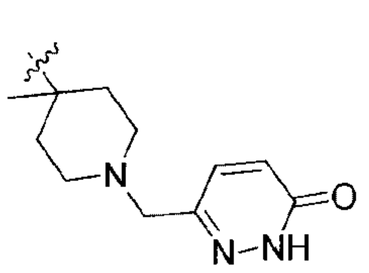
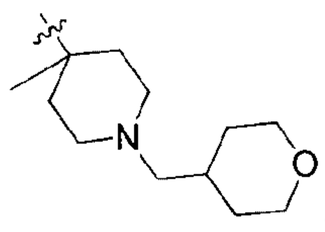
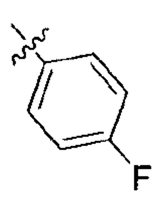
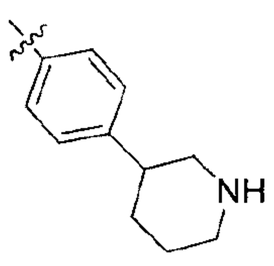
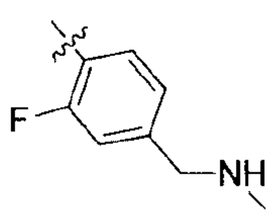
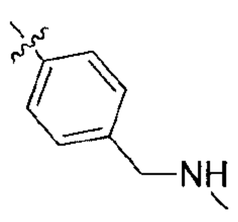
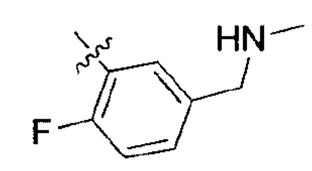
12. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,







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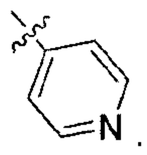


13. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

1) 6-fluoro-3-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
2) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
3) 6-fluoro-3-(1-(2-fluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
4) 3-(1-cyclopropylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
5) 3-(1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
6) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
7) 6-fluoro-3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
8) 3-(1-(cyclopropanecarbonyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
9) 6-fluoro-3-(1-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
10) 6-fluoro-3-(1-isopropylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
11) 6-fluoro-3-(1-(oxetan-3-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
12) 6-fluoro-3-(1-propylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
13) 3-(1-(2-aminoethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
14) 3-(1-(2-(dimethylamino)ethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-

8-carboxamide;

15) 6-fluoro-3-(1-(2-methoxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carbox amide;
16) 6-fluoro-3-(1-(2-hydroxyethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxa mide;
17) 3-(1-ethylpiperidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
18) 3-(1-ethylazepan-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
19) 6-fluoro-3-(1-methylazepan-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
20) 6-fluoro-3-(1-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
21) 3-(1-ethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
22) 6-fluoro-3-(1-isopropylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
23) 6-fluoro-3-(pyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
24) 6-fluoro-3-(1-propylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
25) 6-fluoro-3-(1-methylpyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
26) 3-(1-ethylpyrrolidin-2-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
27) 3-(1-ethylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
28) 6-fluoro-3-(3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
29) 3-(3-ethyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
30) 3-(3-cyclobutyl-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
31) 3-(3-(cyclopropylmethylene)-3-azabicyclo[3.1.0]hexan-1-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
32) 6-fluoro-3-(3-isopropyl-3-azabicyclo[3.1.0]hexan-1-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
33) 3-(3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
34) 3-(3-ethyl-3-azabicyclo[3.1.0]hexan-6-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
35) 3-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
36) 6-fluoro-3-(4-hydroxypyrrolidin-2-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
37) 3-cyano-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
38) 3-cyano-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
39) 3-(aminomethyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
40) 3-(cyclopropanecarboxamidomethylene)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
41) 6-fluoro-3-(4-fluorophenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
42) 6-fluoro-3-(2-fluoro-4-((methylamino)methylene)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
43) 6-fluoro-3-(4-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
44) 6-fluoro-3-(2-fluoro-5-((methylamino)methyl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-

8-carboxamide;

45) 6-fluoro-3-(pyridin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

46) 6-fluoro-3-(4-(piperidin-3-yl)phenyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

47) 6-fluoro-3-(tetrahydro-2H-pyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

48) 3-(4-(dimethylamino)cyclohexyl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

49) 6-fluoro-3-(4-methylpiperazine-1-carbonyl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

50) 3-(1-(cyclopropylmethyl)piperidin-4-yl)-4,4,6-trifluoro-4H-pyrazolo[1,5-α]indole-8-carboxamide;

51) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4-hydroxy-4H-pyrazolo[1,5-α]indole-8-carboxamide;

52) 3-(1-ethylpiperidin-4-yl)-6-fluoro-4-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

53) 6-fluoro-3-(4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

54) 3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

55) 3-(1-cyclopropyl-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide ;

56) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

57) 3-(1-(cyclopropylmethylene)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

58) 3-(1-(4,4-difluorocyclohexyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

59) 6-fluoro-3-(4-methyl-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

60) 6-fluoro-3-(1-(2-fluoroethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

61) 6-fluoro-3-(4-methyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

62) 6-fluoro-3-(4-methyl-1-(3,3,3-trifluoropropyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

63) 3-(1-((1-cyanocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

64) 3-(1-((1-cyanocyclobutyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

65) 6-fluoro-3-(4-methyl-1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

66) 6-fluoro-3-(4-methyl-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

67) 3-(1-((1-aminocyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

68) 6-fluoro-3-(4-methyl-1-(oxetan-3-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

69) 6-fluoro-3-(1-(2-methoxyethyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
70) 6-fluoro-3-(1-((1-hydroxycyclopropyl)methyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
71) 6-fluoro-3-(4-methyl-1-((3-methyloxetan-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
72) 6-fluoro-3-(1-(3-methoxypropyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
73) 6-fluoro-3-(4-methyl-1-((1-(methylsulfonyl)cyclopropyl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
74) 6-fluoro-3-(4-methyl-1-(thiazol-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
75) 6-fluoro-3-(4-methyl-1-(methylsulfonyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
76) 6-fluoro-3-(1-(3-fluorocyclobutyl)-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
77) 6-fluoro-3-(4-methyl-1-(thiophen-2-ylmethyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
78) 3-(1-((1-ethylpiperidin-4-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
79) 6-fluoro-3-(4-methyl-1-((1-methylazetidin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
80) ethyl 2-((4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-4-methylpiperidin-1-yl)methyl)cyclopropanecarboxylate;
81) 3-(1-((2-(dimethylcarbamoyl)cyclopropyl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
82) 6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
83) 6-fluoro-3-(4-methyl-1-((4-methylthiazol-5-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
84) 6-fluoro-3-(4-methyl-1-((1-methyl-1H-imidazol-2-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
85) 3-(1-((1,2-dimethyl-1H-imidazol-5-yl)methyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide
86) 3-(1'-ethyl-4-methyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
87) 6-fluoro-3-(4-methyl-1-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
88) 3-(1-(2-cyanoethyl)-4-methylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
89) 6-chloro-3-(1-ethyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;
90) 3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxa

mide;

91) 3-(1,3-dimethylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

92) 6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

93) 3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

94) 6-fluoro-3-(3-methyl-1-(oxetan-3-yl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

95) 6-fluoro-3-(1-(2-fluoroethyl)-3-methylpyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

96) 3-(1-((2,2-difluorocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

97) 6-fluoro-3-(3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

98) 6-fluoro-3-(3-methyl-1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

99) 6-fluoro-3-(3-methyl-1-(3,3,3-trifluoropropyl)pyrrolidin-3-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

100) 3-(1-((1-aminocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

101) 3-(1-((1-cyanocyclobutyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

102) 3-(1-((1-cyanocyclopropyl)methyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

103) 3-(1-(2-cyanoethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

104) 3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

105) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

106) 6-fluoro-3-(4-methyl-1,1-dioxido-2H-thiopyran-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

107) 3-(1,4-diethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

108) 3-(4-cyano-1-(cyclopropylmethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

109) 3-(1-(cyclopropylmethyl)-4-(hydroxymethyl)piperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

110) Methyl 4-(8-carbamoyl-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazol-3-yl)-1-(cyclopropylmethyl)piperidine-4-carboxylate;

111) 3-(1-(cyclopropylmethyl)-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

112) 3-(1-ethyl-4-methylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8

-carboxamide;

113) 6-fluoro-3-(1-isobutyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

114) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

115) 3-(1,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

116) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-4-methylpiperidin-4-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

117) 3-(1-ethyl-2,4-dimethylpiperidin-4-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

118) 3-(1-ethyl-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

119) 6-fluoro-3-(1-isopropyl-3-methylpyrrolidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

120) 3-(1-(cyclopropylmethyl)-3-methylpyrrolidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

121) 3-(1,3-dimethylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

122) 3-(1-ethyl-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

123) 6-fluoro-3-(1-isopropyl-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

124) 3-(1-(cyclopropylmethyl)-3-methylazetidin-3-yl)-6-fluoro-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

125) 6-fluoro-3-(1-(2-hydroxy-2-methylpropyl)-3-methylazetidin-3-yl)-2-methyl-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

126) 6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-2-methoxy-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

127) 2-(benzyloxy)-6-fluoro-3-(1-isopropyl-4-methylpiperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

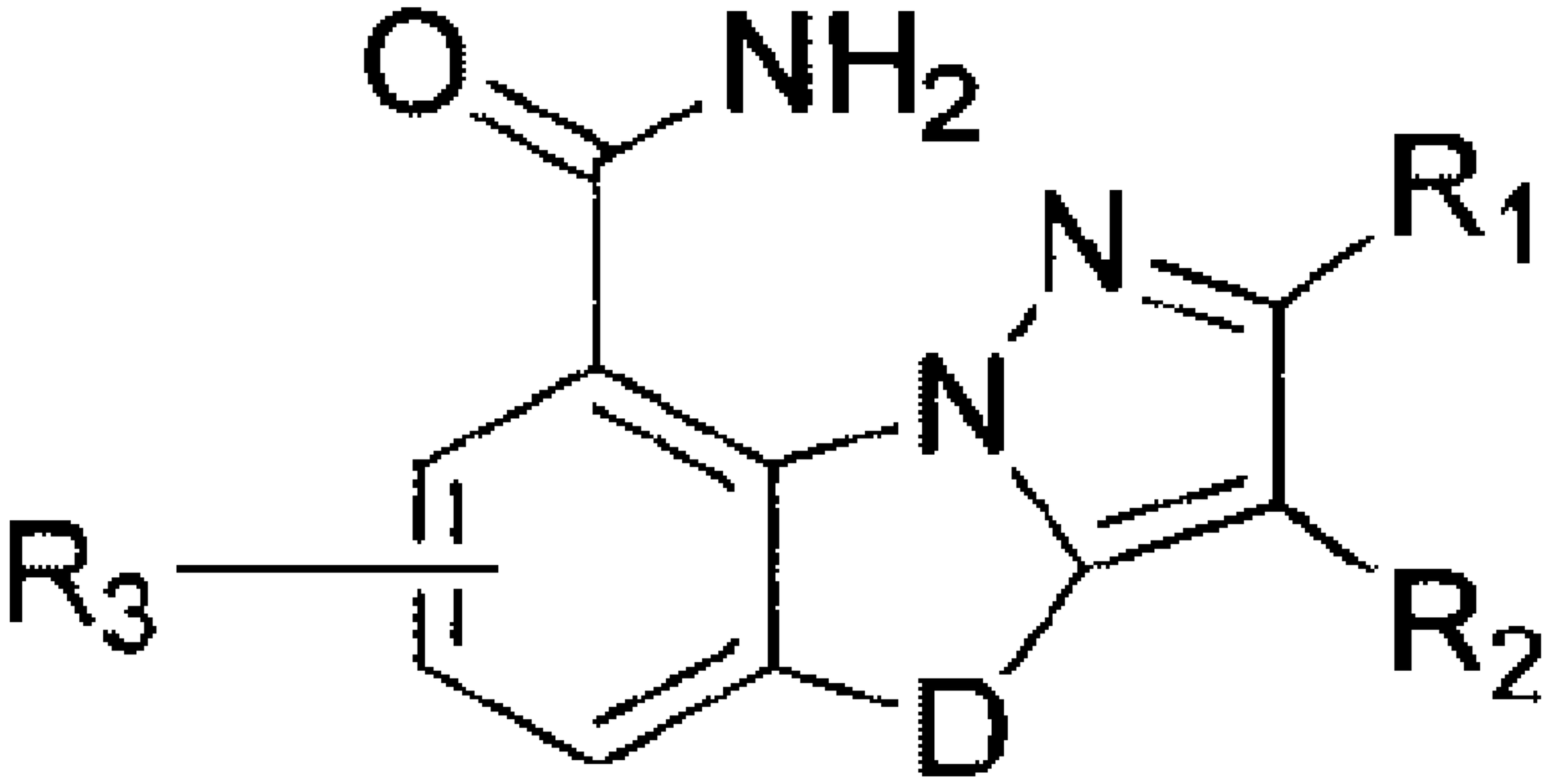
128) 6-fluoro-2-(piperidin-4-yl)-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide;

129) 2-(1-ethylpiperidin-4-yl)-6-fluoro-4H-benzo[4,5]imidazo[1,2-b]pyrazole-8-carboxamide.

14. A therapeutic agent for cancer, stroke, cardiac ischemia, inflammation or diabetes, comprising the compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof.

15. A use of the compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof in manufacturing a medicament for treating cancer, stroke, cardiac ischemia, inflammation and diabetes.

16. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, stroke, cardiac ischemia, inflammation or diabetes.



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