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(54) Title: SUBSTITUTED REVERSE PYRIMIDINE BMI-1 INHIBITORS

(57) Abstract: Amine substituted reverse pyrimidine compounds and forms thereof that inhibit the function and reduce the level of B-cell specific Moloney murine leukemia virus integration site 1 (Bmi-1) protein and methods for their use to inhibit Bmi-1 function and reduce the level of Bmi-1 to treat a cancer mediated by Bmi-1 are described herein.

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Substituted Reverse Pyrimidine Bmi-1 Inhibitors

INTRODUCTION

Substituted reverse pyrimidine compounds that inhibit the function of the B-cell specific Moloney murine leukemia virus integration site 1 (Bmi-1) protein and reduce the level thereof and methods of using such compounds to treat a cancer mediated by Bmi-1 are described. More particularly, amine substituted reverse pyrimidine compounds that inhibit Bmi-1 function and reduce the level of Bmi-1 are useful for treating a cancer mediated by Bmi-1.

BACKGROUND

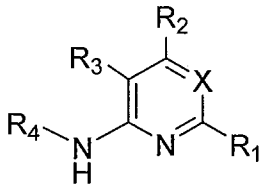
Bmi-1 was originally identified by its over-expression in various leukemias and lymphomas. Subsequently, Bmi-1 has been shown to have oncogenic activity when overexpressed in normal cells and to play a role in the maintenance of cancer stem cell populations. Bmi-1 is elevated in many tumor types and is important in hematologic cancers and many solid tumors, including brain cancers. Reduction of Bmi-1 levels in tumor cells by siRNA causes apoptosis and/or cell senescence and increases susceptibility to cytotoxic agents. Bmi-1 serves as the key regulatory component of the PRC1 complex (polycomb repressive complex-1), but has no enzymatic activity. Therefore, targeting Bmi-1 by traditional drug discovery methods has been problematic.

Since Bmi-1 levels within cells are tightly regulated through both transcriptional and post-transcriptional mechanisms, this regulation can be exploited to target this important protein. Accordingly, there remains a need to provide compounds that inhibit Bmi-1 function and reduce the level of Bmi-1 to treat a cancer mediated by Bmi-1.

SUMMARY

Certain amine substituted reverse pyrimidine compounds that inhibit Bmi-1 function and reduce the level of Bmi-1 and methods for their use to treat a cancer mediated by Bmi-1 are described herein.

A compound of Formula (I) is described:



(I)

wherein X, R_1, R_2, R_3 and R_4 are as defined herein, including forms and pharmaceutical compositions thereof, and methods of using such compounds, forms or compositions thereof to treat a cancer mediated by Bmi-1 in a human subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 demonstrates the dose dependent reduction of a CSC population in a BXD GBM model as the result of treatment with a compound of Formula (I), or a form thereof.

Figure 2 demonstrates the reduction of a CSC population in a BXD GBM model as the result of treatment with a compound of Formula (I), or a form thereof.

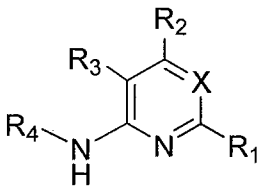
Figure 3 demonstrates the reduction of monolayer and neurosphere CSC populations in a tumorosphere assay as the result of contacting the cells with a compound of Formula (I), or a form thereof.

Figure 4 demonstrates the comparative effect on survival of mice treated with vehicle, temozolomide or a compound of Formula (I), or a form thereof, in an orthotopic model of glioblastoma.

DETAILED DESCRIPTION

Amine substituted reverse pyrimidine compounds for use in inhibiting Bmi-1 function and reducing the level of Bmi-1 and in methods for treating a cancer mediated by Bmi-1 are described.

In one embodiment is a compound of Formula (I):



(I)

or a form thereof, wherein

R_1 is heteroaryl or heterocyclyl optionally substituted on a carbon atom ring member with one, two, three or four R_5 substituents, or on a nitrogen atom ring member with an oxygen atom substituent to form an N-oxide;

X is N or N substituted with an oxygen atom substituent to form an N-oxide;

R_2 is hydrogen, cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkyl-amino-carbonyl-amino, $(C_{1-8}alkyl)_2$-amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-amino, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl, amino-sulfonyl-amino, C_{1-8}alkyl-amino-sulfonyl-amino, $(C_{1-8}alkyl)_2$-amino-sulfonyl-amino, $P(O)(R_7)_2$-amino or heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C_{1-8}alkyl substituents;

R_3 is hydrogen, cyano, halo, C_{1-8}alkyl, amino, C_{1-8}alkyl-amino or $(C_{1-8}alkyl)_2$-amino;

R_4 is C_{3-14}cycloalkyl, aryl, heteroaryl or heterocyclyl, each optionally substituted with one, two, three or four R_6 substituents;

R_5 is independently selected from cyano, halo, hydroxyl, nitro, oxo, C_{1-8}alkyl, cyano-C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino, C_{1-8}alkyl-sulfonyl, C_{3-14}cycloalkyl, aryl, aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino, heteroaryl, heteroaryl-C_{1-8}alkyl or heterocyclyl, wherein C_{3-14}cycloalkyl, aryl, heteroaryl or heterocyclyl and the aryl and heteroaryl portions of aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino and heteroaryl-C_{1-8}alkyl are each

optionally substituted with one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkoxy or carboxyl substituents;

R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, formyl, formyl-oxy, C_{1-8}alkyl-carbonyl, halo-C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-thio, halo-C_{1-8}alkyl-thio, amino, C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, halo-C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino-C_{1-8}alkyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, (C_{1-8}alkyl)$_2$-amino-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, (C_{1-8}alkyl)$_2$-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, imino-C_{1-8}alkyl, hydroxyl-imino-C_{1-8}alkyl, C_{1-8}alkoxy-imino-C_{1-8}alkyl, C_{1-8}alkyl-sulfonyl, halo-C_{1-8}alkyl-sulfonyl, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, (C_{1-8}alkyl)$_2$-amino-sulfonyl, B(OR_8)$_2$, C_{3-14}cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein C_{3-14}cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with one, two, three or four halo or C_{1-8}alkyl substituents;

R_7 is independently hydroxyl or (C_{1-8}alkoxy)$_n$, wherein n represents an integer from 1 to 5; and,

R_8 is independently hydrogen or C_{1-8}alkyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 1H-

imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl, 1H-indol-3-yl, 1H-indol-4-yl, 2H-indazol-3-yl, 4,5,6,7-tetrahydro-2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-7-yl, pyrazolo[1,5-c]pyrimidin-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl, imidazo[1,2-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl, 1H-indol-4-yl, 2H-indazol-3-yl, 4,5,6,7-tetrahydro-2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-7-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl, imidazo[1,2-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl,

1H-indol-4-yl, 2H-indazol-3-yl, 4,5,6,7-tetrahydro-2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-7-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, 7H-purinyl or quinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-indolyl, 1H-benzimidazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrazinyl or imidazo[1,2-a]pyrimidinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-indolyl, 1H-benzimidazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl or 1H-imidazo[4,5-b]pyridinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from imidazo[1,2-a]pyrazinyl or imidazo[1,2-a]pyrimidinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted imidazo[1,2-a]pyrazinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted imidazo[1,2-a]pyrimidinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl, 1H-indol-3-yl, 1H-indol-4-yl, 2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-7-yl, pyrazolo[1,5-c]pyrimidin-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl, 1H-indol-4-yl, 2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-3-yl, pyrazolo[1,5-a]pyridin-7-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, pyridin-4-yl, 1H-indol-1-yl, 1H-indol-4-yl, 2H-indazol-3-yl, 1H-benzimidazol-1-yl, imidazo[2,1-b][1,3]thiazol-5-yl, pyrazolo[1,5-a]pyridin-7-yl, imidazo[1,2-a]pyridin-5-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-3-yl, 7H-purin-7-yl or quinolin-4-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-indol-1-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-benzimidazol-1-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-3-

yl, pyrazolo[1,5-a]pyridin-7-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-5-yl, 1H-imidazo[4,5-b]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl or imidazo[1,2-a]pyrimidin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-indol-3-yl, 1H-benzimidazol-1-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl or imidazo[1,2-a]pyrimidin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazol-4-yl, 1H-indol-3-yl, 1H-benzimidazol-1-yl, pyrazolo[1,5-a]pyridin-3-yl, imidazo[1,2-a]pyridin-3-yl, 1H-imidazo[4,5-b]pyridin-1-yl, imidazo[1,2-a]pyrazin-3-yl or imidazo[1,2-a]pyrimidin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted imidazo[1,2-a]pyrazin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted imidazo[1,2-a]pyrimidin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heterocyclyl selected from 4,5,6,7-tetrahydro-2H-indazolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl or 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl.

Another embodiment includes a compound of Formula (I), wherein R_1 is optionally substituted heterocyclyl selected from 4,5,6,7-tetrahydro-2H-indazol-3-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl or 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl.

Another embodiment includes a compound of Formula (I), wherein X is N.

Another embodiment includes a compound of Formula (I), wherein X is N substituted with an oxygen atom substituent to form an N-oxide.

Another embodiment includes a compound of Formula (I), wherein R_2 is cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, amino-carbonyl,

C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkyl-amino-carbonyl-amino, $(C_{1-8}alkyl)_2$-amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-amino, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl, amino-sulfonyl-amino, C_{1-8}alkyl-amino-sulfonyl-amino, $(C_{1-8}alkyl)_2$-amino-sulfonyl-amino, $P(O)(R_7)_2$-amino or heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_2 is cyano, halo, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino, amino-sulfonyl-amino or heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_2 is cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkyl-amino-carbonyl-amino, $(C_{1-8}alkyl)_2$-amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-amino, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl, amino-sulfonyl-amino, C_{1-8}alkyl-amino-sulfonyl-amino, $(C_{1-8}alkyl)_2$-amino-sulfonyl-amino or $P(O)(R_7)_2$-amino.

Another embodiment includes a compound of Formula (I), wherein R_2 is cyano, halo, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino or amino-sulfonyl-amino.

Another embodiment includes a compound of Formula (I), wherein R_2 is heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_2 heteroaryl is optionally substituted 1H-pyrrolyl.

Another embodiment includes a compound of Formula (I), wherein R_2 heteroaryl is optionally substituted 1H-pyrrol-1-yl.

Another embodiment includes a compound of Formula (I), wherein R_3 is hydrogen.

Another embodiment includes a compound of Formula (I), wherein R_3 is cyano, halo, C_{1-8}alkyl, amino, C_{1-8}alkyl-amino or $(C_{1-8}alkyl)_2$-amino.

Another embodiment includes a compound of Formula (I), wherein R_3 is cyano, halo, C_{1-8}alkyl or amino.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted C_{3-14}cycloalkyl selected from 2,3-dihydro-1H-indenyl; or, optionally substituted aryl selected from phenyl or naphthyl; or, optionally substituted heteroaryl selected from 1,3-thiazolyl, 1,2-oxazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuranyl, benzooxazolyl, 1,3-benzothiazolyl, quinolinyl or isoquinolinyl; or, optionally substituted heterocyclyl selected from 1,3-benzodioxolyl or 2,3-dihydro-1,4-benzodioxinyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted C_{3-14}cycloalkyl selected from 2,3-dihydro-1H-indenyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted C_{3-14}cycloalkyl selected from 2,3-dihydro-1H-inden-2-yl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted aryl selected from phenyl or naphthyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heteroaryl selected from 1,3-thiazolyl, 1,2-oxazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuranyl, benzooxazolyl, 1,3-benzothiazolyl, quinolinyl or isoquinolinyl; or, optionally substituted heterocyclyl selected from 1,3-benzodioxolyl or 2,3-dihydro-1,4-benzodioxinyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heteroaryl selected from 1,3-thiazol-2-yl, 1,2-oxazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, 1H-indol-5-yl, benzofuran-5-yl, benzooxazol-5-yl, 1,3-benzothiazol-2-yl, quinolin-3-yl, quinolin-6-yl or isoquinolin-3-yl; or, optionally substituted heterocyclyl selected from 1,3-benzodioxol-5-yl or 2,3-dihydro-1,4-benzodioxin-6-yl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heteroaryl selected from 1,3-thiazolyl, 1,2-oxazolyl, pyridinyl, pyridinyl,

pyrimidinyl, 1H-indolyl, benzofuranyl, benzooxazolyl, 1,3-benzothiazolyl, quinolinyl or isoquinolinyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heteroaryl selected from 1,3-thiazol-2-yl, 1,2-oxazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, 1H-indol-5-yl, benzofuran-5-yl, benzooxazol-5-yl, 1,3-benzothiazol-2-yl, quinolin-3-yl, quinolin-6-yl or isoquinolin-3-yl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heterocyclyl selected from 1,3-benzodioxolyl or 2,3-dihydro-1,4-benzodioxinyl.

Another embodiment includes a compound of Formula (I), wherein R_4 is optionally substituted heterocyclyl selected from 1,3-benzodioxol-5-yl or 2,3-dihydro-1,4-benzodioxin-6-yl.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, cyano-C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, carboxyl, amino, C_{1-8}alkyl-amino, C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, C_{1-8}alkyl-sulfonyl, C_{3-14}cycloalkyl, aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino, heteroaryl or heteroaryl-C_{1-8}alkyl, wherein heteroaryl and the aryl and heteroaryl portions of aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino and heteroaryl-C_{1-8}alkyl are each optionally substituted with one, two, three or four halo or halo-C_{1-8}alkoxy substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from cyano, halo, hydroxyl, nitro, oxo, C_{1-8}alkyl, cyano-C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino or C_{1-8}alkyl-sulfonyl.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, cyano-C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, carboxyl, amino, C_{1-8}alkyl-amino, C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl or C_{1-8}alkyl-sulfonyl.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from optionally substituted C_{3-14}cycloalkyl selected from cyclopropyl or cyclobutyl; or, aryl, aryl-C_{1-8}alkyl, aryl-amino or aryl-C_{1-8}alky-amino optionally substituted on aryl and the aryl portions, wherein aryl is selected from phenyl; and, wherein the optional substituents on C_{3-14}cycloalkyl, aryl and the aryl portions are selected from one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkyl or carboxyl substituents; or, heteroaryl or heteroaryl-C_{1-8}alkyl optionally substituted on heteroaryl and the heteroaryl portion, wherein heteroaryl is selected from tetrazolyl or pyridinyl; and, wherein the optional substituents on heteroaryl and the heteroaryl portion are selected from one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkyl or carboxyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from optionally substituted C_{3-14}cycloalkyl selected from cyclopropyl or cyclobutyl; or, aryl-C_{1-8}alkyl, aryl-amino or aryl-C_{1-8}alky-amino optionally substituted on the aryl portions, wherein aryl is selected from phenyl; and, wherein the optional substituents on C_{3-14}cycloalkyl and the aryl portions are selected from one, two, three or four halo or halo-C_{1-8}alkoxy substituents; or, heteroaryl or heteroaryl-C_{1-8}alkyl optionally substituted on heteroaryl and the heteroaryl portion, wherein heteroaryl is selected from tetrazolyl or pyridinyl; and, wherein the optional substituents on heteroaryl and the heteroaryl portion are selected from one, two, three or four halo or halo-C_{1-8}alkoxy substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from optionally substituted C_{3-14}cycloalkyl selected from cyclopropyl or cyclobutyl.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from aryl, aryl-C_{1-8}alkyl, aryl-amino or aryl-C_{1-8}alky-amino optionally substituted on aryl and the aryl portions, wherein aryl is selected from phenyl; and, wherein the optional substituents are selected from one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkyl or carboxyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from aryl-C_{1-8}alkyl, aryl-amino or aryl-C_{1-8}alky-amino optionally substituted on the aryl portions, wherein aryl is selected from phenyl; and, wherein the optional substituents are selected from one, two, three or four halo or halo-C_{1-8}alkoxy substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from heteroaryl or heteroaryl-C_{1-8}alkyl optionally substituted on heteroaryl and the heteroaryl portion, wherein heteroaryl is selected from tetrazolyl or pyridinyl; and, wherein the optional substituents are selected from one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkyl or carboxyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from heteroaryl or heteroaryl-C_{1-8}alkyl optionally substituted on heteroaryl and the heteroaryl portion, wherein heteroaryl is selected from tetrazolyl or pyridinyl; and, wherein the optional substituents are selected from one, two, three or four halo or halo-C_{1-8}alkoxy substituents.

Another embodiment includes a compound of Formula (I), wherein R_5 is independently selected from heteroaryl or heteroaryl-C_{1-8}alkyl optionally substituted on heteroaryl and the heteroaryl portion, wherein heteroaryl is selected from 2H-tetrazol-2-yl, tetrazol-1-yl, pyridin-2-yl, pyridin-3-yl or pyridin-4-yl; and, wherein the optional substituents are selected from one, two, three or four halo or halo-C_{1-8}alkoxy substituents.

Another embodiment includes a compound of Formula (I), wherein R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{2-8}alkynyl, formyl, formyl-oxy, C_{1-8}alkyl-carbonyl, halo-C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-thio, halo-C_{1-8}alkyl-thio, amino,

C_{1-8}alkyl-carbonyl, C_{1-8}alkoxy-carbonyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-imino-C_{1-8}alkyl, C_{1-8}alkyl-sulfonyl, $B(OR_8)_2$, C_{3-14}cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein C_{3-14}cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally substituted with one, two, three or four halo or C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, formyl, formyl-oxy, C_{1-8}alkyl-carbonyl, halo-C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-thio, halo-C_{1-8}alkyl-thio, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, halo-C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino-C_{1-8}alkyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, imino-C_{1-8}alkyl, hydroxyl-imino-C_{1-8}alkyl, C_{1-8}alkoxy-imino-C_{1-8}alkyl, C_{1-8}alkyl-sulfonyl, halo-C_{1-8}alkyl-sulfonyl, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl or $B(OR_8)_2$.

Another embodiment includes a compound of Formula (I), wherein R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{2-8}alkynyl, formyl, formyl-oxy, C_{1-8}alkyl-carbonyl, halo-C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-thio, halo-C_{1-8}alkyl-thio, amino, C_{1-8}alkyl-carbonyl, C_{1-8}alkoxy-carbonyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-imino-C_{1-8}alkyl, C_{1-8}alkyl-sulfonyl, C_{1-8}alkyl-amino-sulfonyl or $B(OR_8)_2$.

Another embodiment includes a compound of Formula (I), wherein R_6 is independently selected from C_{3-14}cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein

C_{3-14}cycloalkyl, heterocyclyl, aryl and heteroaryl are each optionally substituted with one, two, three or four halo or C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_6 is independently selected from C_{3-14}cycloalkyl or heterocyclyl, wherein C_{3-14}cycloalkyl and heterocyclyl are each optionally substituted with two C_{1-8}alkyl substituents.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted C_{3-14}cycloalkyl is selected from cyclopropyl; optionally substituted heterocyclyl is selected from morpholinyl or 1,3,2-dioxaborolanyl; optionally substituted aryl is selected from phenyl; or, optionally substituted heteroaryl is selected from 1H-pyrazolyl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted C_{3-14}cycloalkyl is selected from cyclopropyl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted heterocyclyl is selected from morpholinyl or 1,3,2-dioxaborolanyl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted heterocyclyl is selected from morpholin-4-yl or 1,3,2-dioxaborolan-2-yl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted aryl is selected from phenyl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted heteroaryl is selected from 1H-pyrazolyl.

Another embodiment includes a compound of Formula (I), wherein R_6 optionally substituted heteroaryl is selected from 1H-pyrazol-1-yl.

Another embodiment includes a compound of Formula (I), wherein R_7 is hydroxyl.

Another embodiment includes a compound of Formula (I), wherein R_7 is $(C_{1-8}\text{alkoxy})_n$, wherein n represents an integer from 1 to 5.

Another embodiment includes a compound of Formula (I), wherein R_8 is hydrogen.

Another embodiment includes a compound of Formula (I), wherein R_8 is C_{1-8}alkyl.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid, free base, salt, ester,

hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid, free base, salt, ester, hydrate, solvate or polymorph thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid, free base, salt, hydrate or polymorph thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid, free base, hydrate, solvate or polymorph thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a salt, hydrate, solvate or polymorph thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid, free base or salt thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a free acid or free base thereof.

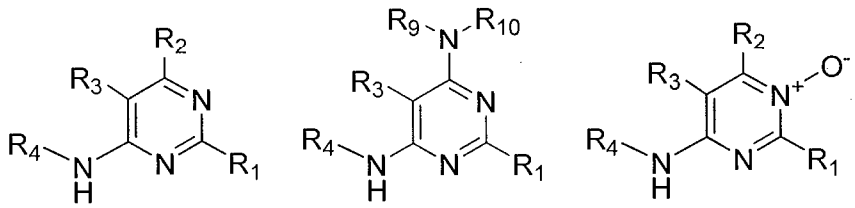
Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a salt thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is selected from a polymorph thereof.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is pharmaceutically acceptable.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the form of the compound of Formula (I) is isolated.

Another embodiment includes a compound of Formula (I) or a form thereof, wherein the compound is a compound of Formula (II), Formula (III) or Formula (IV):



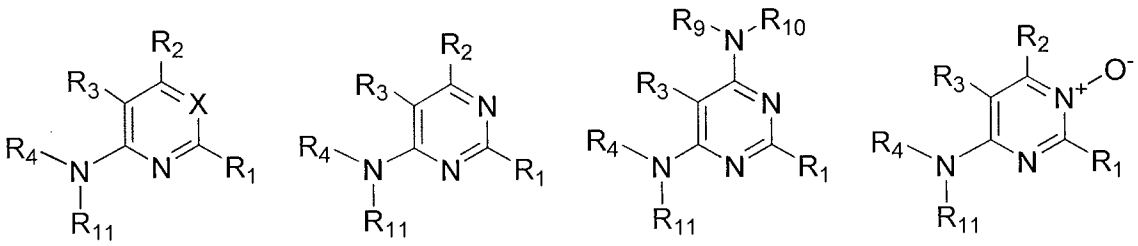
Formula (II), Formula (III) or Formula (IV)

or a form thereof, wherein

R_9 and R_{10} are independently hydrogen, hydroxyl, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl, C_{1-8}alkyl-carbonyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, C_{1-8}alkoxy-carbonyl, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl or $P(O)(R_7)_2$.

Another embodiment includes a compound of Formula (III), wherein one of R_9 and R_{10} is hydrogen and the other is hydroxyl, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl, C_{1-8}alkyl-carbonyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, C_{1-8}alkoxy-carbonyl, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl or $P(O)(R_7)_2$.

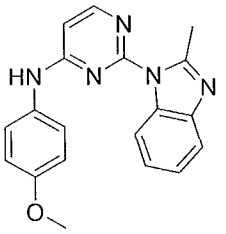
Another embodiment includes a compound of Formula (I) or a form thereof, wherein the compound is a compound of Formula (Ia), Formula (IIa), Formula (IIIa) or Formula (IVa):



Formula (Ia), Formula (IIa), Formula (IIIa) or Formula (IVa)

or a form thereof, wherein R_2, R_3, R_9, R_{10} or R_{11} are independently deuterium.

Another embodiment includes a compound of Formula (I) or a form thereof selected from the group consisting of:



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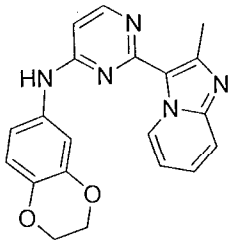

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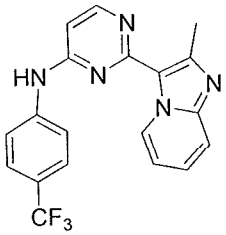

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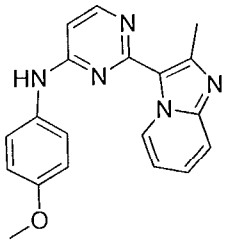

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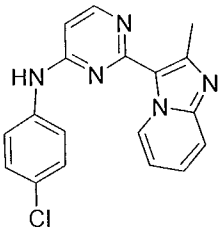

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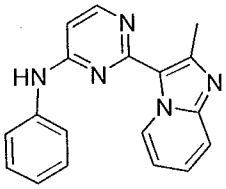

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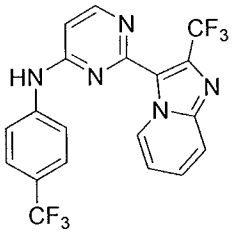

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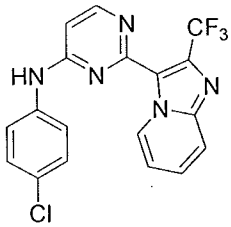

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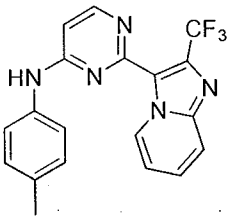

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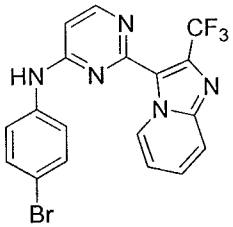

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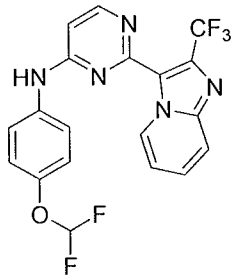

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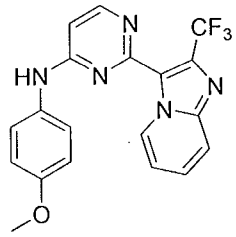

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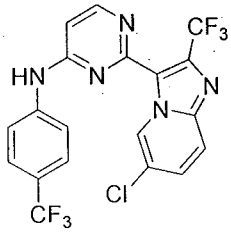

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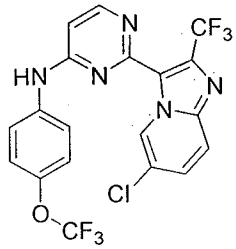

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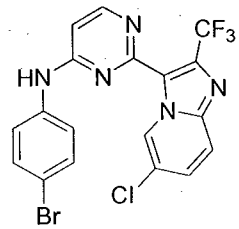

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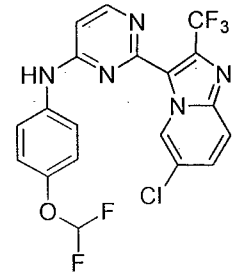

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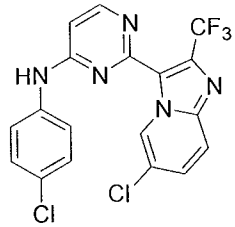

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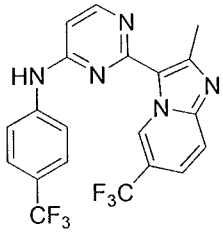

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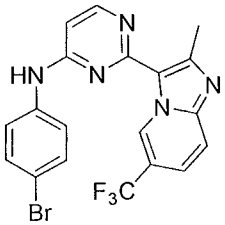

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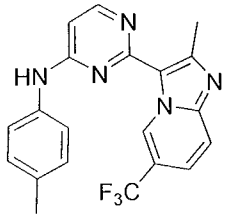

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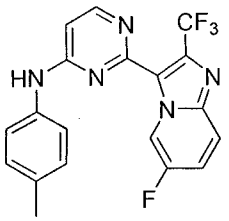

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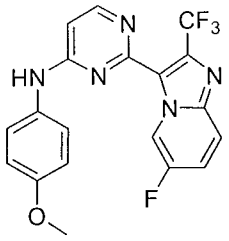

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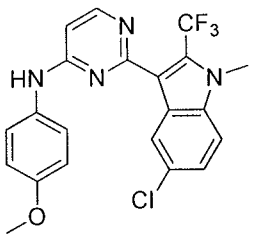

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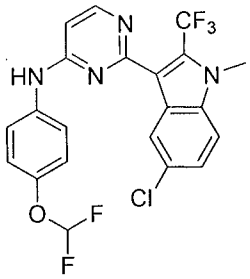

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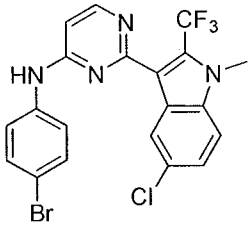

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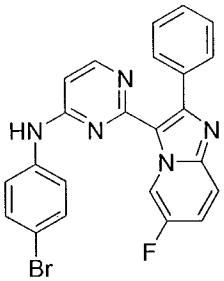

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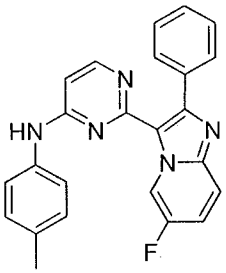

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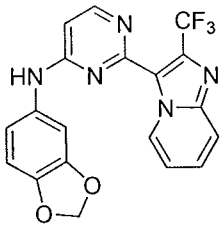

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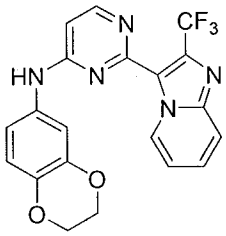

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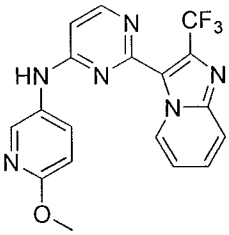

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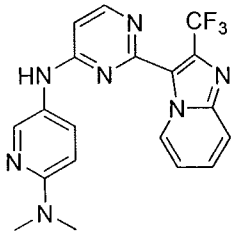

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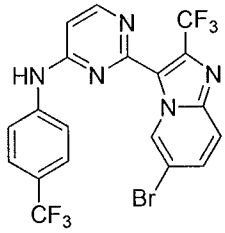

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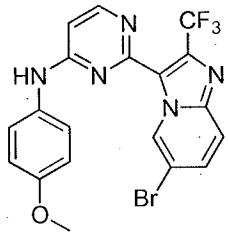

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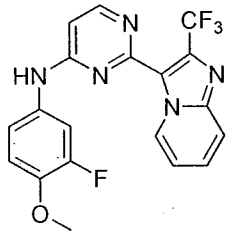

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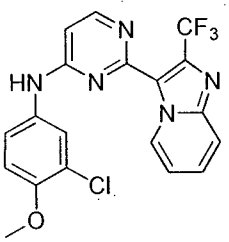

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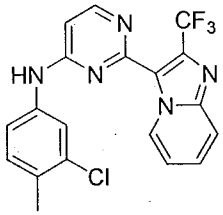

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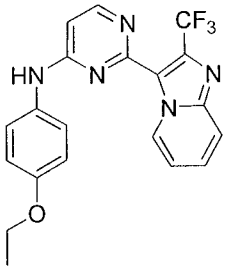

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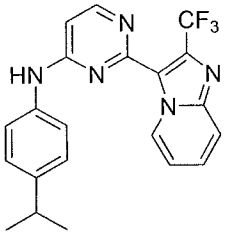

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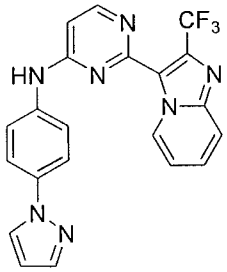

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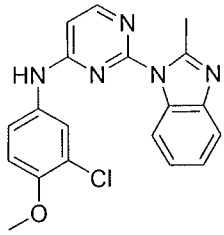

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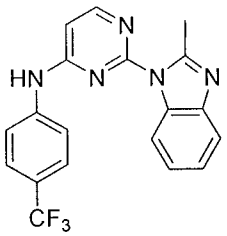

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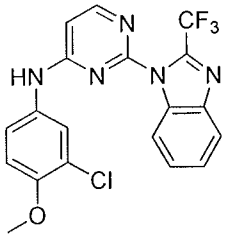

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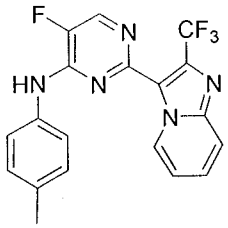

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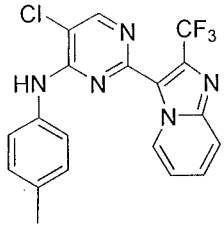

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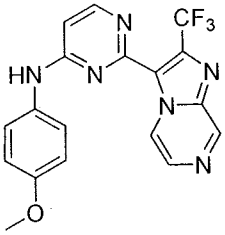

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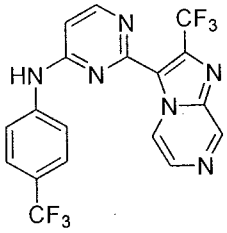

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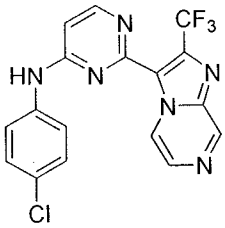

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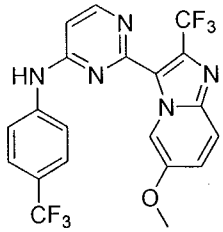

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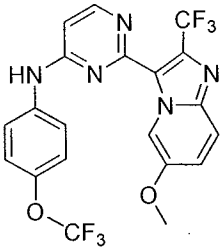

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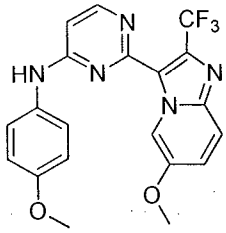

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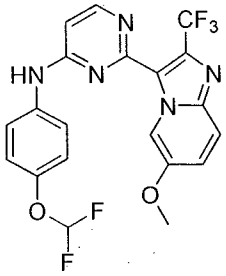

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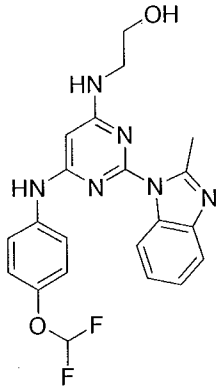

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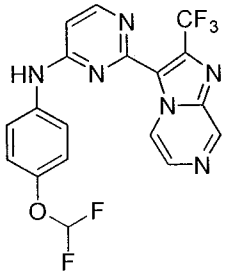

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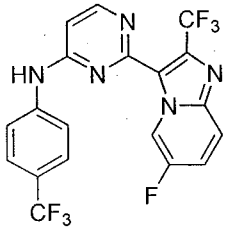

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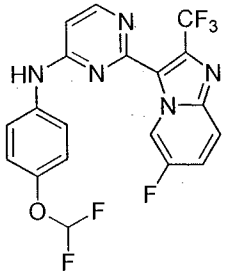

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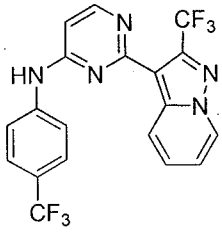

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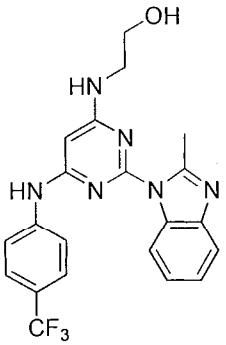

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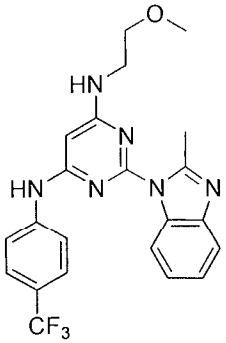

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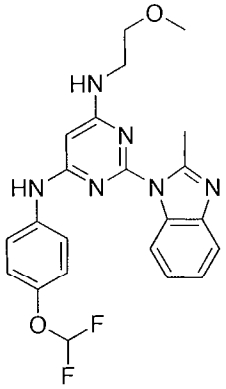

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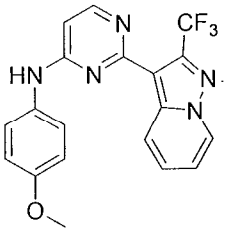

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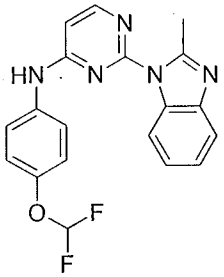

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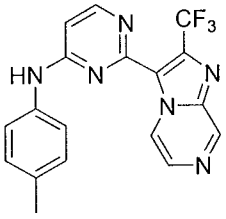

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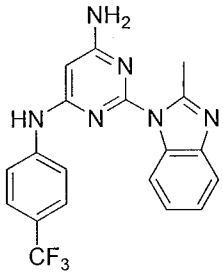

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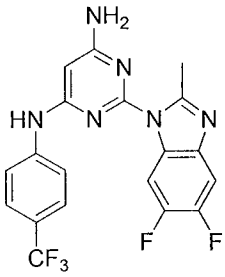

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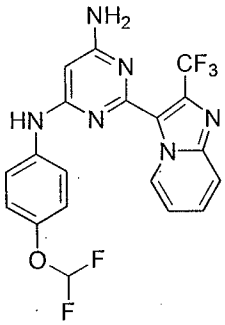

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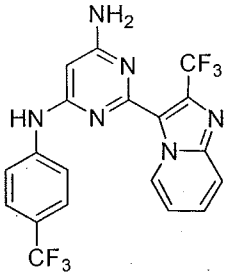

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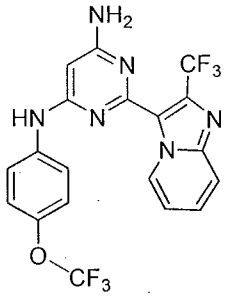

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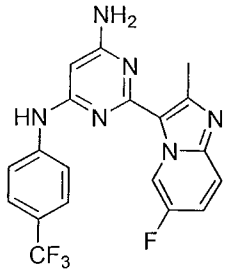

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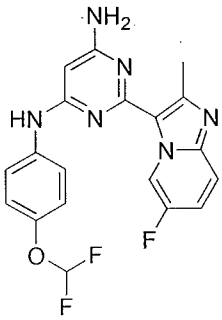

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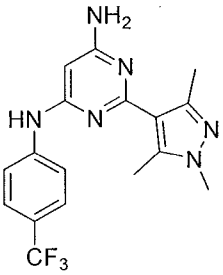

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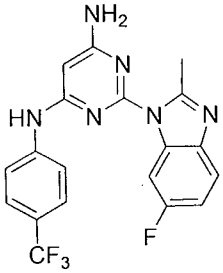

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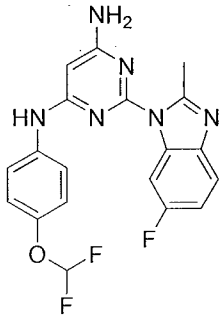

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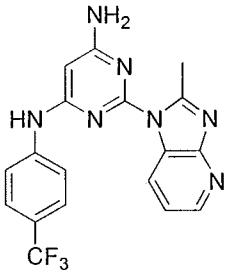

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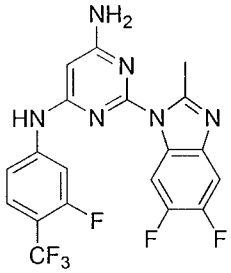

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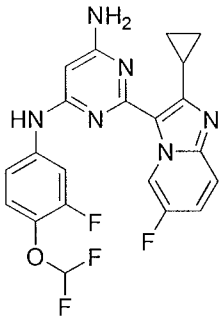

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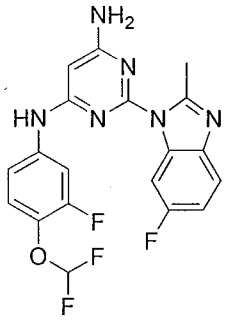

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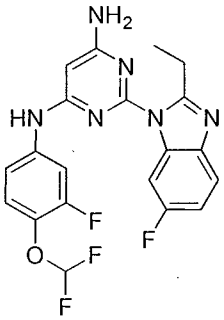

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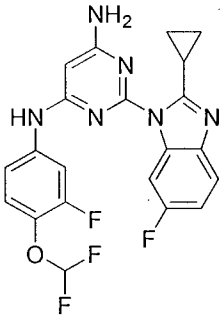

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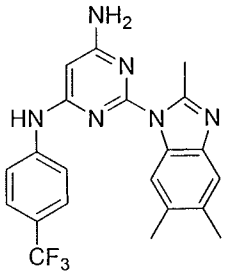

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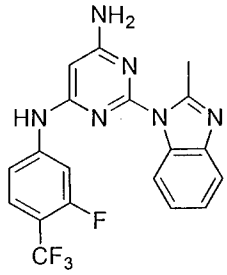

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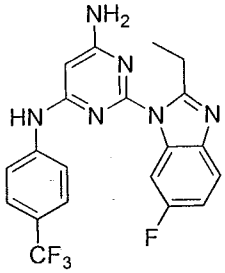

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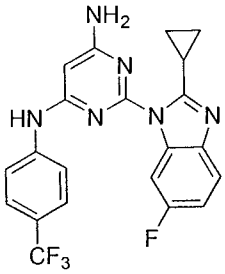

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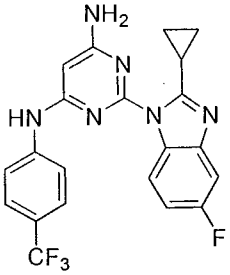

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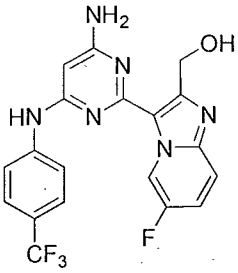

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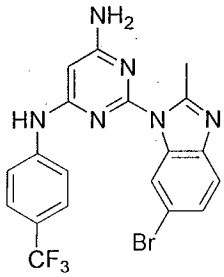

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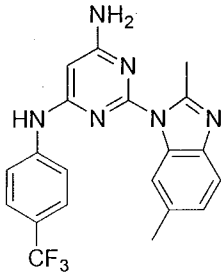

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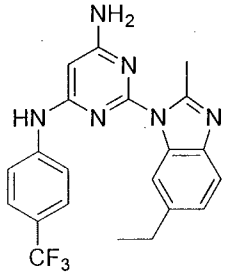

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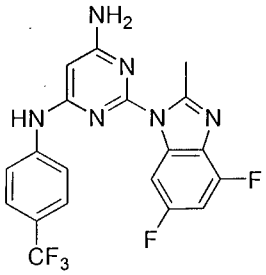

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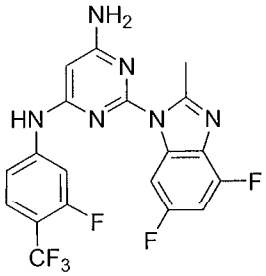

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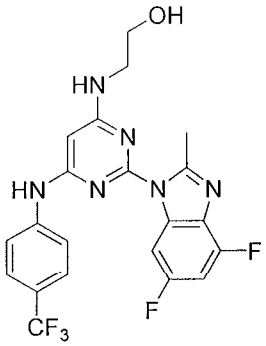

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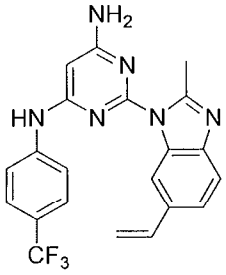

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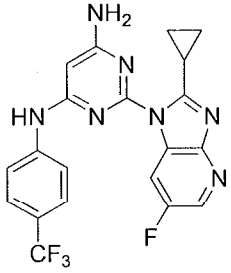

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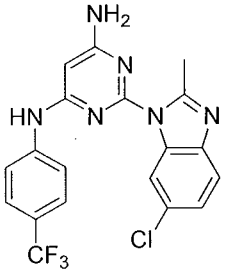

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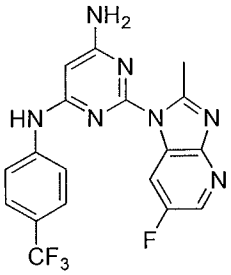

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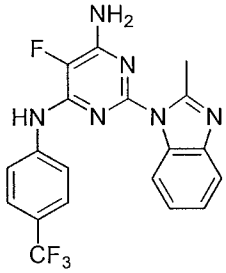

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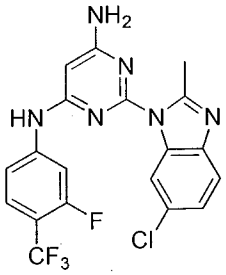

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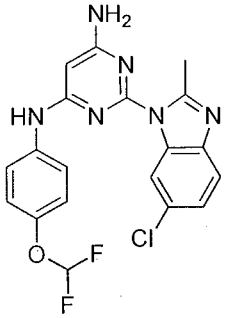

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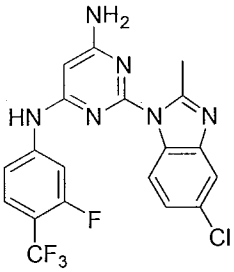

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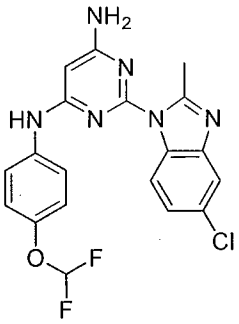

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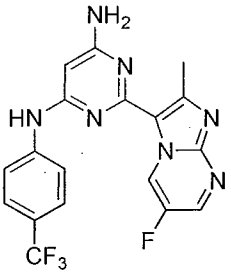

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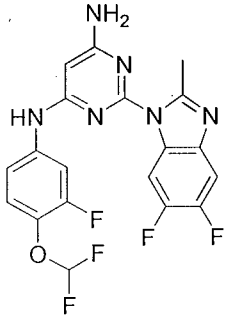

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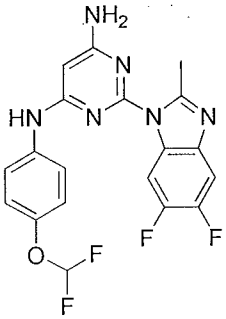

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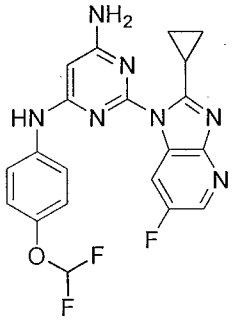

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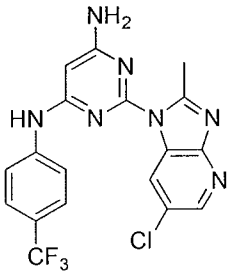

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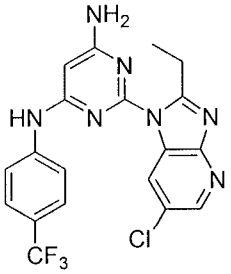

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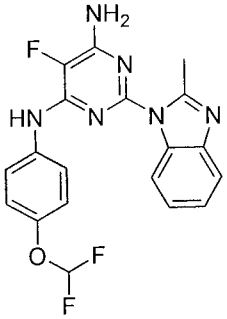

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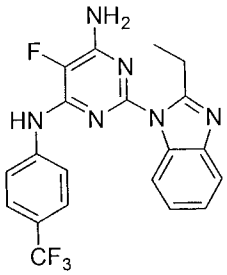

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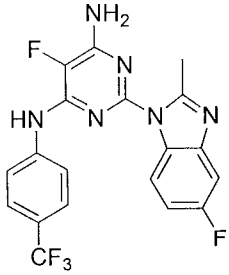

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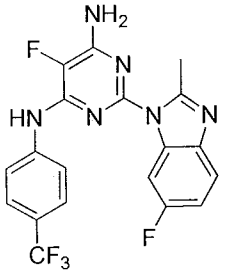

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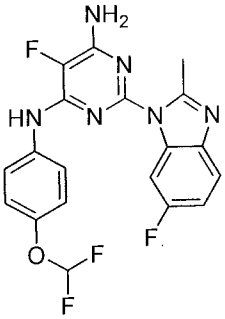

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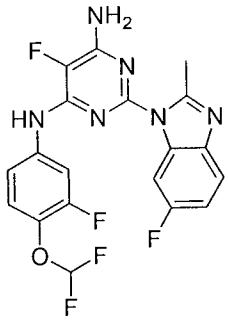

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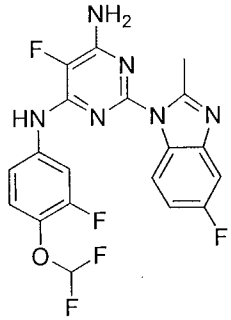

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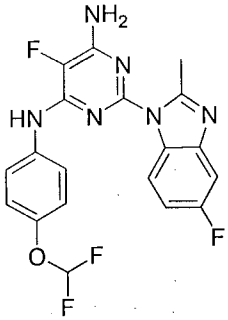

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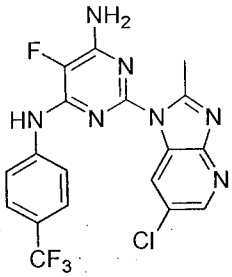

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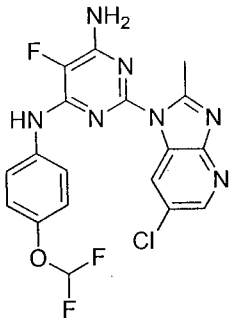

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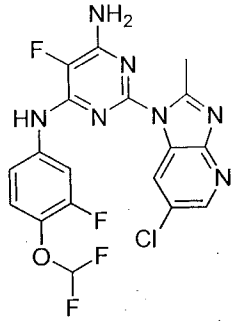

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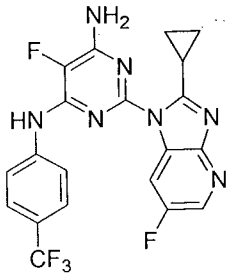

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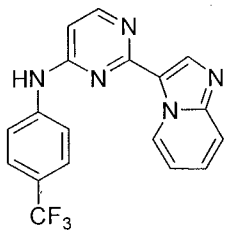

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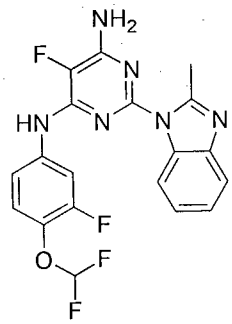

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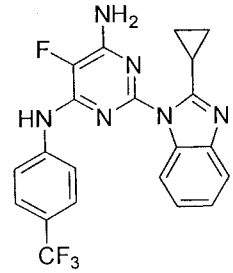

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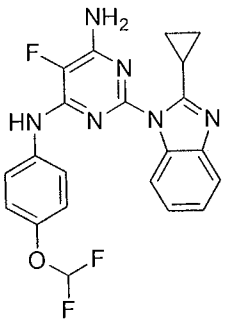

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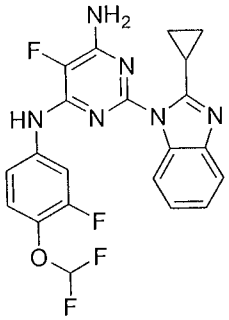

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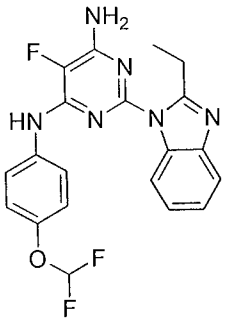

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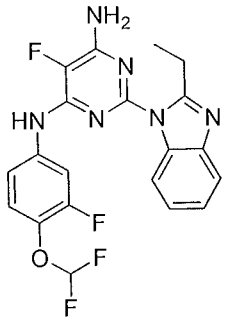

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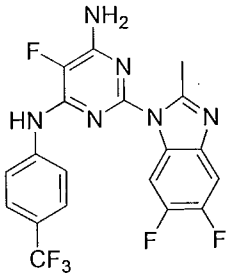

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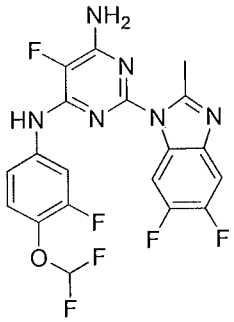

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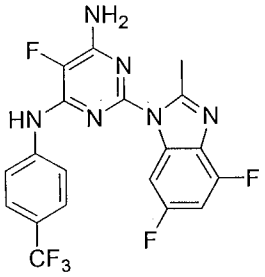

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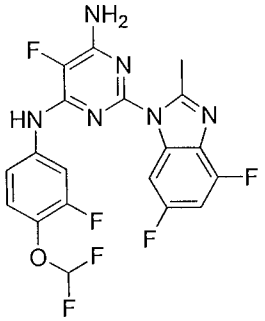

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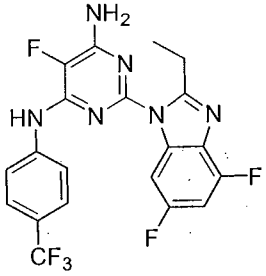

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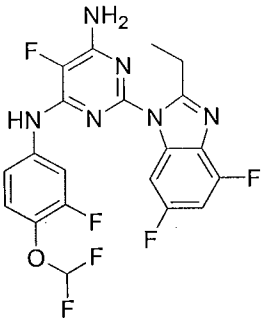

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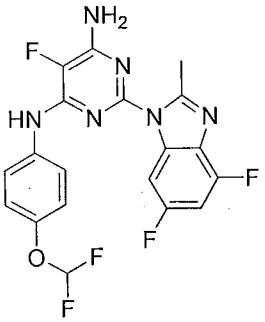

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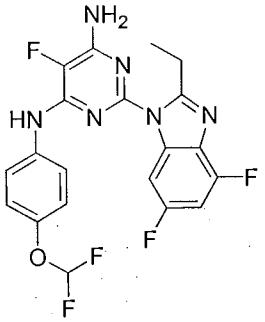

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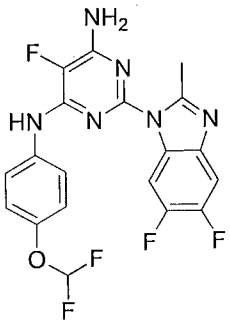

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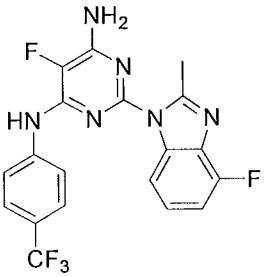

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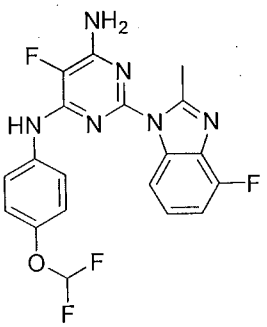

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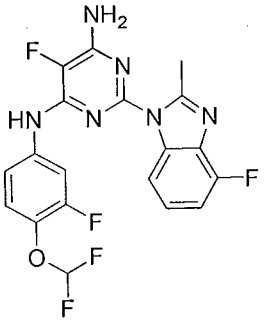

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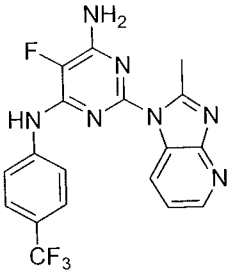

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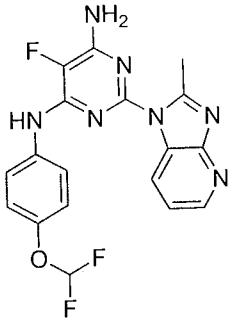

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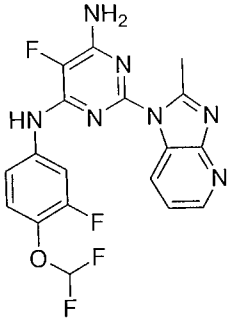

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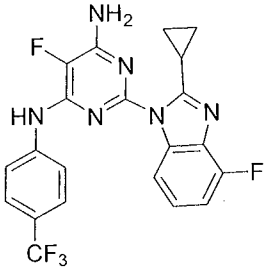

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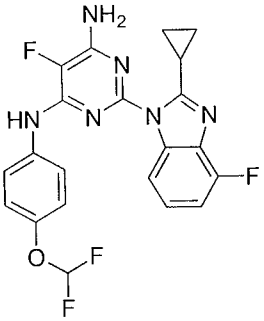

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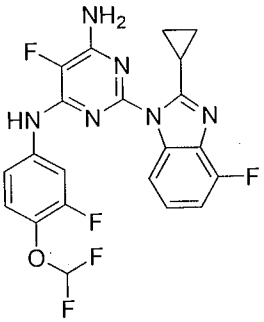

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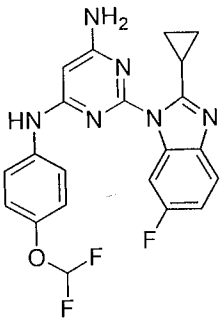

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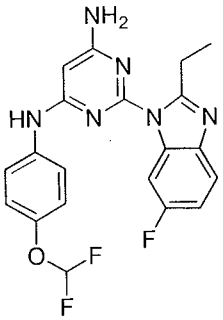

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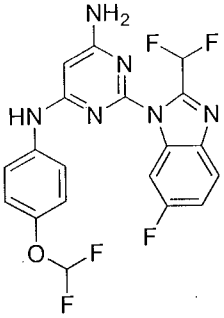

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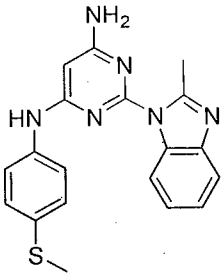

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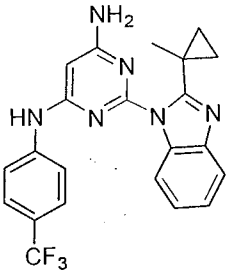

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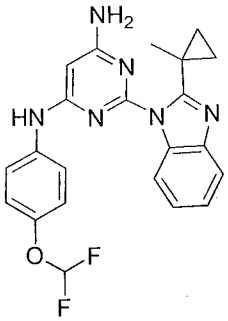

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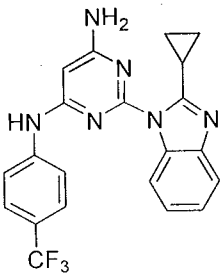

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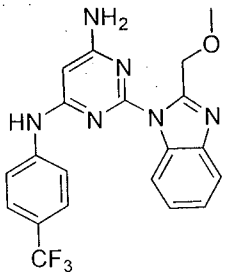

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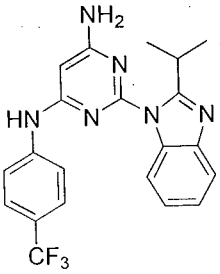

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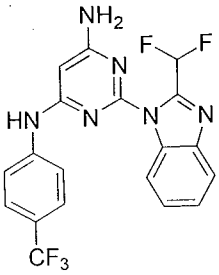

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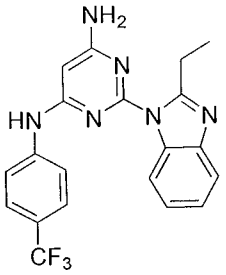

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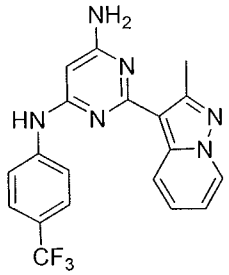

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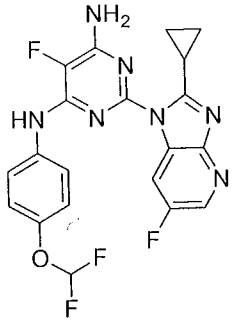

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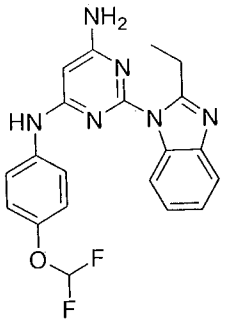

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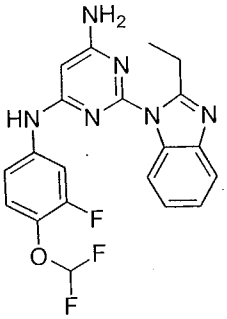

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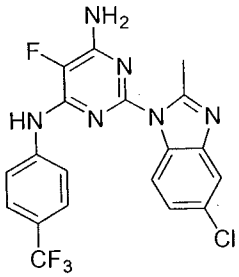

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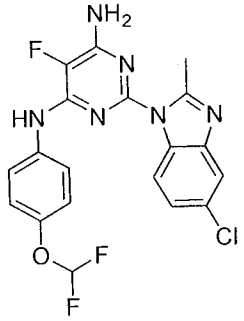

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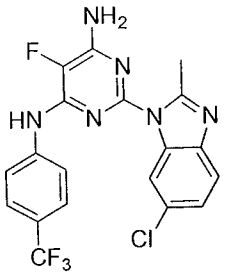

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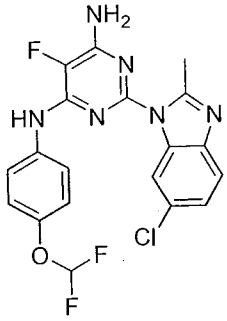

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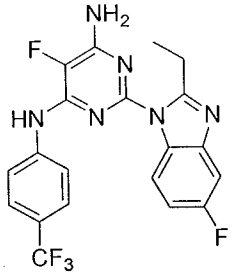

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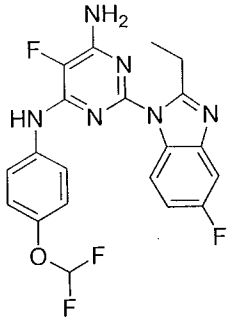

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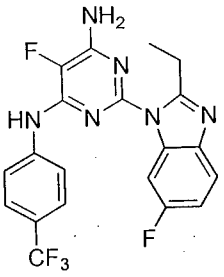

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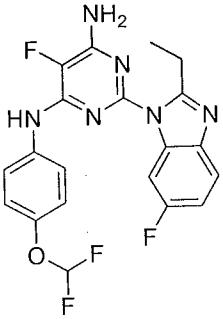

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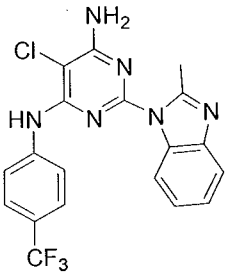

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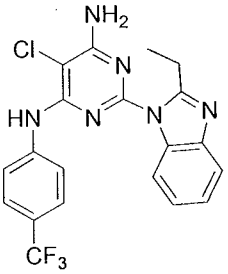

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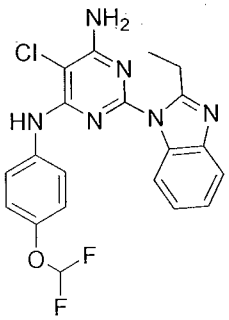

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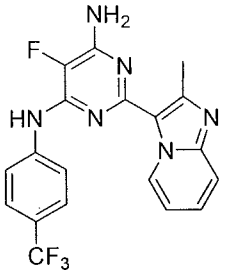

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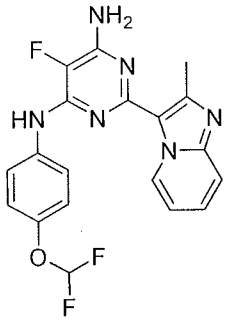

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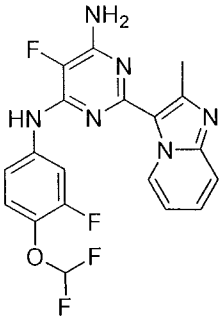

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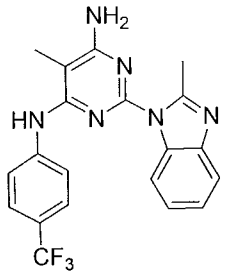

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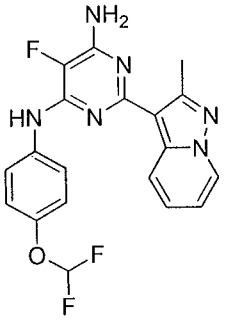

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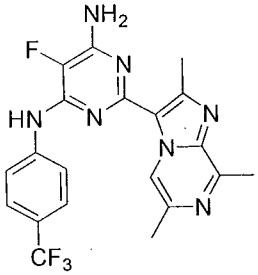

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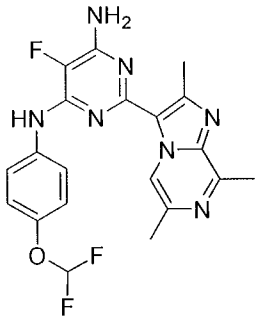

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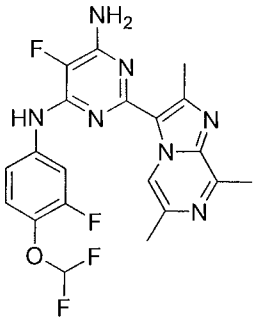

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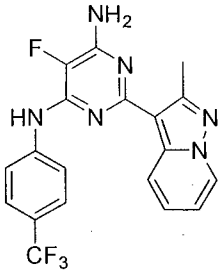

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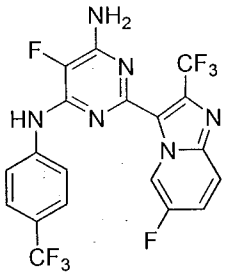

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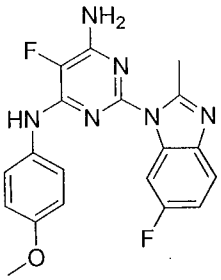

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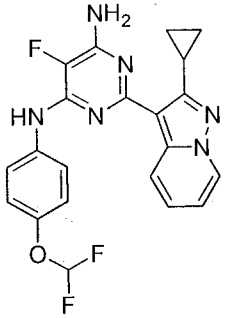

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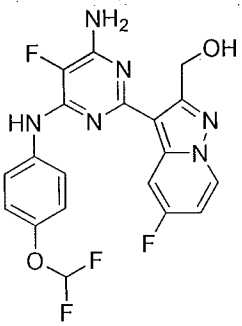

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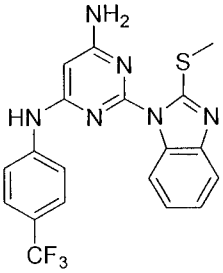

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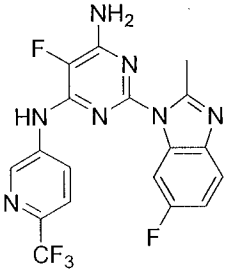

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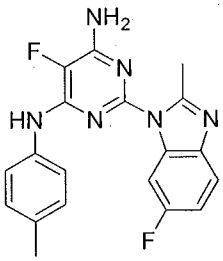

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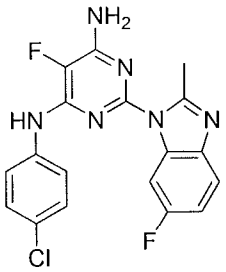

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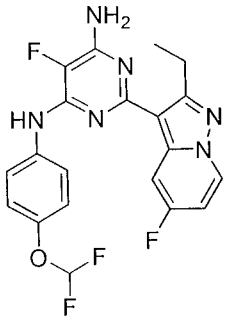

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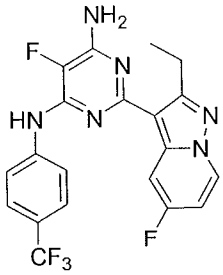

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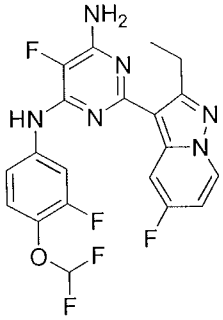

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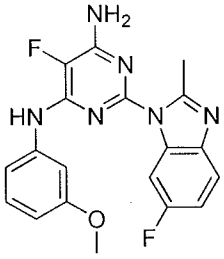

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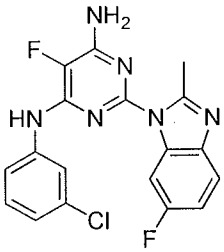

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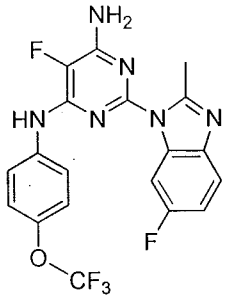

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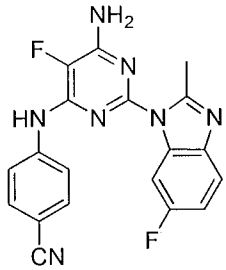

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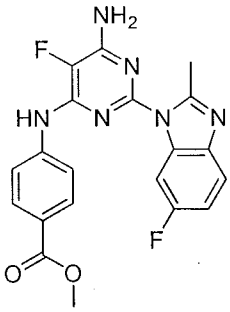

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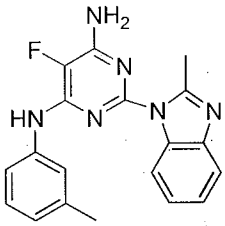

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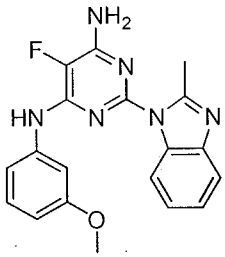

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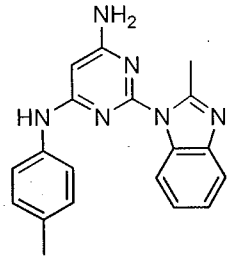

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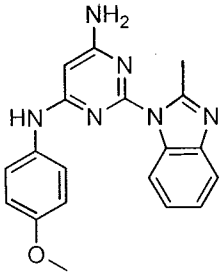

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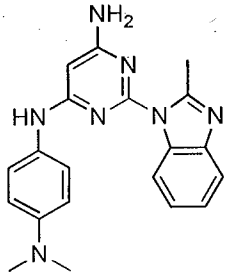

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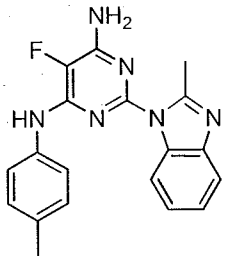

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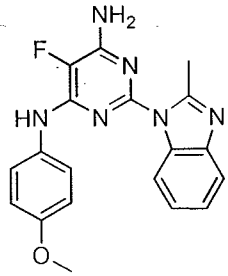

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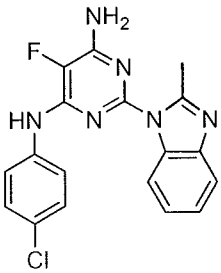

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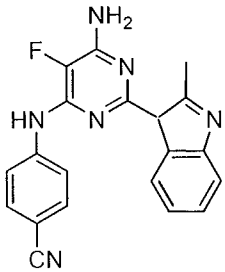

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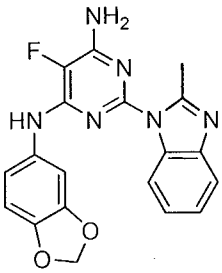

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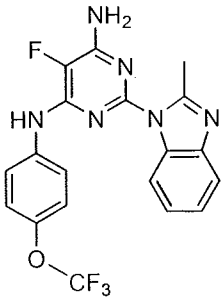

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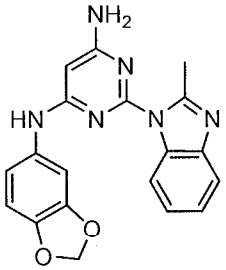

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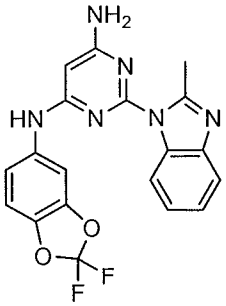

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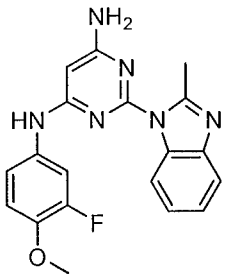

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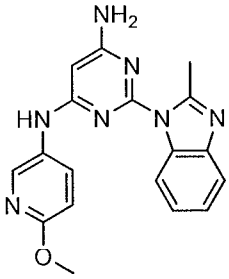

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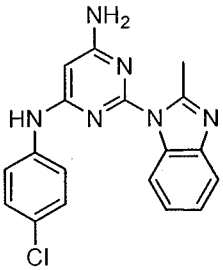

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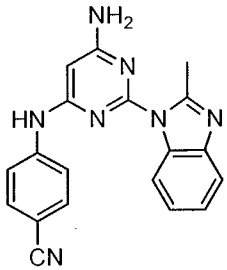

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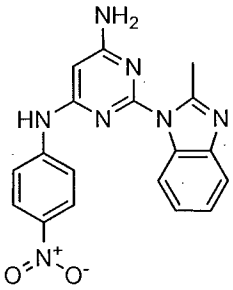

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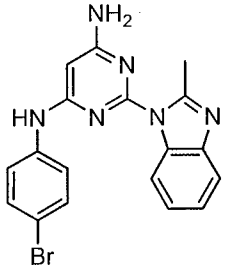

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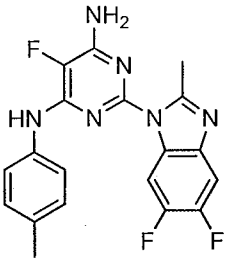

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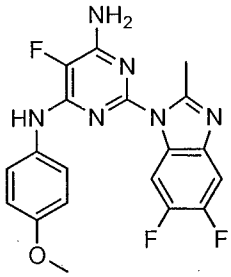

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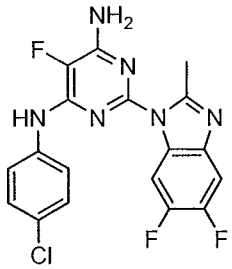

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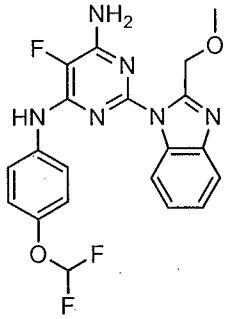

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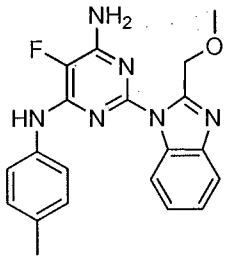

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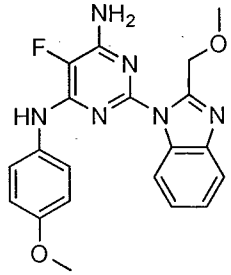

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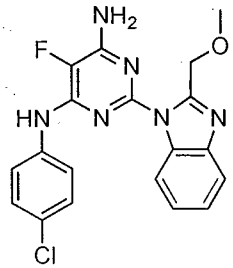

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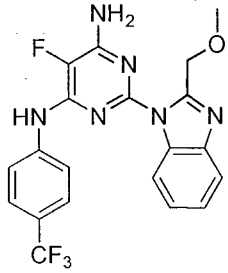

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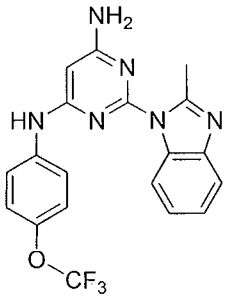

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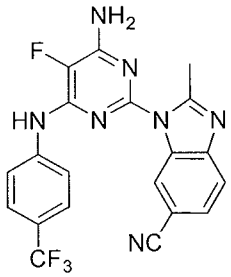

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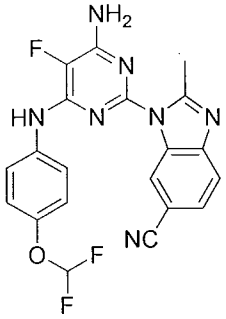

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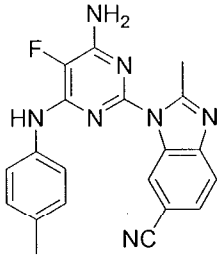

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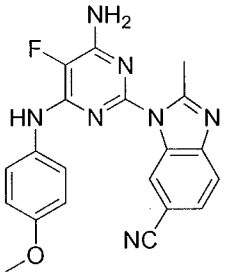

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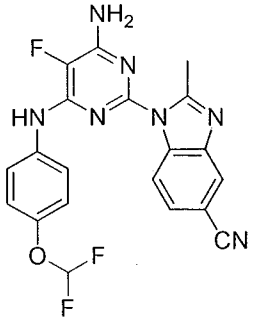

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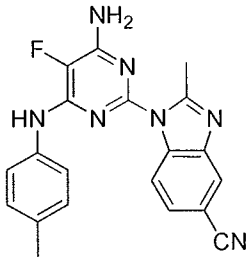

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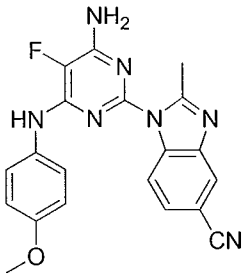

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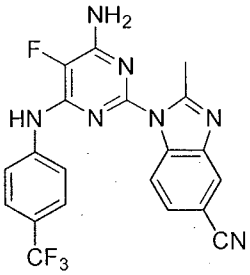

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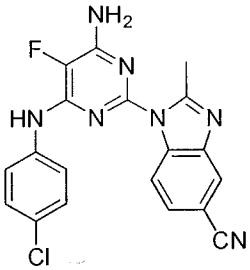

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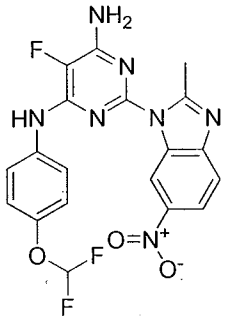

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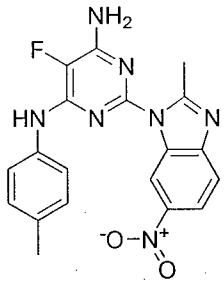

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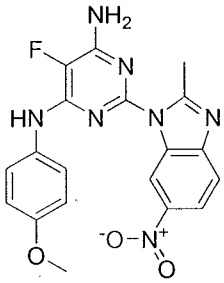

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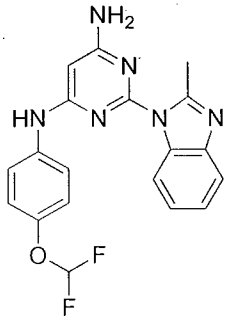

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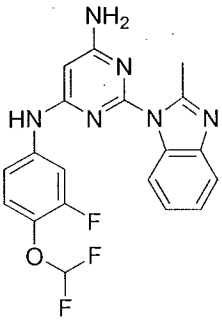

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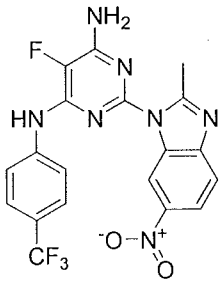

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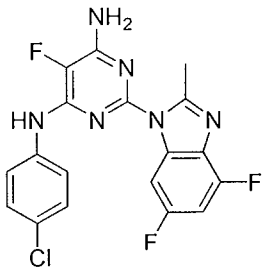

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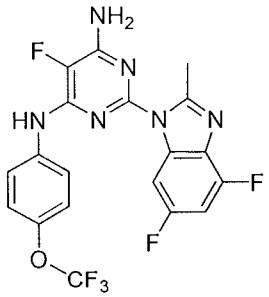

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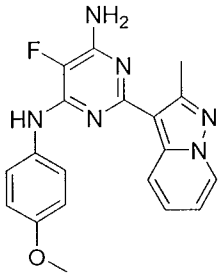

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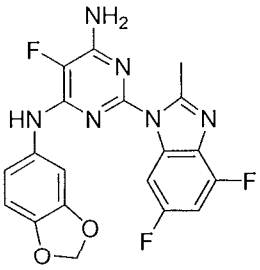

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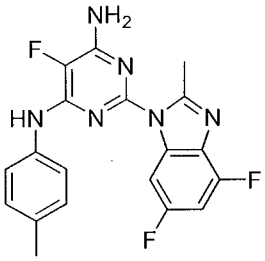

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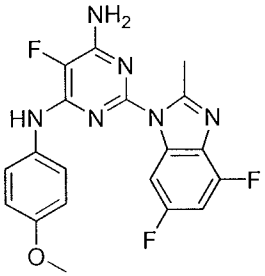

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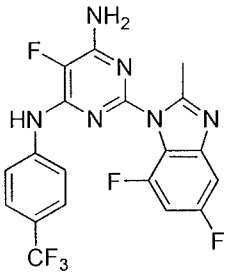

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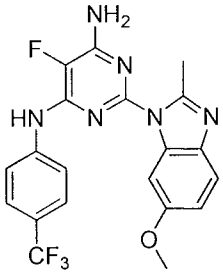

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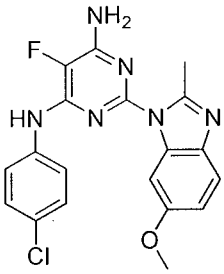

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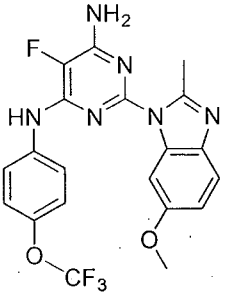

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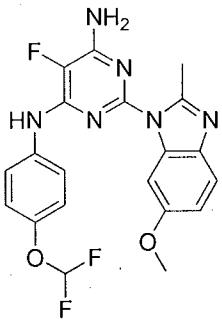

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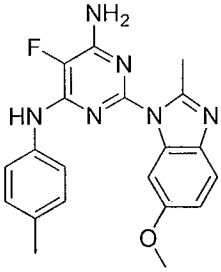

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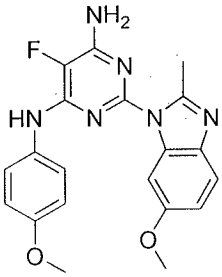

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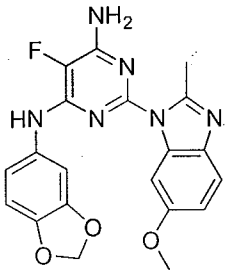

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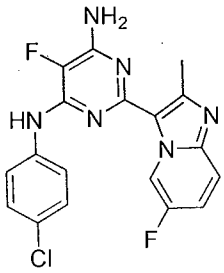

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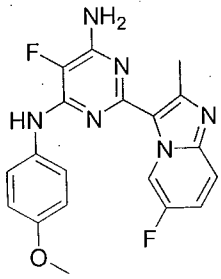

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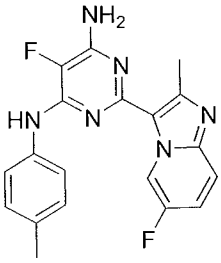

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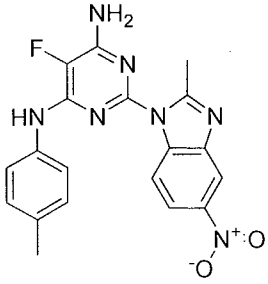

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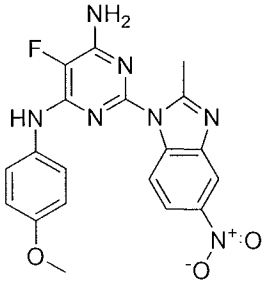

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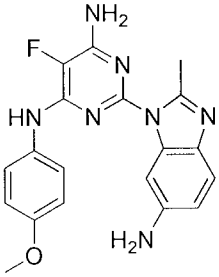

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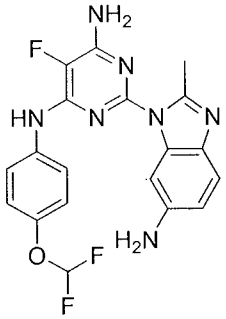

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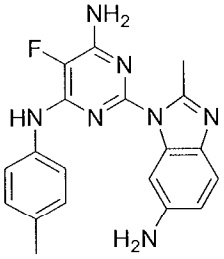

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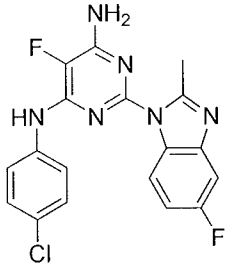

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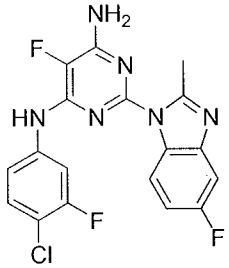

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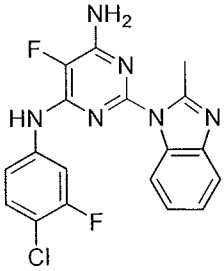

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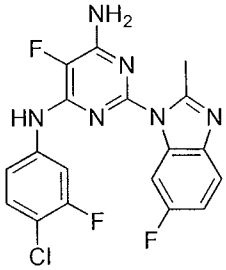

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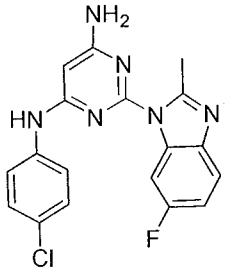

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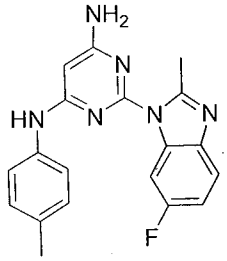

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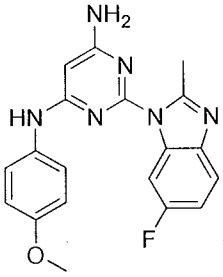

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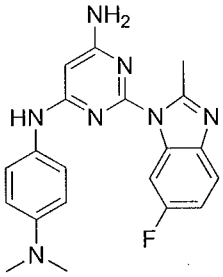

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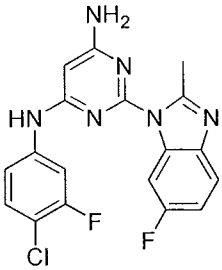

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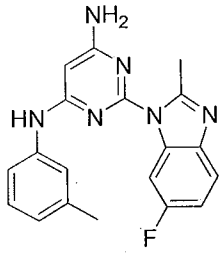

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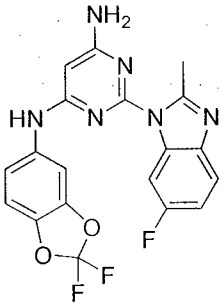

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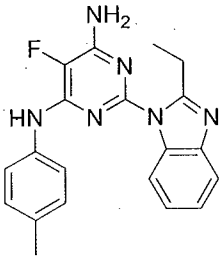

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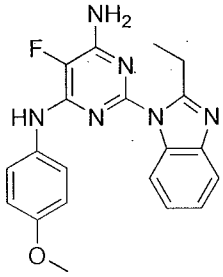

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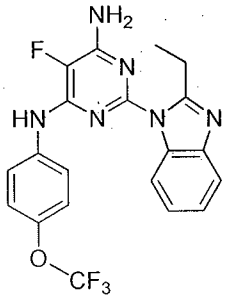

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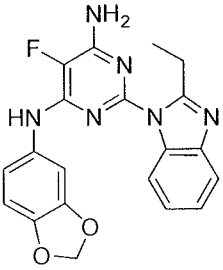

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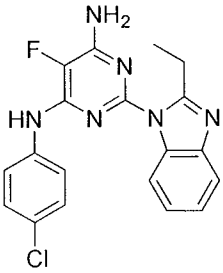

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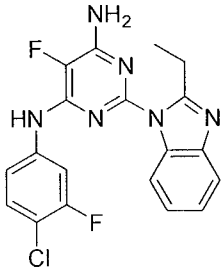

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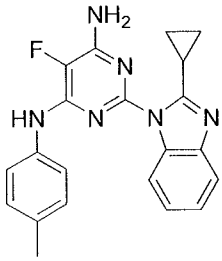

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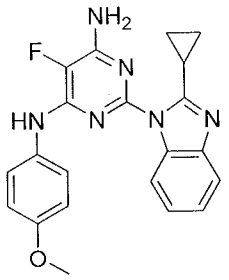

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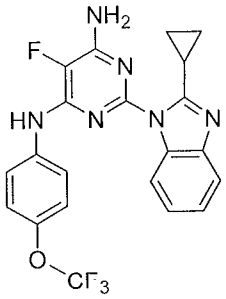

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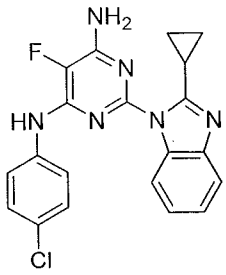

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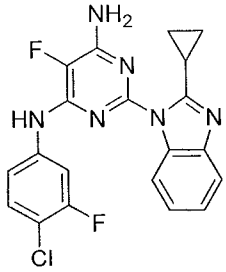

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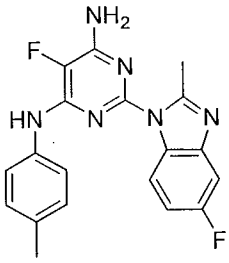

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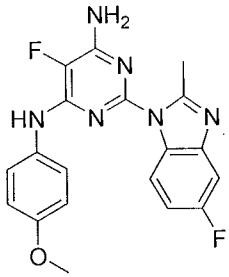

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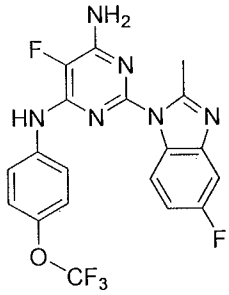

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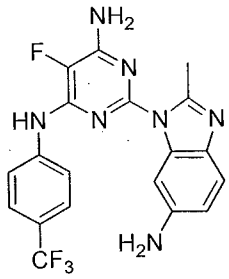


284;

wherein the form of the compound of Formula (I) is selected from a salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

Another embodiment includes a compound of Formula (I) or a form thereof selected from the group consisting of:

Cpd	Name
1	N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine
2	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
3	2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine
4	N-(4-methoxyphenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
5	N-(4-chlorophenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
6	2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-phenylpyrimidin-4-amine
7	2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine
8	N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
9	N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
10	N-(4-bromophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

11 N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

12 N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

13 2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

14 2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine

15 N-(4-bromophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

16 2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine

17 N-(4-chlorophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

18 2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

19 N-(4-bromophenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

20 N-(4-methylphenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

21 2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methylphenyl)pyrimidin-4-amine

22 2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

23 2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

24 2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine

25 N-(4-bromophenyl)-2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]pyrimidin-4-amine

26 N-(4-bromophenyl)-2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine

27 2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidin-4-amine

28 N-(1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

29 N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

30 N-(6-methoxypyridin-3-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

31 N^2,N^2-dimethyl-N^5-{2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-yl}pyridine-2,5-diamine

32 2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

33 2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

34 N-(3-fluoro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

35 N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

36 N-(3-chloro-4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

37 N-(4-ethoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

38 N-[4-(propan-2-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

39 N-[4-(1H-pyrazol-1-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

40 N-(3-chloro-4-methoxyphenyl)-2-(2-methyl-1*H*-benzimidazol-1-yl)pyrimidin-4-amine

41 2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

42 N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]pyrimidin-4-amine

43 5-fluoro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

44 5-chloro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

45 N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

46 2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

47 N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

48 2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

49 2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine

50 N-(4-methoxyphenyl)-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

51 N-[4-(difluoromethoxy)phenyl]-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

52 2-{[6-{[4-(difluoromethoxy)phenyl]amino}-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}ethanol

53 N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

54 2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

55 N-[4-(difluoromethoxy)phenyl]-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

56 N-[4-(trifluoromethyl)phenyl]-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine

57 2-{[2-(2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol

58 N^4-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)-N^6-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

59 N^4-[4-(difluoromethoxy)phenyl]-N^6-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

60 N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine

61 N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine

62 N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

63 2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

64 2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

65 N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine

66 2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

67 N-[4-(trifluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine

68 2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

69 N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

70 N-[4-(trifluoromethyl)phenyl]-2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrimidine-4,6-diamine

71 2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

72 N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

73 2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

74 2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

75 2-(2-cyclopropyl-6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine

76 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

77 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

78 2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine

79 N-[4-(trifluoromethyl)phenyl]-2-(2,5,6-trimethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

80 N-[3-fluoro-4-(trifluoromethyl)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

81 2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

82 2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

83 2-(2-cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

84 [3-(4-amino-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridin-2-yl]methanol

85 2-(6-bromo-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

86 2-(2,6-dimethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

87 2-(6-ethyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

88 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

89 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

90 2-{[2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol

91 2-(6-ethenyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

92 2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

93 2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

94 2-(6-fluoro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

95 5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

96 2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

97 2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

98 2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

99 2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

100 2-(6-fluoro-2-methylimidazo[1,2-a]pyrimidin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

101 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

102 N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

103 2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

104 2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

105 2-(6-chloro-2-ethyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

106 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

107 2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

108 5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

109 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

110 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

111 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

112 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

113 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

114 2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

115 2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

116 2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

117 2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

118 2-(imidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

119 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

120 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

121 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

122 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

123 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

124 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

125 2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

126 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

127 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

128 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

129 2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

130 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

131 N-[4-(difluoromethoxy)phenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

132 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

133 N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

134 5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

135 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

136 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

137 5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

138 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine

139 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine

140 2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

141 2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

142 2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

143 2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

144 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

145 N-[4-(difluoromethoxy)phenyl]-2-[2-(difluoromethyl)-6-fluoro-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

146 2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(methylsulfanyl)phenyl]pyrimidine-4,6-diamine

147 2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

148 N-[4-(difluoromethoxy)phenyl]-2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

149 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

150 2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

151 2-[2-(propan-2-yl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

152 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

153 2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

154 2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

155 2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

156 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

157 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

158 2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

159 2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

160 2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

161 2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

162 2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

163 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

164 2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

165 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

166 5-chloro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

167 5-chloro-2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

168 5-chloro-N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

169 5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

170 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

171 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

172 5-methyl-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

173 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine

174 5-fluoro-N-[4-(trifluoromethyl)phenyl]-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

175 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

176 N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

177 5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

178 5-fluoro-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

179 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

180 2-(2-cyclopropylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

181 [3-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-5-fluoropyrazolo[1,5-a]pyridin-2-yl]methanol

182 2-[2-(methylsulfanyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

183 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[6-(trifluoromethyl)pyridin-3-yl]pyrimidine-4,6-diamine

184 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

185 N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

186 N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine

187 2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

188 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine

189 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methoxyphenyl)pyrimidine-4,6-diamine

190 N-(3-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

191 5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

192 4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

193 methyl 4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzoate

194 5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine

195 5-fluoro-N-(3-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

196 2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

197 N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

198 N-[4-(dimethylamino)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

199 5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

200 5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

201 N-(4-chlorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

202 4-{[6-amino-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

203 N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

204 5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

205 N-(1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

206 N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

207 N-(3-fluoro-4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

208 N-(6-methoxypyridin-3-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

209 N-(4-chlorophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

210 4-{[6-amino-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

211 2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-nitrophenyl)pyrimidine-4,6-diamine

212 N-(4-bromophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

213 2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

214 2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

215 N-(4-chlorophenyl)-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

216 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

217 5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methylphenyl)pyrimidine-4,6-diamine

218 5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

219 N-(4-chlorophenyl)-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

220 5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

221 2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

222 1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile

223 1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile

224 1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile

225 1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile

226 1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile

227 1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

228 1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

229 1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile

230 1-{4-amino-6-[(4-chlorophenyl)amino]-5-fluoropyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

231 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

232 5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

233 5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

234 N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

235 N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

236 5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

237 N-(4-chlorophenyl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

238 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

239 5-fluoro-N-(4-methoxyphenyl)-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine

240 N-(1,3-benzodioxol-5-yl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

241 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

242 2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

243 2-(5,7-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

244 5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

245 N-(4-chlorophenyl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

246 5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

247 N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

248 5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

249 5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

250 N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

251 N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

252 5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

253 5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

254 5-fluoro-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

255 5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

256 2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

257 2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

258 2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

259 N-(4-chlorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

260 N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

261 N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

262 N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

263 N-(4-chlorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

264 2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

265 2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

266 N-[4-(dimethylamino)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

267 N-(4-chloro-3-fluorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

268 2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine

269 N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

270 2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

271 2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

272 2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

273 N-(1,3-benzodioxol-5-yl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

274 N-(4-chlorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

275 N-(4-chloro-3-fluorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

276 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

277 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

278 2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

279 N-(4-chlorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

280 N-(4-chloro-3-fluorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

281 5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

282 5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

283 5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine, and

284 2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine;

wherein the form of the compound of Formula (I) is selected from a salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

Terminology

The chemical terms used above and throughout the description herein, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.

5 As used herein, the term "C_{1-8}alkyl" refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including, without limitation, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like. In some embodiments, C_{1-8}alkyl includes C_{1-6}alkyl, C_{1-4}alkyl and the like. A C_{1-8}alkyl radical may be optionally substituted where
10 allowed by available valences.

As used herein, the term "C_{2-8}alkenyl" refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon double bonds therein, including, without limitation, ethenyl, allyl, propenyl and the like. In some embodiments, C_{2-8}alkenyl includes C_{2-6}alkenyl,
15 C_{2-4}alkenyl and the like. A C_{2-8}alkenyl radical may be optionally substituted where allowed by available valences.

As used herein, the term "C_{2-8}alkynyl" refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon triple bonds therein, including, without limitation, ethynyl,
20 propynyl and the like. In some embodiments, C_{2-8}alkynyl includes C_{2-6}alkynyl, C_{2-4}alkynyl and the like. A C_{2-8}alkynyl radical may be optionally substituted where allowed by available valences.

As used herein, the term "C_{1-8}alkoxy" refers to saturated hydrocarbon radicals of from one to eight carbon atoms having a straight or branched chain configuration of the
25 formula: -O-C_{1-8}alkyl, including, without limitation, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, n-hexoxy and the like. In some embodiments, C_{1-8}alkoxy includes C_{1-6}alkoxy, C_{1-4}alkoxy and the like. A C_{1-8}alkoxy radical may be optionally substituted where allowed by available valences.

As used herein, the term "C_{3-14}cycloalkyl" refers to a saturated monocyclic, bicyclic
30 or polycyclic hydrocarbon radical, including, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1H-indanyl, indenyl, 2,3-dihydro-1H-

indenyl, tetrahydro-naphthalenyl and the like. In some embodiments, C_{3-14}cycloalkyl includes C_{3-8}cycloalkyl, C_{5-8}cycloalkyl, C_{3-10}cycloalkyl and the like. A C_{3-14}cycloalkyl radical may be optionally substituted where allowed by available valences.

As used herein, the term "aryl" refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, without limitation, phenyl, naphthyl (also referred to as naphthalenyl), anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical may be optionally substituted where allowed by available valences.

As used herein, the term "heteroaryl" refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom, including, without limitation, furanyl, thienyl (also referred to as thiophenyl), pyrrolyl, pyrazolyl (also referred to as 1H-pyrazolyl), imidazolyl (also referred to as 1H-imidazolyl), isoxazolyl (also referred to as 1,2-oxazolyl), isothiazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyranyl, thiopyranyl, pyridinyl (also referred to as pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl (also referred to as 1H-indolyl), azaindolyl, indazolyl (also referred to as 2H-indazolyl), azaindazolyl, isoindolyl, indolizinyl, benzofuranyl, benzothienyl, benzimidazolyl (also referred to as 1H-benzimidazolyl), benzothiazolyl, benzoxazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl, 9H-purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, acridinyl and the like and associated homologs and regioisomers thereof. A heteroaryl radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

As used herein, the term "heterocyclyl" refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including, without limitation, oxiranyl, oxetanyl, azetidinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, pyrrolinyl, pyrrolidinyl, dihydropyrazolyl, pyrazolinyl, pyrazolidinyl, dihydroimidazolyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl,

oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, 1,3-dioxolanyl, dihydro-2H-pyranyl, tetrahydro-2H-pyranyl, dihydro-pyridinyl, tetrahydro-pyridinyl, dihydro-pyrimidinyl, tetrahydro-pyrimidinyl, dihydro-pyrazinyl, tetrahydro-pyrazinyl, dihydro-pyridazinyl, tetrahydro-pyridazinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro-triazinyl, tetrahydro-triazinyl, hexahydro-triazinyl, 1,4-diazepanyl, dihydro-indolyl, indolinyl, tetrahydro-indolyl, dihydro-indazolyl, tetrahydro-indazolyl, dihydro-isoindolyl, dihydro-benzofuranyl, tetrahydro-benzofuranyl, dihydro-benzothienyl, tetrahydro-benzothienyl, dihydro-benzoimidazolyl, tetrahydro-benzoimidazolyl, dihydro-benzooxazolyl, tetrahydro-benzooxazolyl, dihydro-benzooxazinyl, tetrahydro-benzooxazinyl, benzo[1,3]dioxolyl (also referred to as 1,3-benzodioxolyl), benzo[1,4]dioxanyl (also referred to as 1,4-benzodioxanyl or 2,3-dihydro-1,4-benzodioxinyl), benzo[1,4]dioxinyl (also referred to as 1,4-benzodioxinyl), 4,5,6,7-tetrahydro-2H-indazolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, dihydro-purinyl, tetrahydro-purinyl, dihydro-quinolinyl, tetrahydro-quinolinyl, dihydro-isoquinolinyl, tetrahydro-isoquinolinyl, dihydro-quinazolinyl, tetrahydro-quinazolinyl, dihydro-quinoxalinyl, tetrahydro-quinoxalinyl and the like and associated homologs thereof. A heterocyclyl radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

As used herein, the term "$B(OR_8)_2$" refers to a radical of the formula: –B[(-OH)(-OH)] when R_8 is hydrogen; or, –B[(-OH)(-O-C_{1-8}alkyl)] when R_8 is independently hydrogen or C_{1-8}alkyl; or, -B[(-O-C_{1-8}alkyl)(-O-C_{1-8}alkyl)] when R_8 is C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-C_{2-8}alkenyl" refers to a radical of the formula: -C_{2-8}alkenyl-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-C_{2-8}alkynyl" refers to a radical of the formula: -C_{2-8}alkynyl-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-carbonyl" refers to a radical of the formula: -C(O)-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-C(O)-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-carbonyl-amino" refers to a radical of the formula: -NH-C(O)-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-carbonyl-amino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-NH-C(O)-O-C_{1-8}alkyl.

As used herein, the term "C_{1-8}alkoxy-imino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl(=N-O-C_{1-8}alkyl).

As used herein, the term "C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino" refers to a radical of the formula: -N$(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-NH-C_{1-8}alkyl.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-N$(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-NH-C_{1-8}alkyl.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-N$(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-carbonyl" refers to a radical of the formula: -C(O)-NH-C_{1-8}alkyl.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-carbonyl" refers to a radical of the formula: -C(O)-N$(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-carbonyl-amino" refers to a radical of the formula: -NH-C(O)-NH-C_{1-8}alkyl.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-carbonyl-amino" refers to a radical of the formula: $-NH-C(O)-N(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-sulfonyl" refers to a radical of the formula: $-SO_2-NH-C_{1-8}alkyl$.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-sulfonyl" refers to a radical of the formula: $-SO_2-N(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-amino-sulfonyl-amino" refers to a radical of the formula: $-NH-SO_2-NH-C_{1-8}alkyl$.

As used herein, the term "$(C_{1-8}alkyl)_2$-amino-sulfonyl-amino" refers to a radical of the formula: $-NH-SO_2-N(C_{1-8}alkyl)_2$.

As used herein, the term "C_{1-8}alkyl-carbonyl" refers to a radical of the formula: $-C(O)-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-carbonyl-amino" refers to a radical of the formula: $-NH-C(O)-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-carbonyl-amino-C_{1-8}alkyl" refers to a radical of the formula: $-C_{1-8}alkyl-NH-C(O)-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-carbonyl-oxy" refers to a radical of the formula: $-O-C(O)-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl" refers to a radical of the formula: $-C_{1-8}alkyl-O-C(O)-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-sulfonyl" refers to a radical of the formula: $-SO_2-C_{1-8}alkyl$.

As used herein, the term "C_{1-8}alkyl-thio" refers to a radical of the formula: $-S-C_{1-8}alkyl$.

As used herein, the term "amino" refers to a radical of the formula: $-NH_2$.

As used herein, the term "amino-C_{1-8}alkyl" refers to a radical of the formula: $-C_{1-8}alkyl-NH_2$.

As used herein, the term "amino-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-NH_2.

As used herein, the term "amino-carbonyl" refers to a radical of the formula: -C(O)-NH_2.

As used herein, the term "amino-carbonyl-amino" refers to a radical of the formula: -NH-C(O)-NH_2.

As used herein, the term "amino-sulfonyl" refers to a radical of the formula: -SO_2-NH_2.

As used herein, the term "amino-sulfonyl-amino" refers to a radical of the formula: -NH-SO_2-NH_2.

As used herein, the term "aryl-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-aryl.

As used herein, the term "aryl-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-aryl.

As used herein, the term "aryl-amino" refers to a radical of the formula: -NH-aryl.

As used herein, the term "carboxyl" refers to a radical of the formula: -COOH, -C(O)OH or -CO_2H.

As used herein, the term "formyl" refers to a radical of the formula: -C(O)-H.

As used herein, the term "formyl-oxyl" refers to a radical of the formula: -O-C(O)-H.

As used herein, the terms "halo" or "halogen" refer to a halogen atom radical, including fluoro, chloro, bromo and iodo.

As used herein, the term "halo-C_{1-8}alkoxy" refers to a radical of the formula: -O-C_{1-8}alkyl-halo, wherein C_{1-8}alkyl may be partially or completely substituted where allowed by available valences with one or more halogen atoms. In some embodiments, halo-C_{1-8}alkoxy includes halo-C_{1-6}alkoxy, halo-C_{1-4}alkoxy and the like.

As used herein, the term "halo-C_{1-8}alkoxy-carbonyl" refers to a radical of the formula: -C(O)-O-C_{1-8}alkyl-halo.

As used herein, the term "halo-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-halo, wherein C_{1-8}alkyl may be partially or completely substituted where allowed by available valences with one or more halogen atoms. In some embodiments, halo-C_{1-8}alkyl includes halo-C_{1-6}alkyl, halo-C_{1-4}alkyl and the like.

As used herein, the term "halo-C_{1-8}alkyl-carbonyl" refers to a radical of the formula: -C(O)-C_{1-8}alkyl-halo.

As used herein, the term "halo-C_{1-8}alkyl-sulfonyl" refers to a radical of the formula: -SO_2-C_{1-8}alkyl-halo.

As used herein, the term "halo-C_{1-8}alkyl-thio" refers to a radical of the formula: -S-C_{1-8}alkyl-halo.

As used herein, the term "heteroaryl-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-heteroaryl.

As used herein, the term "hydroxyl-C_{1-8}alkoxy" refers to a radical of the formula: -O-C_{1-8}alkyl-OH, wherein C_{1-8}alkyl may be partially or completely substituted where allowed by available valences with one or more hydroxyl radicals.

As used herein, the term "hydroxyl-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-OH, wherein C_{1-8}alkyl may be partially or completely substituted where allowed by available valences with one or more hydroxyl radicals.

As used herein, the term "hydroxyl-amino" refers to a radical of the formula: -NH-OH.

As used herein, the term "hydroxyl-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-OH.

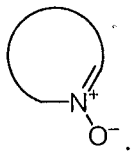
As used herein, the term "hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl-NH-C_{1-8}alkyl-OH.

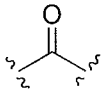
As used herein, the term "hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino" refers to a radical of the formula: -NH-C_{1-8}alkyl-NH-C_{1-8}alkyl-OH.

As used herein, the term "hydroxyl-imino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl(=N-OH).

As used herein, the term "imino" refers to a radical of the formula: =NH.

As used herein, the term "imino-C_{1-8}alkyl" refers to a radical of the formula: -C_{1-8}alkyl(=NH).

As used herein, the term "N-oxide" refers to a moiety of the formula:  .

As used herein, the term "oxo" refers to a moiety of the formula:  .

As used herein, the term "$P(O)(R_7)_2$-amino" refers to a radical of the formulae: -NH-P(O)(-O-C_{1-8}alkyl)(OH) when R_7 is independently hydroxyl and $(C_{1-8}alkoxy)_n$, where n is 1; or, -NH-P(O)$(OH)_2$ when R_7 is hydroxyl; or, -NH-P(O)(-O-C_{1-8}alkyl)$_2$ when R_7 is $(C_{1-8}alkoxy)_n$, where n is 1.

As used herein, the term "substituent" means positional variables on the atoms of a core molecule that are attached at a designated atom position, replacing one or more hydrogen atoms on the designated atom, provided that the atom of attachment does not exceed the available valence or shared valence, such that the substitution results in a stable compound. Accordingly, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. Any carbon atom as well as heteroatom with a valence level that appears to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown.

As used herein, the term "and the like," with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural isomers), hydration of ring systems (including saturation or partial unsaturation of monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.

For the purposes of this description, where one or more substituent variables for a compound of Formula (I) encompass functionalities incorporated into a compound of Formula (I), each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.

As used herein, the terms "independently selected," or "each selected" refer to functional variables in a substituent list that may be attached more than once on the structure of a core molecule, where the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent variable on a core structure for a compound described herein is understood to include the replacement of the generic substituent with specie substituents that are included within the particular genus, *e.g.*, aryl may be replaced with phenyl or naphthalenyl and the like, such that the resulting compound is to be included within the scope of the compounds described herein.

As used herein, the term "optionally substituted" means that the specified substituent variables, groups, radicals or moieties represent the scope of the genus and may be independently chosen as needed to replace one or more hydrogen atoms on the designated atom of attachment of a core molecule.

As used herein, the terms "stable compound' or "stable structure" mean a compound that is sufficiently robust to be isolated to a useful degree of purity from a reaction mixture and formulations thereof into an efficacious therapeutic agent.

Compound names used herein were obtained using the ACD Labs Index Name software provided by ACD Labs and/or ChemDraw Ultra software provided by CambridgeSoft. When the compound name disclosed herein conflicts with the structure depicted, the structure shown will supercede the use of the name to define the compound intended.

Compound Forms

As used herein, the terms a "compound of Formula (Ia)," "a compound of Formula (II)," "compound of Formula (IIa)," "compound of Formula (III)," "compound of Formula (IIIa)," "compound of Formula (IV)" or "compound of Formula (IVa)" refer to subgenera of the compound of Formula (I) or a form thereof, as defined herein. Rather than repeat the various subgenera of the compound of Formula (I), in certain embodiments, the term "compound(s) of Formula (I) or a form thereof" is used inclusively to refer to compound(s) of Formula (Ia) or a form thereof, compound(s) of Formula (II) or a form thereof, compound(s) of Formula (IIa) or a form thereof, compound(s) of Formula (III) or a form thereof, compound(s) of Formula (IIIa) or a form thereof, compound(s) of Formula (IV) or a

form thereof or compound(s) of Formula (IVa) or a form thereof, either separately or together. Thus, embodiments and references to "a compound of Formula (I)" are intended to be inclusive of compounds of Formula (Ia), compounds of Formula (II), compounds of Formula (IIa), compounds of Formula (III), compounds of Formula (IIIa), compounds of Formula (IV) and compounds of Formula (IVa).

As used herein, the term "form" means a compound of Formula (I) selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer, or tautomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is selected from a salt, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is selected from a free acid, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is selected from a free base, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is a free acid, free base or salt thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is an isotopologue thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is a stereoisomer, racemate, enantiomer or diastereomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is a tautomer thereof.

In certain embodiments described herein, the form of the compound of Formula (I) is a pharmaceutically acceptable form.

In certain embodiments described herein, the compound of Formula (I) or a form thereof is isolated for use.

As used herein, the term "isolated" means the physical state of a compound of Formula (I) or a form thereof after being isolated and/or separated and/or purified from a synthetic process (*e.g.,* from a reaction mixture) or natural source or combination thereof according to an isolation, separation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.,* chromatography, recrystallization and the like) in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

As used herein, the term "protected" means that a functional group on a compound of Formula (I) or a form thereof is in a form modified to preclude undesired side reactions of the functional group when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (2007), Wiley, New York.

Prodrugs and solvates of the compounds of Formula (I) or a form thereof described herein are also contemplated.

As used herein, the term "prodrug" means that a functional group on a compound of Formula (I) is in a form (*e.g.*, acting as an active or inactive drug precursor) that is transformed *in vivo* to yield an active or more active compound of Formula (I) or a form thereof. The transformation may occur by various mechanisms (*e.g.*, by metabolic and/or non-metabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by V.J. Stella, et. al., "Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards," American Association of Pharmaceutical Scientists and Springer Press, 2007.

In one example, when a compound of Formula (I) or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formula (I) or a form thereof contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a functional group such as alkyl or carbonyloxy and the like. In another example, when a compound of Formula (I) or a form thereof contains an amine functional

group, a prodrug can be formed by the replacement of one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl.

Pharmaceutically acceptable prodrugs of compounds of Formula (I) or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters (e.g., a phosphoramidic acid used to derive a phosphoramidic acid) and mono-, di- or triphosphate esters further substituted with alkyl, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formula (I) or a form thereof as a prodrug.

The compounds of Formula (I) or a form thereof can form salts, which are intended to be included within the scope of this description. Reference to a compound of Formula (I) or a form thereof herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) or a form thereof contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of Formula (I) or a form thereof described herein that are safe and effective (*i.e.*, non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds of Formula (I) or a form thereof described herein. Embodiments of acid addition salts include, and are not limited to, acetate, acid phosphate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, hydrobromide, hydrochloride, dihydrochloride, hydroiodide,

isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate, trifluoroacetic acid salt and the like. One or more embodiments of acid addition salts include chloride, hydrochloride, dihydrochloride, trihydrochloride, hydrobromide, acetate, diacetate, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like. More particular embodiments include a chloride, hydrochloride, dihydrochloride, hydrobromide, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like.

In certain embodiments of the compounds of Formula (I) or a form thereof described herein, the compound is isolated as a salt form, wherein the compound is conjugated with the salt in a ratio represented as, in a non-limiting example, "compound:salt (A:B)," wherein "A" and "B" represent the equivalents of compound to salt in the isolated form.

Additionally, acids which are considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. Certain compounds of Formula (I) or a form thereof described herein can also form pharmaceutically acceptable salts with organic bases (for example, organic amines) such as, but not limited to, dicyclohexylamines, *tert*-butyl amines and the like, and with various amino acids such as, but not limited to, arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

Compounds of Formula (I), and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formula (I) or a form thereof as described herein.

The compounds of Formula (I) or a form thereof may contain asymmetric or chiral centers, and, therefore, may exist in different stereoisomeric forms. The present description is intended to include all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures.

The compounds of Formula (I) or a form thereof described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one embodiment, the compounds of Formula (I) or a form thereof described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another embodiment, the compounds of Formula (I) or a form thereof described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds of Formula (I) or a form thereof described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) isomer, as defined by *IUPAC* Nomenclature Recommendations.

As used herein, the term "substantially pure" refers to compounds of Formula (I) or a form thereof consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*S*) enantiomer present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an

amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*R*) enantiomer present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

As used herein, the term "racemate" refers to any mixture of isometric forms that are not "enantiomerically pure", including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20, about 85/15 or about 90/10.

In addition, the compounds of Formula (I) or a form thereof described herein embrace all geometric and positional isomers. For example, if a compound of Formula (I) or a form thereof incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures thereof, are embraced within the scope of the compounds of Formula (I) or a form thereof described herein.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of a chiral HPLC column or other chromatographic methods known to those skilled in the art.

Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds of Formula (I) or a form thereof (including salts, solvates, esters and prodrugs and transformed prodrugs thereof), which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, diastereomeric and regioisomeric forms, are contemplated within the scope of the description herein. Individual stereoisomers of the

compounds of Formula (I) or a form thereof described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described *supra*.

The use of the terms "salt," "solvate," “ester,” "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates, isotopologues or prodrugs of the instant compounds.

The term "isotopologue" refers to isotopically-enriched compounds of Formula (I) or a form thereof which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) or a form thereof described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as H^2, H^3, C^{13}, C^{14}, N^{15}, O^{18}, O^{17}, P^{31}, P^{32}, S^{35}, F^{18}, Cl^{35} and Cl^{36}, respectively, each of which is also within the scope of this description.

Certain isotopically-enriched forms of compounds of Formula (I) or a form thereof described herein (*e.g.*, those labeled with H^3 and C^{14}) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, H^3) and carbon-14 (*i.e.*, C^{14}) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium (*i.e.*, "deuterium enriched") may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life), increased solubility, reduced dosage requirements (*e.g.*, increased bioavailability)) or reduced toxicity (e.g., reduced inhibition of metabolic enzymes) and hence may be preferred in some circumstances.

One or more compounds of Formula (I) or a form thereof described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

As used herein, the term “solvate” means a physical association of a compound of Formula (I) or a form thereof described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including

hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, "solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

One or more compounds of Formula (I) or a form thereof described herein may optionally be converted to a solvate. Preparation of solvates is generally known. A typical, non-limiting process involves dissolving a compound of Formula (I) or a form thereof in a desired amount of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example infrared spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

As used herein, the term "hydrate" means a solvate wherein the solvent molecule is water.

Polymorphic crystalline and amorphous forms of the compounds of Formula (I) or a form thereof, and of the salts, solvates, esters and prodrugs of the compounds of Formula (I) or a form thereof, are further intended to be included in the scope of the compounds of Formula (I) or a form thereof described herein.

Compound Uses

The *Bmi-1* oncogene was first identified as part of a key insertion/activation region of the Moloney murine leukemia virus in the early 1990's (*1-6*). *Bmi-1* is a member of the Polycomb group (PcG) of transcriptional repressors and was identified as a necessary regulator of hematopoietic stem cell (HSC) self-renewal (*76*, *77*). Park found that Bmi-1 is highly expressed in purified mouse and human HSCs and that the absence of Bmi-1, as demonstrated by *Bmi-1* knockout mice, results in the progressive loss of all hematopoietic lineages (*76*). Furthermore, the transplantation of *Bmi-1*$^{-/-}$ day 14.5 fetal liver cells into lethally irradiated normal mice, demonstrated that the cells were unable to reconstitute myeloid cells, B cells, and T cells because *Bmi-1*$^{-/-}$ HSCs were unable to renew (*76*).

In addition to the role of *Bmi-1* in HSC self renewal, it was found that *Bmi-1* transgene expression induced lymphoma in mice (*2*). Bmi-1 was also found to be

overexpressed in many tumor types, including acute myeloid leukemia, medulloblastoma, neuroblastoma, colorectal cancer, lung cancer, and prostate cancer, and was found to increase with malignancy (*34*, *78*, *61*, *79*, *80*, *65*, *43*). Loss of Bmi-1 in various human cancer cell lines via *Bmi-1* specific RNA interference (RNAi) was shown to lead to acute cell death and growth inhibition, whereas loss of Bmi-1 in various normal cell lines was shown to lead to only moderate growth inhibition and not significant cell death (*69*). Thus, Bmi-1 is necessary for the survival of cancer cells but has minimal effect on the survival of normal cells.

Bmi-1 has been subsequently shown to act as an oncogene experimentally and has proven particularly potent in conjunction with c-myc to initiate lymphoma in mice (*7*, *8*). The role of Bmi-1 in lymphomagenesis has been attributed partially to transcriptional repression of the INK4a locus (containing both the $p16^{INK4A}$ and $p14^{ARF}$ genes) leading to maintenance of cancer and tumor cell proliferation and prevention of differentiation (*7*, *9*). Loss of expression of the INK4a locus due to promoter silencing has been extensively studied and is both important for the progression and prognosis of many types of hematologic cancers (*10*, *11*). The INK4a locus is occasionally lost by deletion in leukemia and lymphoma (*12*, *13*).

However, Bmi-1 has been shown to play a role in tumorigenesis in models lacking the INK4a locus, indicating that other loci important in cancer are regulated by this protein (*14*). Experimental results have demonstrated further that loss of Bmi-1 induces growth arrest and senescence in fibrosarcoma cells known to lack INK4a (*15*). There is also evidence that Bmi-1 is important for the hedgehog (Hh) pathway in breast cancer. Activation of Hh signaling increases *Bmi-1* expression, while down-regulation of *Bmi-1* (via siRNA) abrogates the effects of Hh signaling on mammosphere formation *in vitro* and inhibits ductal/alveolar development in mice (*16*). Recent work has demonstrated the role of Bmi-1 in the regulation of Hox gene expression. Knockdown of Bmi-1 caused a global and loci-specific loss of H2A ubiquitination, upregulation of the HoxC5 gene, and inhibition of the growth of HeLa cells (*17*). Another study demonstrated that E2F6 and Bmi-1 cooperate in the regulation of Hox gene expression (particularly Hox C10 and B9), and consequently affect axial skeleton development, but not in the repression of the Ink4a-Arf locus. These findings underscore the significance of the E2F6-Bmi-1 interaction and suggest that the Hox and Ink4a-Arf loci are regulated by somewhat different Bmi-1-dependent mechanisms (*18*). Current research

suggests that Bmi-1 has different roles dependent upon cell types and/or developmental stages. Other genes regulated by Bmi-1 remain to be identified.

Bmi-1 is found to be highly expressed in malignancies, such as diffuse large B cell lymphomas (DLBCL), B cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, acute myeloid leukemia, colorectal carcinoma, liver carcinoma, non-small cell lung cancer, breast carcinoma and medulloblastoma. The study of *Bmi-1* knockout mice has revealed that Bmi-1 is required for the self-renewal of both leukemic and normal hematopoietic stem cells.

Additionally, evidence exists linking Bmi-1 levels to blood tumor types, particularly Burkitt's lymphoma, mantle cell lymphoma, Hodgkin's lymphoma (*21-23*), non-Hodgkin's lymphoma, some T cell lymphomas (*2, 24-31*), acute myeloid leukemia and T-ALL (*32-35*). Raaphorst *et al* observed that, in Hodgkin's lymphoma, Reed-Sternberg cells (HRS) co-express Bmi-1, EZH2, and Mib-1/Ki-67. Because HRS cells are thought to originate from germinal center lymphocytes that express Bmi-1, such lymphocytes should lose the ability to express Bmi-1 (and gain the ability to express EZH2) as they differentiate. These observations suggest that Hodgkin's lymphoma is associated with aberrant co-expression of Bmi-1 and EZH2 in these cells (*22*). An assessment of acute myeloid leukemia stem cell populations by van Gosliga *et al* (*36*) showed that $CD34^+/CD38^-$ cells capable of forming leukemic-cobblestone colonies on a bone marrow substrate through at least two rounds of expansion represented an extreme minority of the cell population. Further analysis showed that this cell population expresses high levels of *Bmi-1* mRNA and can establish an aggressive leukemia in mice, while those cells that have lower levels of *Bmi-1* mRNA cannot (*36*). Such studies implicate Bmi-1 in tumor growth and cell survival and suggest a central function in tumor initiation and maintenance of cancer and tumor stem cells.

The levels of Bmi-1 have been shown to have prognostic relevance in a number of tumor types. An example of this is found in acute myeloid leukemia based on results from a study assessing the prognostic value of high Bmi-1 levels in 64 patients (*32*). On the basis of the median value of Bmi-1 (54.58%), patients were divided into two groups and monitored for survival. Patients with lower Bmi-1 positivity (<55%, n=33) had significantly longer overall survival (P=0.0001), relapse-free survival (P=0.0072) and remission duration (P=0.0065) when compared to the patients with higher levels of Bmi-1 (>55%, n=31, respectively), regardless of age group (*32*). Similarly, Van Galen *et al* (*37*) have shown that

Bmi-1 levels are highly prognostic in diffuse large B cell lymphomas (DLBCL) (*37*). Neoplastic cells in DLBCL cases originate from germinal centre B (GCB) cells or their descendents(*38*). Recent microarray analyses have shown that some DLBCL phenotypically resemble non-neoplastic GCB cells, while some show an expression profile similar to that of activated B cells (ABC) (*39*).

Furthermore, patients with a GCB-like phenotype have a considerably better prognosis than those with an ABC-like phenotype (*40*). *Bmi-1* was identified as one of the genes that distinguish the ABC-like DLBCL (*39*),(*41*). Other groups have linked elevated Bmi-1 levels with poor prognosis in mantle cell lymphoma (MCL), non-Hodgkin's lymphoma and other leukemias (*22, 26, 27, 29, 42-44*), as well as many other tumour types including neuroblastoma, glioblastoma, hepatocellular carcinoma, and breast, colorectal, prostate, lung, gastric and salivary gland cancers (*45-57*). The loss of expression from the INK4A locus has also been shown to have prognostic value (*12, 13*). Taken together, these data strongly implicate Bmi-1 in cancer and suggest that inhibiting uncontrolled cell proliferation by inhibiting Bmi-1 function and reducing the level of Bmi-1 in a cancer cell, tumor cell, cancer stem cell or tumor stem cell will have a beneficial therapeutic effect in patients with multiple cancer types, particularly in those afflicted with hematological cancers.

For example, MCL is a rare, aggressive and incurable B cell non-Hodgkin's lymphoma that is refractory (*i.e.*, resistant to conventional chemotherapy) and is associated with a poor prognosis. MCL is characterized by the t(11;14)(q13;q32) translocation, resulting in amplification and overexpression of the polycomb group gene *Bmi-1*, which normally functions for self-renewal of hematopoietic stem cells but has the capacity to induce tumors when overexpressed.

Multiple myeloma is another fatal B-cell malignancy characterized by the accumulation of abnormal plasma cells in the bone marrow. Standard therapy for multiple myeloma is similar to the course for MCL and normally consists of combination chemotherapy that often results in a 60-70% response rate. However, most patients will eventually relapse, leaving patients with limited therapeutic options. Recent gene expression profiling of multiple myeloma cells revealed elevated expression of Bmi-1 compared to that in normal plasma cells, as confirmed by immunoblotting.

Bmi-1 has been shown to be regulated transcriptionally by a number of factors including SALL4, FoxM1, c-Myc, E2F-1 and Mel18. Bmi-1 and SALL4 are putative oncogenes that modulate stem cell pluripotency and play a role in leukemigenesis (also referred to as leukemogenesis). Murine Sall4 also has been shown to play an essential role in maintaining the properties of ES (embryonic stem) cells and governing the fate of the primitive inner cell mass. Yang *et al* demonstrated that transcription from the *Bmi-1* promoter is markedly activated by SALL4 in a dose-dependent manner (*35*). The Forkhead box transcription factor FoxM1 is expressed in proliferating cells and has been shown to upregulate the levels of Bmi-1 in transformed NIH 3T3 cells in response to oxidative stress through c-myc activation (*58*). The *Bmi-1* homologue, Mel18, acts as a potent repressor on the expression of Bmi-1. The *Bmi-1* promoter region contains a functional E-box through which c-Myc and Mel-18 can regulate *Bmi-1* expression. Since Mel18 downregulates c-Myc expression and *Bmi-1* is a c-Myc target, these data suggest that Mel18 regulates expression of Bmi-1 via repression of c-Myc during cellular senescence and, thus, link c-Myc and polycomb function (*59*). Similarly, a recent report suggests that E2F-1 may also regulate the levels of Bmi-1 in neuroblastoma (*60*). The *Bmi-1* promoter contains a putative E2F binding site required for the activation of a *Bmi-1* promoter-dependent reporter construct by E2F-1. Neither post-transcriptional nor post-translational control of Bmi-1 production has been reported.

Without being limited by theory, the compounds of Formula (I) or a form thereof described herein activate the apoptotic pathway as determined by annexin-V expression, as well as cleavage of poly (ADP-ribose) polymerase (PARP) and caspase-9 and caspase-7. Cell cycle analyses of cells treated with these compounds of Formula (I) or a form thereof have further demonstrated a block at the G_2/M phase followed by the development of polyploidy. These findings suggest that Bmi-1 may also play a role in DNA repair and/or regulation of mitosis. The compounds of Formula (I) or a form thereof described herein are useful inhibitors of Bmi-1 function and cause a reduction in the level of Bmi-1 protein and are thus potential therapeutics for any cancer cell, tumor cell, cancer stem cell or tumor stem cell that overexpresses Bmi-1. Additionally, the compounds of Formula (I) or a form thereof described herein inhibit the function of Bmi-1 and reduce Bmi-1 levels in cancer stem cell and tumor stem cell environments and are thus useful in targeting cancer cell populations that have been shown to be resistant to current therapies (e.g., such as those using large and small

molecule chemotherapeutic agents and radiation therapies, as well as targeted therapies that primarily function by indiscriminately damaging mitotic cells).

As used herein, the italicized form of "*Bmi-1*," unless otherwise specified or clear from the context of the specification, refers to the *Bmi-1* gene. The nonitalicized form of "Bmi-1," the capitalized form of "BMI-1" or the term "Bmi-1 protein," unless otherwise specified or clear from the context of the specification, collectively refer to Bmi-1 protein.

As used herein, the term "Bmi-1 inhibitor" or the phrase (or variations thereof) "inhibit Bmi-1 function and reduce the level of Bmi-1" refer to post-translational inhibition of the function of Bmi-1 protein and subsequent degradation, resulting in decreased levels of Bmi-1 protein present in a tumor environment including, but not limited to, *in vitro* and *in vivo* environments comprising cancer stem cells or tumor stem cells or cancer stem cells and tumor stem cells.

In accordance with the present description, compounds of Formula (I) or a form thereof that inhibit Bmi-1 function and reduce the level of Bmi-1 also inhibit proliferation of tumor cells *in vitro* and *in vivo* and enhance sensitivity of intrinsically resistant populations (*e.g.*, either "cancer stem cells," "tumor stem cells" or both) to chemotherapeutics. Elevated expression of human Bmi-1 has been reported in multiple cancer samples and cancer cell lines (*2, 42, 51, 56, 61-68*). Applicants have identified compounds of Formula (I) or a form thereof that inhibit Bmi-1 function and reduce the level of Bmi-1 *in vitro* and *in vivo*, with concurrent inhibition of tumor cell growth and xenograft growth *in vivo*.

One embodiment described herein is directed to a method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising contacting a cell having elevated Bmi-1 levels from the subject with an amount of a compound of Formula (I) or a form thereof, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell, determining an effective amount of the compound of Formula (I) or a form thereof that inhibits Bmi-1 function in the cell and subsequently administering the effective amount of the compound of Formula (I) or a form thereof to the subject.

Another embodiment described herein is directed to a method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in

need thereof comprising administering to the subject an effective amount of the compound of Formula (I) or a form thereof.

Another embodiment described herein is directed to a method for treating a cancer mediated by Bmi-1 in a subject in need thereof comprising contacting a cell having elevated Bmi-1 levels from the subject with an amount of a compound of Formula (I) or a form thereof, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell.

Another embodiment described herein is directed to a method further comprising contacting a cell having elevated Bmi-1 levels from the subject with an amount of the compound of Formula (I) or a form thereof, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell, determining an effective amount of the compound of Formula (I) or a form thereof that inhibits Bmi-1 function in the cell and subsequently administering the effective amount of the compound of Formula (I) or a form thereof to the subject.

Another embodiment described herein is directed to a method wherein the effective amount of the compound of Formula (I) or a form thereof determined to inhibit Bmi-1 function in the contacted cell reduces Bmi-1 levels in the contacted cell.

An embodiment of the method described herein comprises administering an effective amount of a compound of Formula (I) or a form thereof to inhibit the function of Bmi-1 in a cancer cell *in vivo* or *in vitro*, in a tumor cell *in vivo* or *in vitro*, in a cancer stem cell population *in vivo* or *in vitro*, or in a tumor stem population *in vivo* or *in vitro*.

An embodiment of the method described herein comprises administering an effective amount of a compound of Formula (I) or a form thereof to reduce the level of Bmi-1 in a cancer cell *in vivo* or *in vitro*, in a tumor cell *in vivo* or *in vitro*, in a cancer stem cell population *in vivo* or *in vitro*, or in a tumor stem population *in vivo* or *in vitro*.

An embodiment of the method described herein comprises administering an effective amount of a compound of Formula (I) or a form thereof to inhibit cancer cell proliferation, tumor cell proliferation, cancer stem cell proliferation or tumor stem cell proliferation.

An embodiment described herein includes the use of a compound of Formula (I) or a form thereof in the manufacture of a medicament for inhibiting Bmi-1 function and reducing

the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering an effective amount of the medicament to the subject.

Without being limited by theory, any type of cancer mediated by or dependent on the presence of overexpressed Bmi-1 can be treated in accordance with the intended use of the compounds of Formula (I) or a form thereof described herein.

As used herein, the term "cancer" refers to cells in which Bmi-1 is aberrantly expressed or overexpressed and the cell depends on Bmi-1 for survival or proliferation. Without being limited by theory, the cells may be either stem-like or more differentiated, but the cell relies on Bmi-1 to enable uncontrolled cell division and develop resistance to cytotoxic, chemotherapeutic agents.

In another embodiment, the term "a cancer mediated by Bmi-1" refers to a cancer that is characterized by cells or a fraction of cells from a cancer patient that overexpress Bmi-1 compared to cells from a cancer-free patient (*i.e.,* a patient with no detectable cancer as determined by conventional techniques, such as MRI, CAT scan, etc.). Alternatively, the term refers to cells or a fraction of cells from a cancer patient that, relative to the cancer patient's cells from surrounding normal tissues, express a level of Bmi-1 that differs by at least 2%, 4%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%. 90%, or 95% more, as detected by any method routinely used in the art, or described herein, *e.g.,* in an ELISA.

Non-limiting examples of a cancer mediated by Bmi-1 that can be treated with the intended use described herein: leukemias, such as but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias, such as, myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia leukemias and myelodysplastic syndrome; chronic leukemias, such as but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, hairy cell leukemia; polycythemia vera; lymphomas such as but not limited to Hodgkin's lymphoma, non-Hodgkin's lymphoma; multiple myelomas such as but not limited to smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, placancer cell leukemia, solitary placancercytoma and extramedullary placancercytoma; Waldenström's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone and connective tissue sarcomas such as but not limited to bone sarcoma, osteosarcoma,

chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, neurilemmoma, rhabdomyosarcoma, synovial sarcoma; glial brain tumors (i.e., gliomas) such as but not limited to, astrocytoma, ependymoma, oligodendroglioma, brain stem glioma, optic glioma, diffuse intrinsic pontine glioma, mixed glioma (i.e., oligoastrocytoma), glioblastoma, glioblastoma multiforme, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, primary brain lymphoma; breast cancer including but not limited to ductal carcinoma, adenocarcinoma, lobular (cancer cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, Paget's disease, and inflammatory breast cancer; adrenal cancer such as but not limited to pheochromocytom and adrenocortical carcinoma; thyroid cancer such as but not limited to papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancer such as but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers such as but limited to Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipius; eye cancers such as but not limited to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; vaginal cancers such as squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancer such as squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; cervical cancers such as but not limited to, squamous cell carcinoma, and adenocarcinoma; uterine cancers such as but not limited to endometrial carcinoma and uterine sarcoma; ovarian cancers such as but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; esophageal cancers such as but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, placancercytoma, verrucous carcinoma, and oat cell (cancer cell) carcinoma; stomach cancers such as but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; rectal cancers; liver cancers such as but not limited to hepatocellular carcinoma and hepatoblastoma; gallbladder cancers such as adenocarcinoma; cholangiocarcinomas such as but not limited to papillary, nodular, and diffuse; lung cancers

such as non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; testicular cancers such as but not limited to germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, choriocarcinoma (yolk-sac tumor), prostate cancers such as but not limited to, prostatic intraepithelial neoplasia, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; penal cancers; oral cancers such as but not limited to squamous cell carcinoma; basal cancers; salivary gland cancers such as but not limited to adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers such as but not limited to squamous cell cancer, and verrucous; skin cancers such as but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acral lentiginous melanoma; kidney cancers such as but not limited to renal cell carcinoma, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/ or uterer); Wilms' tumor; bladder cancers such as but not limited to transitional cell carcinoma, squamous cell cancer, adenocarcinoma, carcinosarcoma. In addition, cancers include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinomas (for a review of such disorders, see Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

The compounds of Formula (I) or a form thereof are also useful in the treatment, prevention and/or management of a variety of cancers mediated by Bmi-1 or other abnormal proliferative diseases (where such disease is mediated by overexpressed Bmi-1 or elevated levels of Bmi-1), including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T cell lymphoma, Burkitt's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma; other tumors,

including melanoma, seminoma, tetratocarcinoma, neuroblastoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and Schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscarama, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma. In some embodiments, cancers associated with aberrations in apoptosis are treated in accordance with the methods described herein. Such cancers may include, but are not limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis, and myelodysplastic syndromes. In specific embodiments, malignancy or dysproliferative changes (such as metaplasias and dysplasias), or hyperproliferative disorders of the skin, lung, liver, bone, brain, stomach, colon, breast, prostate, bladder, kidney, pancreas, ovary, and/or uterus are treated in accordance with the methods described herein. In other specific embodiments, a sarcoma, or melanoma is treated as described herein.

In a specific embodiment, the cancer mediated by Bmi-1 being treated as described herein is leukemia, lymphoma or myeloma (*e.g.*, multiple myeloma). Non-limiting examples of leukemias and other blood-borne cancers mediated by Bmi-1 that can be treated with the methods described herein include acute lymphoblastic leukemia (ALL), acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia (AML), acute promyelocytic leukemia (APL), acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocyctic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), and hairy cell leukemia.

Non-limiting examples of lymphomas mediated by Bmi-1 that can be treated in accordance with the methods described herein include Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, Waldenström's macroglobulinemia, heavy chain disease, and polycythemia vera.

In another embodiment, the cancer mediated by Bmi-1 being treated as described herein is a solid tumor. Examples of solid tumors that can be treated in accordance with the methods described herein include, but are not limited to fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma,

endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon cancer, colorectal cancer, kidney cancer, pancreatic cancer, bone cancer, breast cancer, ovarian cancer, prostate cancer, esophageal cancer, stomach cancer, oral cancer, nasal cancer, throat cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, uterine cancer, testicular cancer, small cell lung carcinoma, bladder carcinoma, lung cancer, epithelial carcinoma, glioma, glioblastoma multiforme, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, skin cancer, melanoma, neuroblastoma, and retinoblastoma.

In certain embodiments, a cancer mediated by Bmi-1 includes, but is not limited to, brain cancer, gastric cancer, hematologic cancer, lung cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, salivary gland cancer, colorectal carcinoma, hepatocellular carcinoma, liver carcinoma, breast carcinomas or sarcomas, esophageal carcinomas or sarcomas, stomach carcinomas or sarcomas, fibrosarcoma, glioblastoma, diffuse intrinsic pontine glioma, medulloblastoma, neuroblastoma, diffuse large B cell lymphomas, B cell non-Hodgkin's lymphoma, Hodgkin's lymphoma or chronic or acute myeloid leukemia.

In certain embodiments, a cancer mediated by Bmi-1 includes, but is not limited to, tumors that relapse after therapy despite improved surgical and irradiation techniques. Tumor relapse may occur for a number of reasons, with one plausible explanation being the existence of cancer stem cells (CSC) or tumor stem cells (tumor initiating cells) in the tumor population. CSCs are defined as a population of stem cells relative to any type of blood cancer, solid tumor cancer or metastatic cancer. Tumor stem cells are those specifically found within a tumor. Both have characteristics similar to normal stem cells. Like normal stem cells, CSCs and tumor stem cells have the potential to self renew. Unlike normal stem cells, though, due to the sustained presence of high levels of Bmi-1, the CSCs and tumor stem cells fail to terminally differentiate and proliferate unchecked. Their enhanced DNA repair capacity also enables them to become resistant to cytotoxic, chemotherapeutic drugs designed to kill cancer cells and tumor cells. Therefore, targeting CSCs and tumor stem cells that

overexpress Bmi-1 could be an approach for effective cancer treatment. One further approach is to target various transcription factors responsible for maintenance of the self renewal capacity of CSCs and tumor stem cells.

As used herein, the term "treat," "treatment" or "treating" refers to: (i) preventing a disease, disorder and/or condition from occurring in a subject that may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having said disease, disorder and/or condition; (ii) inhibiting a disease, disorder and/or condition, i.e., arresting its development; and/or (iii) relieving a disease, disorder and/or condition, i.e., causing regression of the disease, disorder and/or condition.

As used herein, the term "subject" refers to members of the human, equine, porcine, bovine, murine, rattus, canine and feline species. In some embodiments, the subject is a mammal or a warm-blooded vertebrate animal. In other embodiments, the subject is a human. As used herein, the term "patient" may be used interchangeably with "subject" and "human".

In certain embodiments, the subject is a human that is 0 to 6 months old, 6 to 12 months old, 6 to 18 months old, 18 to 36 months old, 1 to 5 years old, 5 to 10 years old, 10 to 15 years old, 15 to 20 years old, 20 to 25 years old, 25 to 30 years old, 30 to 35 years old, 35 to 40 years old, 40 to 45 years old, 45 to 50 years old, 50 to 55 years old, 55 to 60 years old, 60 to 65 years old, 65 to 70 years old, 70 to 75 years old, 75 to 80 years old, 80 to 85 years old, 85 to 90 years old, 90 to 95 years old or 95 to 100 years old. In some embodiments, the subject is a human infant. In other embodiments, the subject is a human toddler. In other embodiments, the subject is a human child. In other embodiments, the subject is human adult. In yet other embodiments, the subject is an elderly human.

As used herein, the term "elderly human" refers to a human 65 years or older; the term "human adult" refers to a human that is 18 years or older; the term "human child" refers to a human that is 1 year to 18 years old; the term "human infant" refers to a newborn to 1 year old year human; and, the term "human toddler" refers to a human that is 1 year to 3 years old.

In certain embodiments, the subject is in an immunocompromised state or immunosuppressed state or at risk for becoming immunocompromised or immunosuppressed. In certain embodiments, the subject is receiving or recovering from an immunosuppressive

therapy. In certain embodiments, the subject has or is at risk of getting cancer, AIDS, or a bacterial infection. In certain embodiments, the subject is, will or has undergone surgery, chemotherapy and/or radiation therapy. In certain embodiments, the subject has cystic fibrosis, pulmonary fibrosis or another condition affecting the lungs. In certain embodiments, the subject has, will have or had a tissue transplant.

In some embodiments, the subject's cancer, due to the overexpression of Bmi-1 in cancer cells, tumor cells, cancer stem cells or tumor stem cells thereof, has proven refractory to conventional "standard of care" therapies (excluding treatment with a compound of Formula (I) or a form thereof), such that the patient has discontinued the conventional therapy. In one embodiment, without being limited by theory, the term "refractory" means that at least some significant portion of the cancer cells, tumor cells, cancer stem cells or tumor stem cells continue to proliferate due to the overexpression of Bmi-1, despite therapy. The determination of whether the cancer is refractory toa particular therapy can be made either in *vivo or in vitro* by any method known in the art for assaying the effect of a therapy on the cancer cells, tumor cells, cancer stem cells or tumor stem cells, using the art-accepted meanings of "refractory" in such a context. In certain embodiments, a patient having a refractory cancer due to the overexpression of Bmi-1 is a patient in which the cancer is non-responsive or resistant to a conventional or "standard of care" therapy. In certain embodiments, a patient with refractory cancer has a cancer mediated by Bmi-1 that progresses. Disease progression, as a lack of clinical response to a therapy, is demonstrated when the tumor or neoplasm has not been significantly eradicated and/or the symptoms have not been significantly alleviated. The determination of whether a patient has a refractory cancer mediated by Bmi-1 can be made either *in vivo* or *in vitro* by any method known in the art for assaying the effectiveness of the therapy for the treatment of the cancer, using art-accepted meanings of "refractory" in such a context.

In certain embodiments, the patient to be treated in accordance with the methods described herein is a patient already being treated with antibiotics, anti-virals, anti-fungals, or other biological therapy, immunotherapy or anti-cancer therapy. Among these patients are patients with a refractory cancer mediated by Bmi-1 or patients too young for conventional therapies. In some embodiments, the patient being treated is treatment naive, not having received any prior therapy. In any of the foregoing embodiments, a patient to be treated may receive a small molecule therapy.

In some embodiments, a compound of Formula (I) or a form thereof may be prophylactically administered to a patient to prevent the onset of cancer mediated by Bmi-1 in a patient at risk of developing cancer. In some embodiments, a compound of Formula (I) or a form thereof may be therapeutically administered to a patient that is susceptible to adverse reactions to conventional therapies. In some embodiments, the subject being administered one or more compounds of Formula (I) or a form thereof has not received prior therapy. In other embodiments, one or more compounds of Formula (I) or a form thereof are administered to a subject who has received a prior therapy. In some embodiments, the subject administered a compound of Formula (I) or a form thereof has discontinued a prior therapy due to lack of benefit from the therapy, adverse effects from the therapy or unacceptable levels of toxicity.

In some embodiments, the subject being administered one or more compounds of Formula (I) or a form thereof, will or has undergone surgery, chemotherapy, antibody therapy, hormonal therapy and/or radiation therapy. In certain embodiments, the patient has undergone surgery to remove the tumor or neoplasm. In certain embodiments, the subject will have, or has had, or is undergoing a tissue or organ transplant.

As used herein, the terms “effective amount,” “prophylactically effective amount” or "therapeutically effective amount" mean an amount of a compound of Formula (I) or a form thereof that is effective in inhibiting Bmi-1 protein function and reducing the level of Bmi-1 protein, as described herein, and thus producing the desired prophylactic, therapeutic, ameliorative, inhibitory or preventative effect in a cancer mediated by Bmi-1 in a patient in need thereof.

As used herein, the term “effective amount,” in the context of administering a compound of Formula (I) or a form thereof to a patient, refers to the amount of a compound of Formula (I) or a form thereof which is sufficient to achieve at least one or more of the following effects, as applicable, in a patient or in patient cell(s): (i) inhibition of Bmi-1 protein function; (ii) reduction in the level or quantity of Bmi-1 protein; (iii) reduction or amelioration in the severity of a cancer mediated by Bmi-1 or a symptom associated therewith; (iv) prevention of the progression of a cancer mediated by Bmi-1 or a symptom associated therewith; (v) regression of a cancer mediated by Bmi-1 or a symptom associated therewith; (vi) prevention of the development or onset of a cancer mediated by Bmi-1 or a

symptom associated therewith; (vii) prevention of the recurrence of a cancer mediated by Bmi-1 or a symptom associated with a cancer mediated by Bmi-1; (viii) reduction of the duration of a symptom associated with a cancer mediated by Bmi-1; (ix) reduction or elimination of the cancer stem cell or tumor stem cell population; (x) reduction or elimination of the growth of a tumor or neoplasm overexpressing Bmi-1; (xi) reduction or elimination of the proliferation of cancer cells or tumor cells; (xii) reduction or elimination of the formation of a tumor or neoplasm overexpressing Bmi-1; (xiii) eradication or control of a primary, regional and/or metastatic cancer mediated by Bmi-1; (xiv) reduction in patient mortality; (xv) increased number of patients in remission; (xvi) increased length of remission in patients; (xvii) the size of a tumor or neoplasm overexpressing Bmi-1 is maintained or controlled such that the size does not increase or increases less than the size of the tumor after administration of a standard therapy as measured by conventional methods available to one of skill in the art, such as MRI, X-ray and CAT scan; (xviii) increased delay in disease progression; (xix) increased patient survival; (xx) reduction in incidences of patient hospitalization; (xxi) reduction in the length of patient hospitalization; (xxii) enhancement or improvement in the prophylactic or therapeutic effect(s) of another therapy; (xxiii) reduction in the number of symptoms associated with a cancer mediated by Bmi-1; (xxiv) increased cancer-free survival of patients; and/or (xxv) increased symptom-free survival of cancer patients.

In general, the term "effective amount" also includes that amount of a compound of Formula (I) or a form thereof administered to a patient which is in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day, or about 0.01 mg/Kg/day to about 500 mg/Kg/day, or about 0.1 mg to about 500 mg/Kg/day, or about 1.0 mg/day to about 500 mg/Kg/day, in single, divided, or a continuous dose for a patient or subject having a weight in a range of between about 40 to about 200 Kg (which dose may be adjusted for patients or subjects above or below this range, particularly children under 40 Kg). The typical adult subject is expected to have a median weight in a range of between about 60 to about 100 Kg. The effective amount for the subject will also depend upon various factors, including the body weight, size and health of the subject. An effective amount for a given patient can be determined according to the skill and judgment of the clinician.

In another embodiment, where daily doses are adjusted based upon the weight of the subject or patient, compounds of Formula (I) or a form thereof described herein may be

formulated for delivery at about 0.02, 0.025, 0.03, 0.05, 0.06, 0.075, 0.08, 0.09, 0.10, 0.20, 0.25, 0.30, 0.50, 0.60, 0.75, 0.80, 0.90, 1.0, 1.10, 1.20, 1.25, 1.50, 1.75, 2.0, 5.0, 10, 20 or 50 mg/Kg/day. Daily doses adjusted based upon the weight of the subject or patient may be administered as a single, divided, or continuous dose. In embodiments where a dose of a compound of Formula (I) or a form thereof is given more than once per day, the dose may be administered once, twice, three times, or more per day. In another embodiment, a subject is administered one or more doses of an effective amount of a compound of Formula (I) or a form thereof, wherein the effective amount may not be the same for each dose.

Another embodiment described herein iincludes an effective amount of the compound of Formula (I) or a form thereof in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day.

Within the scope described herein, the "effective amount" of a compound of Formula (I) or a form thereof for use in the manufacture of a medicament or in a method for treating a cancer mediated by Bmi-1 in a subject in need thereof, is intended to include an amount in a range of from about 0.1 ng to about 3500 mg administered daily; from about 0.1 μg to about 3500 mg administered daily; from about 0.1 mg to about 3500 mg administered daily; from about 1 mg to about 3500 mg administered daily; from about 1 mg to about 3000 mg administered daily; from about 0.05 mg to about 1500 mg administered daily; from about 0.5 mg to about 1500 mg administered daily; from about 1 mg to about 1500 mg administered daily; from about 5 mg to about 1500 mg administered daily; from about 10 mg to about 600 mg administered daily; from about 0.5 mg to about 2000 mg administered daily; or, an amount in a range of from about 5.0 mg to about 1500 mg administered daily.

Another embodiment described herein iincludes an effective amount of the compound of Formula (I) or a form thereof in a range of from about 0.1 ng to about 3500 mg.

For any compound of Formula (I) or a form thereof, the effective amount can be estimated initially by results from cell culture assays or from relevant animal models, such as the mouse, chimpanzee, marmoset or tamarin animal model. Relevant animal models may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically

effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between the toxic and therapeutic effect is referred to as the therapeutic index, and can be expressed as the ratio, LD_{50}/ED_{50}. In some embodiments, the effective amount is such that a large therapeutic index is achieved. In further embodiments, the dosage is within a range of plasma concentrations that include an ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

More specifically, the concentration-biological effect (pharmacodynamic) relationship observed with regard to a compound of Formula (I) or a form thereof suggests a target plasma concentration ranging from about 0.001 μg/mL to about 50 μg/mL, from about 0.01 μg/mL to about 20 μg/mL, from about 0.05 μg/mL to about 10 μg/mL, or from about 0.1 μg/mL to about 5 μg/mL. To achieve such plasma concentrations, the compounds of Formula (I) or a form thereof described herein may be administered at doses that vary from 0.001 μg to 100,000 mg, depending upon the route of administration in single, divided, or continuous doses for a patient weighing between about 40 to about 100 kg (which dose may be adjusted for patients above or below this weight range, particularly for children under 40 kg).

The exact dosage will be determined by the practitioner, in light of factors related to the subject. Dosage and administration may be adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Administration factors that may be taken into account include the severity of the disease state, general health of the subject, ethinicity, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, tolerance for toxicity related to drug metabolites, experience with other cancer therapies and regimens, and tolerance/response to such therapies and regimens. Long-acting pharmaceutical compositions may be administered every 2, 3 or 4 days, once every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

The compounds of Formula (I) or a form thereof described herein may be administered to the subject via any drug delivery route known in the art. Nonlimiting examples include oral, ocular, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intraveneous (bolus and infusion), intracerebral, transdermal, and pulmonary routes of administration.

Compound Metabolites

Also falling within the scope described herein are the *in vivo* metabolic products of the compounds of Formula (I) or a form thereof. Such products may result, for example, from the oxidation, reduction, hydrolysis, amidation, glucuronidation, esterification and the like of the administered compound of Formula (I) or a form thereof, primarily due to enzymatic processes. Accordingly, the compounds of Formula (I) or a form thereof described herein include those produced by a process comprising contacting a compound of Formula (I) or a form thereof described herein with a mammalian tissue or a mammal for a period of time sufficient to yield a metabolic product thereof.

Such products typically are identified by preparing a radio-labeled (*e.g.* C^{14} or H^3) compound of Formula (I) or a form thereof described herein, administering it in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to a mammal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours), and isolating its conversion products from urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites may be done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of Formula (I) or a form thereof described herein even if they possess no biological activity of their own.

Combination Therapies

The methods of treating a cancer mediated by Bmi-1 in a subject in need thereof, in addition to those previously described herein, further comprise administering to the subject in need thereof an effective amount of one or more of the compounds of Formula (I) or a form thereof alone or in combination with one or more additional agents selected from anti-cancer agents, anti-proliferative agents, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, anti-inflammatory agents, an alkylating agents, steroidal and non-steriodal anti-inflammatory agents, pain relievers, leukotriene antagonists, β2-agonists, anticholinergic agents, hormonal agents, biological agents, tubulin binding agents, glucocorticoids,

corticosteroid agents, antibacterial agents, antihistamines, anti-malarial agents, anti-viral agents, antibiotics and the like; and, optionally with radiation therapy.

In another embodiment, one or more compounds of Formula (I) or a form thereof alone or in combination with one or more additional agents may be administered to the subject in combination with a supportive therapy, a pain relief therapy, or other therapy that does not have an effect on a cancer mediated by Bmi-1.

In some embodiments, one or more compounds of Formula (I) or a form thereof described herein and one or more additional agents described herein are administered as the same pharmaceutical composition. In certain embodiments, one or more compounds of Formula (I) or a form thereof described herein and one or more additional agents described herein are administered in different pharmaceutical compositions. In certain embodiments, one or more compounds of Formula (I) or a form thereof described herein and one or more additional agents described herein are administered by the same route of administration. In certain embodiments, one or more compounds of Formula (I) or a form thereof described herein and one or more additional agents described herein are administered by different routes of administration.

In other embodiments are pharmaceutical compositions wherein one or more compounds of Formula (I) or a form thereof are administered in a combination product with one or more additional agents useful in the treatment of a cancer mediated by Bmi-1. The skilled artisan will recognize that a variety of active ingredients may be administered in a combination with the compounds of Formula (I) or a form thereof described herein whereby the product may act to augment or synergistically enhance the anticancer activity of either or both the additional agent(s) and the compound(s) of Formula (I) or a form thereof described herein.

As used herein, the term "synergistic," refers to the effect of the administration of a combination product as described herein which is more effective than the additive effects of any two or more single agents. In a specific embodiment, a synergistic effect of a combination product permits the use of lower dosages of one or more agents and/or less frequent administration of said agents to a subject with a cancer mediated by Bmi-1. In certain embodiments, the ability to utilize lower dosages of an agent and/or to administer said agents less frequently reduces the toxicity associated with the administration of said agents to

a subject without reducing the efficacy of said agents in the prevention or treatment of a cancer mediated by Bmi-1. In some embodiments, a synergistic effect results in improved efficacy of each of the agents in treating a cancer mediated by Bmi-1. In some embodiments, a synergistic effect of a combination of agents avoids or reduces adverse or unwanted side effects associated with the use of any single agent. The combination of agents in such a product can be administered to a subject in the same pharmaceutical composition. Alternatively, the agents can be administered concurrently to a subject in separate pharmaceutical compositions. The agents may also be administered to a subject by the same or different routes of administration. In a specific embodiment, at least one of the agents is a compound of Formula (I) or a form thereof described herein.

It is also possible to combine any compound of Formula (I) or a form thereof described herein with such additional agents useful in the treatment of a cancer mediated by Bmi-1, including compounds of Formula (I) or a form thereof as described herein, in a unitary dosage form, or in separate dosage forms intended for simultaneous or sequential administration to a patient in need of treatment. When administered sequentially, the combination may be administered in two or more administrations. In an alternative embodiment, it is possible to administer one or more compounds of Formula (I) or a form thereof described herein and one or more additional agents described herein by different routes.

According to the methods described herein, a combination product may include a combination of active ingredients that may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered sequentially or in parallel as separate formulations; or (3) by any other combination regimen known in the art. When delivered as separate formulations in alternation therapy, the methods described herein may comprise administration or delivery, for example, without limitation, in separate solutions, emulsions, suspensions, tablets, pills or capsules, or by different injections in separate syringes. In general, when administered in alternation, an effective dosage of each active ingredient is administered serially, one dose following another. In contrast, in parallel or simultaneous administration, effective dosages of two or more active ingredients are administered together. Various alternative combinations of intermittent sequential or in parallel combination administration may also be used.

Specific examples of such agents include, but are not limited to, immunomodulatory agents (*e.g.*, interferon, penicillamine and the like), anti-angiogenic agent, anti-inflammatory agents (*e.g.*, adrenocorticoids, corticosteroids (*e.g.*, beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, methylprednisolone, prednisolone, prednisone, hydrocortisone), glucocorticoids, steroidal and non-steriodal anti- inflammatory drugs (*e.g.*, aspirin, ibuprofen, diclofenac, and COX-2 inhibitors)), pain relievers, leukotriene antagonists (*e.g.*, montelukast, methyl xanthines, zafirlukast, and zileuton), β2-agonists (*e.g.*, albuterol, biterol, fenoterol, isoetharie, metaproterenol, pirbuterol, salbutamol, terbutalin formoterol, salmeterol, and salbutamol terbutaline), anticholinergic agents (*e.g.*, ipratropium bromide and oxitropium bromide), antibacterial agents (*e.g.*, sulphasalazine, dapsone and the like), antihistamines, anti-malarial agents (*e.g.*, hydroxychloroquine), anti-viral agents (*e.g.*, nucleoside analogs (*e.g.*, zidovudine, acyclovir, gangcyclovir, vidarabine, idoxuridine, trifluridine, ribavirin, foscarnet, amantadine, rimantadine, saquinavir, indinavir, ritonavir, and AZT) and antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, erythomycin, penicillin, mithramycin, and anthramycin (AMC)).

Specific examples of additional agents that may be used in combination with a compound of Formula (I) or a form thereof described herein include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthracyclin; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bisphosphonates (*e.g.*, pamidronate (Aredria®), sodium clondronate (Bonefos®), zoledronic acid (Zometa®), alendronate (Fosamax®), etidronate, ibandornate, cimadronate, risedromate, and tiludromate); bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; demethylation agents; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; EphA2 inhibitors; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine

phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; 5-fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; histone deacetylase inhibitors; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; imatinib mesylate; interleukin II (including recombinant interleukin II, or rIL2), interferon alpha-2a; interferon alpha-2b; interferon alpha-n1 ; interferon alpha-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; lenalidomide; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; anti-CD2 antibodies; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; volitinib; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride and the like.

Other examples of treating a cancer mediated by Bmi-1 include treatment with an anti-cancer or anti-proliferative agent wherein the anti-cancer or anti-proliferative agent is selected from, but not limited to: 20-Epi-1,25-dihydroxyvitamin D3 (MC 1288, MC 1301, KH 1060); 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide;

angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA (0-palmitoyl-l-thioglycerol); arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole (CaRest M3); CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate (YNK01 or Starasid®); cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; HMG CoA reductase inhibitors (*e.g.*, atorvastatin, cerivastatin, fluvastatin, lescol, lupitor, lovastatin, rosuvastatin, and simvastatin); hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F;

lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide/estrogen/progesterone combinations; leuprorelin; levamisole; LFA-3TIP (see, International Publication No. WO93/0686 and U.S. Patent No. 6,162,432); liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF tautomerase inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A/myobacterium cell wall skeleton (CWS/MPL); mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone/pentazocine combinations; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine (BCX-34); pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol dehydrogenase; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors;

ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; 5-fluorouracil; leucovorin; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; thalidomide; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; volitinib; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer and the like.

In some embodiments, the additional agent used in combination with a compound of Formula (I) or a form thereof described herein is one or more immunomodulatory agent(s). Non-limiting examples of immunomodulatory agents include proteinaceous agents such as cytokines, peptide mimetics, and antibodies (*e.g.*, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or $F(ab)_2$ fragments or epitope binding fragments), nucleic acid molecules (*e.g.*, antisense nucleic acid molecules and triple helices), cancer molecules, organic compounds, and inorganic compounds.

In particular, one or more immunomodulatory agents that may be used in combination with a compound of Formula (I) or a form thereof described herein include, but are not limited to, methotrexate, leflunomide, cyclophosphamide, cytoxan, cyclosporine A, minocycline, azathioprine (Imuran®), antibiotics (*e.g.*, FK506 (tacrolimus)),

methylprednisolone (MP), corticosteroids, steroids, mycophenolate mofetil, rapamycin (sirolimus), mizoribine, deoxyspergualin, brequinar, malononitriloamindes (*e.g.*, leflunamide), T cell receptor modulators, cytokine receptor modulators, and modulators mast cell modulators.

In one embodiment, the immunomodulatory agent is a chemotherapeutic agent. In an alternative embodiment, the immunomodulatory agent is an immunomodulatory agent other than a chemotherapeutic agent. In some embodiments, the additional agent used described herein is not an immunomodulatory agent.

In some embodiments, the additional agent that may be used in combination with a compound of Formula (I) or a form thereof described herein is one or more anti-angiogenic agent(s). Non-limiting examples of anti-angiogenic agents include proteins, polypeptides, peptides, fusion proteins, antibodies (*e.g.*, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab fragments, $F(ab)_2$ fragments, and antigen-binding fragments thereof) such as antibodies that immunospecifically bind to TNF-α, nucleic acid molecules (*e.g.*, antisense molecules or triple helices), organic molecules, inorganic molecules, and cancer molecules that reduce or inhibit angiogenesis. In other embodiments, the additional agent described herein is not an anti-angiogenic agent.

In some embodiments, the additional agent that may be used in combination with a compound of Formula (I) or a form thereof described herein is one or more anti-inflammatory agent(s). Non-limiting examples of anti-inflammatory agents include any anti-inflammatory agent useful in treating inflammatory disorders. Non-limiting examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs, anticholinergics (*e.g.*, atropine sulfate, atropine methylnitrate, and ipratropium bromide (ATROVENT®), β2-agonists (*e.g.*, albuterol (VENTOLIN® and PROVENTIL®), bitolterol (TORNALATE®), levalbuterol (XOPONEX®), metaproterenol (ALUPENT®), pirbuterol (MAXAIR®), terbutlaine (BRETHAIRE® and BRETHINE®), albuterol (PROVENTIL®, REPETABS®, and VOLMAX®), formoterol (FORADIL AEROLIZER®), salmeterol (SEREVENT® and SEREVENT DISKUS®)), methylxanthines (*e.g.*, theophylline (UNIPHYL®, THEO-DUR®, SLO-BID®, AND TEHO-42®)) and the like. Examples of NSAIDs include, but are not limited to, aspirin, ibuprofen, celecoxib (CELEBREX®), diclofenac (VOLTAREN®), etodolac (LODINE®), fenoprofen (NALFON®), indomethacin

(INDOCIN®), ketoralac (TORADOL®), oxaprozin (DAYPRO®), nabumentone (RELAFEN®), sulindac (CLINORIL®), tolmentin (TOLECTIN®), rofecoxib (VIOXX®), naproxen (ALEVE®, NAPROSYN®), ketoprofen (ACTRON®), nabumetone (RELAFEN®) and the like. Such NSAIDs function by inhibiting a cyclooxgenase enzyme (*e.g.*, COX-1 and/or COX-2). Examples of steroidal anti-inflammatory drugs include, but are not limited to, glucocorticoids, dexamethasone (DECADRON®), corticosteroids (*e.g.*, methylprednisolone (MEDROL®)), cortisone, hydrocortisone, prednisone (PREDNISONE® and DELTASONE®), prednisolone (PRELONE® and PEDIAPRED®), triamcinolone, azulfidine, inhibitors of eicosanoids (*e.g.*, prostaglandins, thromboxanes, and leukotrienes) and the like.

In certain embodiments, the additional agent that may be used in combination with a compound of Formula (I) or a form thereof described herein is an alkylating agent, a nitrosourea, an antimetabolite, an anthracyclin, a topoisomerase II inhibitor, a mitotic inhibitor and the like. Alkylating agents include, but are not limited to, busulfan, cisplatin, carboplatin, cholormbucil, cyclophosphamide, ifosfamide, decarbazine, mechlorethamine, mephalen, themozolomide and the like. Nitrosoureas include, but are not limited to carmustine (BiCNU®), lomustine (CeeNU®) and the like. Antimetabolites include, but are not limited to, 5-fluorouracil, capecitabine, methotrexate, gemcitabine, cytarabine, fludarabine and the like. Anthracyclins include but are not limited to daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and the like. Topoisomerase II inhibitors include, but are not limited to, topotecan, irinotecan, etopiside (VP-16), teniposide and the like. Mitotic inhibitors include, but are not limited to taxanes (paclitaxel, docetaxel), and the vinca alkaloids (vinblastine, vincristine, and vinorelbine) and the like.

In more specific embodiments, the additional anti-cancer agent, anti-proliferative agent or chemotherapeutic agent that may be used in combination with a compound of Formula (I) or a form thereof described herein includes, and is not limited to aflibercept, amsacrine, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clofarabine, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin (IV and liposomal), docetaxel, doxorubicin (IV and liposomal), enzastaurin, epirubicin, etoposide, fludarabine, 5-fluorouracil (5-FU), gemcitabine, gliadel implants, hydroxycarbamide, idarubicin, ifosfamide, imatinib mesylate, irinotecan, lanreotide, lenalidomide, leucovorin, lomustine, melphalan, mercaptopurine, mesna,

methotrexate, mitomycin, mitoxantrone, octreotide, oxaliplatin, paclitaxel, pemetrexed, pentostatin, procarbazine, raltitrexed, satraplatin, sorafenib, streptozocin, sunitinib, tegafur-uracil, temozolomide, teniposide, thalidomide, thiotepa, tioguanine, topotecan, treosulfan, vatalanib, vinblastine, vincristine, vindesine, vinorelbine, volitinib, ZD6474, monoclonal antibodies (such as bevacizumab, cetuximab, IMC-A12, IMC-1121B, medi-522, rituximab and the like), hormonal agents (such as anastrozole, bicalutamide, buserelin, cyproterone, diethylstilbestrol, exemestane, flutamide, goserelin (breast and prostrate), letrozole, leuprorelin, medroxyprogesterone, megestrol acetate, tamoxifen, toremifene, triptorelin and the like), biological agents (such as interferon, interleukin-12 and the like), angiogenesis receptor tyrosine kinase (RTK) inhibitors (such as AE-941, angiostatin, carboxyamidotriazole, cilengitide, endostatin, halofuginone hydrobromide, 2-methoxyestradiol, squalamine lactate, SU6668 and the like), tubulin binding agents (such as combretastatin A4 phosphate and the like), matrix metalloproteinase inhibitors (such as BMS-275291 and the like) and/or serine/threonine/tyrosine kinase inhibitors and an optional nonsteroidal or COX-2 anti-inflammatory agents (such as celecoxib and the like) or corticosteroid (such as prednisone and the like).

In more particular embodiments, one or more additional anti-cancer, anti-proliferative or chemotherapeutic agents that may be used in combination with a compound of Formula (I) or a form thereof described herein is selected from bevacizumab, carboplatin, cisplatin, docetaxel, doxorubicin, exemestane, gemcitabine, 5-fluorouracil, imatinib, irinotecan, sorafenib, sunitinib, temozolomide, volitinib or combinations thereof.

In some embodiments, a compound of Formula (I) or a form thereof described herein and one or more additional anti-cancer, anti-proliferative or chemotherapeutic agents is used in combination with radiation therapy comprising the use of x-rays, gamma rays and other sources of radiation to destroy cancer cells or tumor cells. In specific embodiments, the radiation therapy is administered as external beam radiation or teletherapy, wherein the radiation is directed from a remote source. In other embodiments, the radiation therapy is administered as internal therapy or brachytherapy wherein a radioactive source is placed close to cancer cells, tumor cells and/or a tumor mass.

Currently available anti-cancer, anti-proliferative or chemotherapeutic agents, their dosage regimens, routes of administration and recommended usage alone or in combination

are known in the art and have been described in literature such as the *Physician's Desk Reference*.

Any anti-cancer, anti-proliferative or chemotherapeutic agent or anti-cancer therapy which is known to be useful, or which has been used or is currently being used for the treatment of a cancer mediated by Bmi-1, can be used in combination with compounds of Formula (I) or a form thereof described herein. See, *e.g.*, Gilman *et al.*, Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill, New York, 2001; The Merck Manual of Diagnosis and Therapy, Berkow, M.D. *et al.* (eds.), 17th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, 1999; Cecil Textbook of Medicine, 20th Ed., Bennett and Plum (eds.), W.B. Saunders, Philadelphia, 1996, and Physician's Desk Reference for information regarding cancer therapies (*e.g.*, using prophylactic or therapeutic agents) which have been or are currently being used for preventing, treating and/or managing a cancer mediated by Bmi-1.

Pharmaceutical Compositions

The present description is also directed to a pharmaceutical composition comprising an effective amount of a compound of Formula (I) or a form thereof in admixture with a pharmaceutically acceptable excipient.

An embodiment described herein includes a pharmaceutical composition made by the process of admixing a compound of Formula (I) or a form thereof with a pharmaceutically acceptable excipient. The pharmaceutical composition may also be formulated to achieve a physiologically compatible pH of about pH 7, ranging from about pH 3 to about pH 11.

Another embodiment of the present includes the use of a compound of Formula (I) or a form thereof in a pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of a compound of Formula (I) or a form thereof in admixture with a pharmaceutically acceptable excipient.

As used herein, the term "composition" means a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

In another embodiment, the pharmaceutical composition may comprise a combination product of one or more compounds of Formula (I) or a form thereof described herein and one

or more additional agents useful in the treatment of a cancer mediated by Bmi-1, such as an anti-cancer, anti-proliferative, chemotherapeutic or biochemotherapeutic agent.

The term "pharmaceutically acceptable excipient" refers to a pharmacologically inactive substance formulated for administration with an active pharmaceutical agent, such as the compounds of Formula (I) or a form thereof described herein. The term refers to any pharmaceutical excipient that may be administered without undue toxicity. Pharmaceutically acceptable excipients may be determined in part by the particular composition being administered, as well as by the particular mode of administration and/or dosage form. Nonlimiting examples of pharmaceutically acceptable excipients include carriers, solvents, stabilizers, adjuvants, diluents, *etc.* Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions as described herein (*see, e.g.*, Remington's Pharmaceutical Sciences).

Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

The pharmaceutical compositions described herein may be formulated in any form suitable for the intended method of administration. Suitable formulations for oral administration include solids, liquid solutions, emulsions and suspensions, while suitable inhaleable formulations for pulmonary administration include liquids and powders. Alternative formulations include syrups, creams, ointments, tablets, and lyophilized solids which can be reconstituted with a physiologically compatible solvent prior to administration.

When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions

may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

Pharmaceutically acceptable excipients suitable for use in conjunction with tablets include, for example, inert fillers, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

In other embodiments, pharmaceutical compositions described herein may be formulated as suspensions comprising a compound of Formula (I) or a form thereof described herein in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension. In yet other embodiments, pharmaceutical compositions described herein may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of one or more excipient(s).

Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or

more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

Additionally, the pharmaceutical compositions described herein may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. Such emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propane-diol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, isotonic sodium chloride solution and the like. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The compounds of Formula (I) or a form thereof described herein may be substantially modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (*e.g.*, increase solubility, bioactivity, palatability, decrease adverse reactions, *etc.*), for example by esterification, glycosylation, PEGylation and the like.

In some embodiments, the compound of Formula (I) or a form thereof described herein is formulated for oral administration in formulations that enhance the oral

bioavailability of such compounds of Formula (I) or a form thereof. As such, pharmaceutical compositions described herein may comprise a effective amount of a compound of Formula (I) or a form thereof, together with at least one pharmaceutically acceptable excipient selected from medium chain fatty acids or propylene glycol esters thereof (*e.g.*, propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants, such as polyoxyl 40 hydrogenated castor oil and the like.

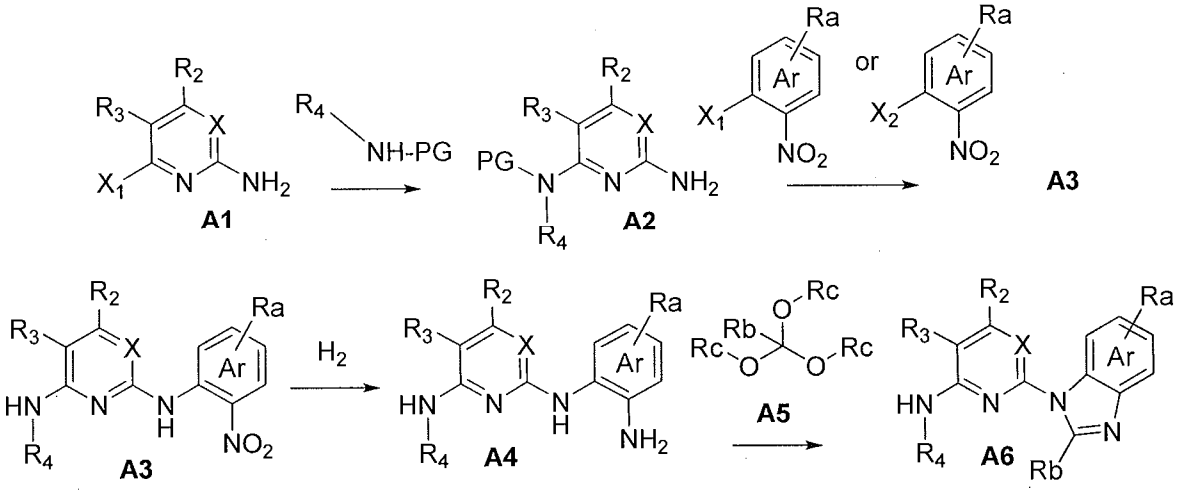
In other embodiments, the bioavailability of a compound of Formula (I) or a form thereof may be enhanced by using particle size optimization techniques including, but not limited to, the preparation of nanoparticles or nanosuspensions using techniques known to those skilled in art. The compound forms present in such preparations include amorphous, partially amorphous, partially crystalline or crystalline forms.

In alternative embodiments, the pharmaceutical composition may further comprise one or more aqueous solubility enhancer(s), such as a cyclodextrin. Nonlimiting examples of cyclodextrin include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin, and hydroxypropyl-β-cyclodextrin (HPBC). In some embodiments, the pharmaceutical composition further comprises HPBC in a range of from about 0.1% to about 20%, from about 1% to about 15%, or from about 2.5% to about 10%. The amount of solubility enhancer employed may depend on the amount of the active pharmaceutical ingredient in the composition.

General Synthetic Examples

As disclosed herein, the methods for preparing the compounds of Formula (I) or a form thereof described herein commonly use standard, well-known synthetic methodology. Many of the starting materials are commercially available or can be prepared in the Specific Synthetic Examples that follow using techniques known to those skilled in the art. Functional transformations to modify substituents may also be undertaken where chemically feasible and are considered to be included within the scope of the General Schemes and the knowledge of a person of ordinary skill in the art. Compounds of Formula (I) or a form thereof can be prepared as described in the Schemes below.

Scheme A Benzimidazole Substituted Pyrimidine Compounds



An amine substituted Compound **A1** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) is coupled with various substituted aryl, heteroaryl or heterocyclyl amines (wherein PG represents an optionally present protecting group monosubstituted on the amine) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^tAm, NaH, NaHMDS and the like) in a solvent (such as THF, DMF and the like) to provide a Compound **A2**.

When one or both of R_2 and R_3 are optionally halogen, the product Compound **A2** is obtained as a mixture of regioisomers, wherein the term "Sep" refers to isolating the desired Compound **A2** isomer to be carried forward from the mixture using separation techniques known to those of ordinary skill in the art, followed by deprotection.

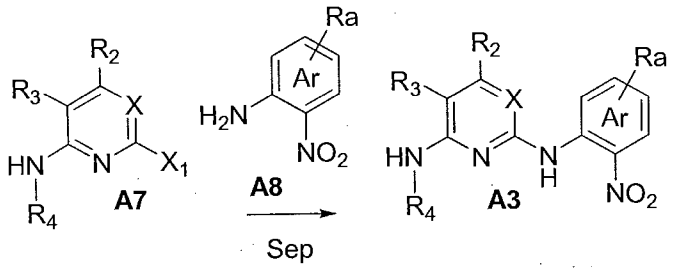
Alternatively, Compound **A2** may be prepared by reacting Compound **A1** with various substituted aryl, heteroaryl or heterocyclyl amines (wherein the protecting group is absent) in the presence of a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used), followed by separation as needed.

Compound **A3** may be prepared by reacting Compound **A2** with a substituted ortho-halo-nitro benzene (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) in the presence of a transition metal catalyst (such as a catalyst containing a metal selected from copper, palladium and the like).

Alternatively, Compound **A3** may be prepared by reacting Compound **A2** with the substituted ortho-halo-nitro benzene (wherein X_2 represents a halogen atom selected from bromo, chloro, fluoro or iodo) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS and the like) in a solvent (such as THF, DMF and the like).

Compound **A4** is prepared by reacting Compound **A3** in the presence of hydrogen and a catalyst (such as nickel, platinum, palladium on carbon and the like).

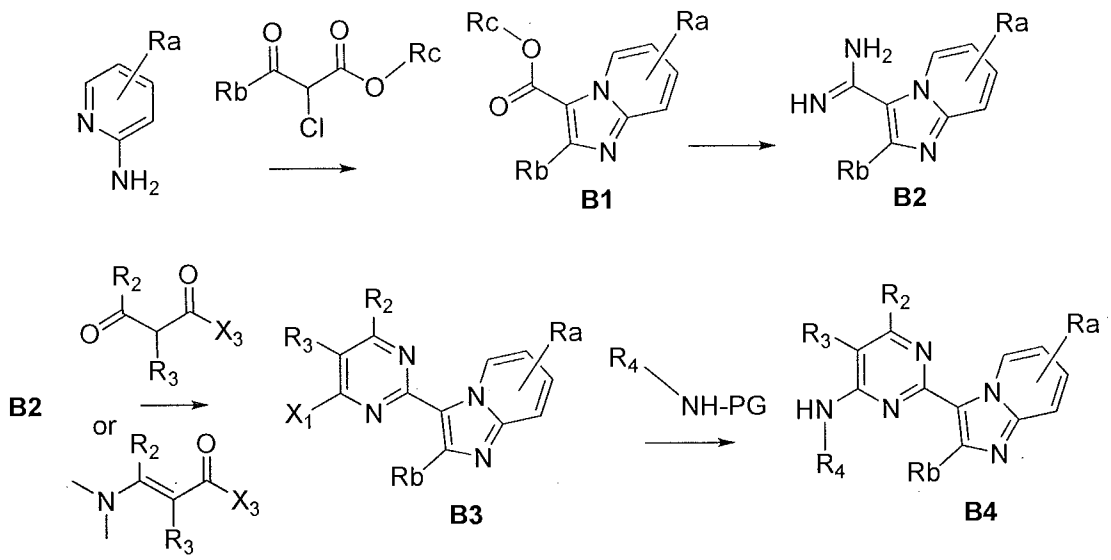
Compound **A6** is prepared by condensation of Compound **A4** with an orthoester Compound **A5** (wherein Rb represents an additional optional R_5 substituent and Rc represents C_{1-3}alkyl). Compound **A6** may also be prepared by cyclizing Compound **A4** with a variety of reactants to obtain the addition of the optional R_5 substituent. For example, the reactant may be TCDI, wherein the additional optional R_5 substituent is a thio-carbonyl which may be further substituted.



Alternatively, Compound **A3** is prepared by cross-coupling of Compound **A7** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) with a nitro substituted amine Compound **A8** (wherein Ar represents an aromatic or heteroaromatic ring; and, wherein Ra represents one, two or three optional R_5 substituents) via a palladium catalyzed cross-coupling reaction using a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2$(allyl), $PdCl_2$(ACN), $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used).

When one or both of R_2 and R_3 are optionally halogen, the product Compound **A3** is obtained as a mixture of regioisomers, wherein the term "Sep" refers to isolating the desired Compound **A3** isomer to be carried forward from the mixture using separation techniques known to those of ordinary skill in the art.

Scheme B Imidazo[1,2-a]pyridine Substituted Pyrimidine Compounds



Compound **B1** is prepared by condensation of a substituted 2-amino-pyridine (wherein Ra represents represents one, two or three optional R_5 substituents) with an α-halogenated ketoester (wherein Rb represents an additional optional R_5 substituent and Rc represents C_{1-3}alkyl).

Compound **B2** is prepared by treating Compound **B1** with an ammonia source (such as NH_4Cl, NH_3 and the like) in the presence of an organoaluminum reagent (such $AlMe_3$ in toluene and the like).

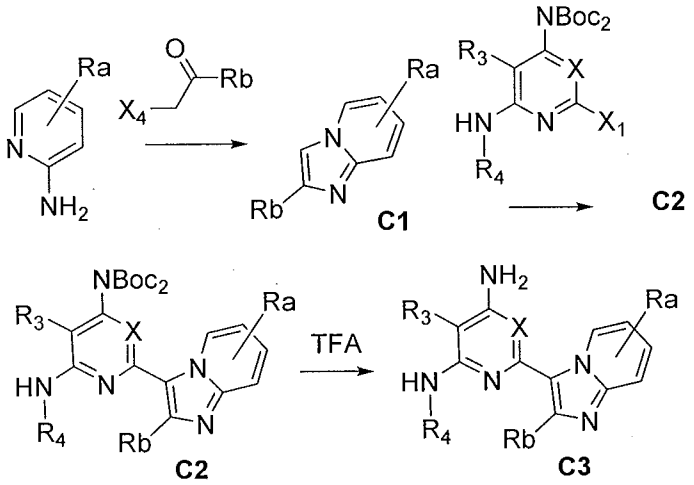
Compound **B3** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) is prepared by condensation of Compound **B2** with a substituted alkyl ester (such as a β-keto ester or a substituted acrylate in a solvent such as phenyl ether and the like; wherein X_3 represents a leaving group such as C_{1-3}alkoxy, benzoxy or halogen) followed by reflux in the presence of a halogenation reagent (such as $POCl_3$, $POBr_3$ and the like).

Compound **B4** is prepared by coupling Compound **B3** with various substituted aryl, heteroaryl or heterocyclyl amines (wherein PG represents an optionally present protecting group monosubstituted on the amine) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^tAm, NaH, NaHMDS and the like) in a solvent (such as THF, DMF and the like).

Alternatively, Compound **B4** may be prepared by reacting Compound **B3** with a substituted aryl, heteroaryl or heterocyclyl amine (wherein the protecting group is absent) via

a palladium catalyzed cross-coupling reaction using a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used).

Scheme C 4,6-Diamino Substituted Pyrimidine Compounds

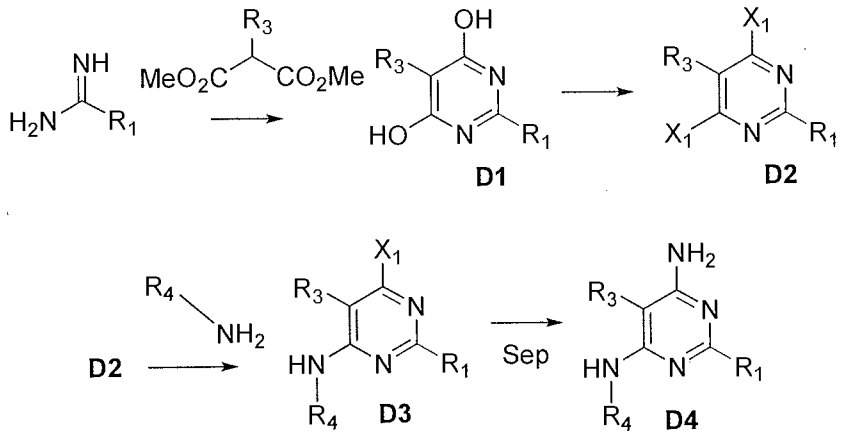


Compound **C1** is prepared by condensation of a substituted 2-amino-pyridine (wherein Ra represents represents one, two or three optional R_5 substituents) and an α-halogenated ketone (wherein X_4 represents a leaving group such as chloro or bromo and Rb represents an additional optional R_5 substituent) at reflux in an organic solvent (such as acetonitrile and the like).

Compound **C2** is prepared by reacting Compound **C1** with a substituted pyrimidine compound (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) via a palladium catalyzed cross-coupling reaction using a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used) and at least 2 equivalents of a base (such as cesium acetate and the like) in an organic solvent (such as dimethylacetamide and the like), undergoing Heck coupling. The reaction may be carried out at elevated temperatures up to 100°C.

Compound **C3** is prepared by treating Compound **C2** with a deprotection reagent (such as 20-40% TFA in DCM and the like) at ambient or elevated temperature.

Scheme D 4,6-Diamino Substituted Pyrimidine Compounds



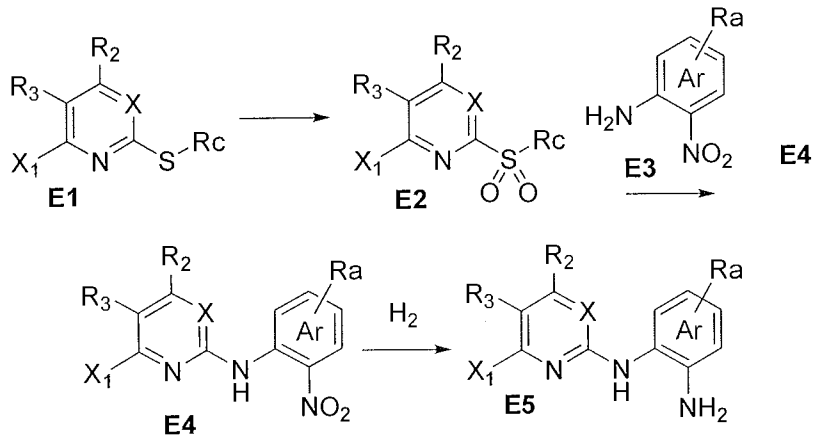
Compound **D1** is prepared by a condensation reaction with a substituted malonate compound and an amidated R_1 group in solution with a sodium alkoxide-solvent mixture (such as NaOMe in MeOH or NaOEt in EtOH and the like).

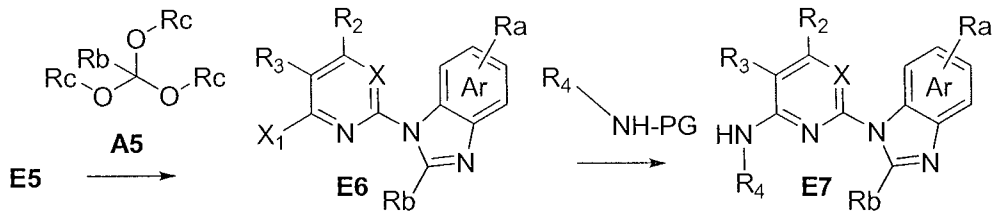
Compound **D2** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) is prepared by refluxing Compound **D1** in the presence of a halogenation reagent (such as $POCl_3$, $POBr_3$ and the like).

Compound **D3** is prepared by mono-amination of Compound **D2** with various substituted aryl, heteroaryl or heterocyclyl amines in a solvent (wherein the solvent is selected from EtOH, THF, DMF, mixtures thereof and the like).

Compound **D4** is prepared by treating Compound **D3** with an aqueous ammonia source in a mixture with a solvent (wherein the solvent is selected from CH_3CN, DMSO, mixtures thereof and the like).

Scheme E Benzimidazole Substituted Pyrimidine Compounds





A 2-methylsulfonyl substituted Compound **E2** is prepared by reacting a 2-methylthio substituted pyrimidine Compound **E1** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo and Rc represents C_{1-3}alkyl) with an oxidizing agent (such as mCPBA, MPS and the like) in a solvent (such as CH_2Cl_2 and the like) at a suitable temperature.

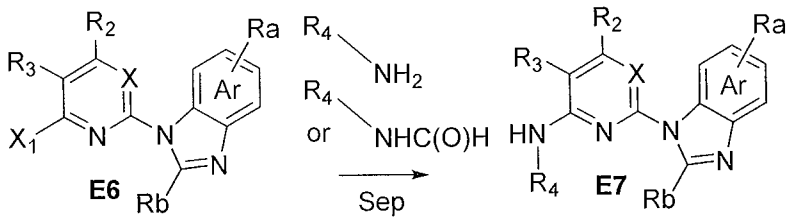
Compound **E4** is prepared by reacting Compound **E2** with a nitro substituted amine Compound **E3** (wherein Ar represents an aromatic or heteroaromatic ring; and, wherein Ra represents one, two or three optional R_5 substituents) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS and the like) in a solvent (such as THF, DMF and the like). The amine substituent on Compound **E3** may be optionally monosubstituted on the amine with a protecting group.

Compound **E5** is prepared by reacting Compound **E4** in the presence of hydrogen and a catalyst (such as nickel, platinum, palladium on carbon and the like).

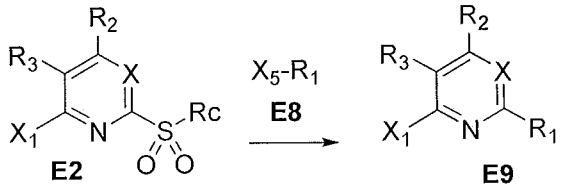
Compound **E6** is prepared by condensation of Compound **E5** with an orthoester Compound **A5** (wherein Rb represents an additional optional R_5 substituent and Rc represents C_{1-3}alkyl). Compound **E6** may also be prepared by cyclizing Compound **E5** with a variety of reactants to obtain the addition of an optional R_5 substituent. For example, the reactant may be TCDI, wherein the additional optional R_5 substituent is a thio-carbonyl which may be further substituted.

Compound **E7** may be prepared by reacting Compound **E6** with various substituted aryl, heteroaryl or heterocyclyl amines in a solvent (wherein the solvent is selected from EtOH, THF, DMF, mixtures thereof and the like).

When R_3 is optionally halogen, the product Compound **E7** is obtained as a mixture of regioisomers, wherein the term "Sep" refers to isolating the desired Compound **E7** isomer to be carried forward from the mixture using separation techniques known to those of ordinary skill in the art, followed by deprotection.

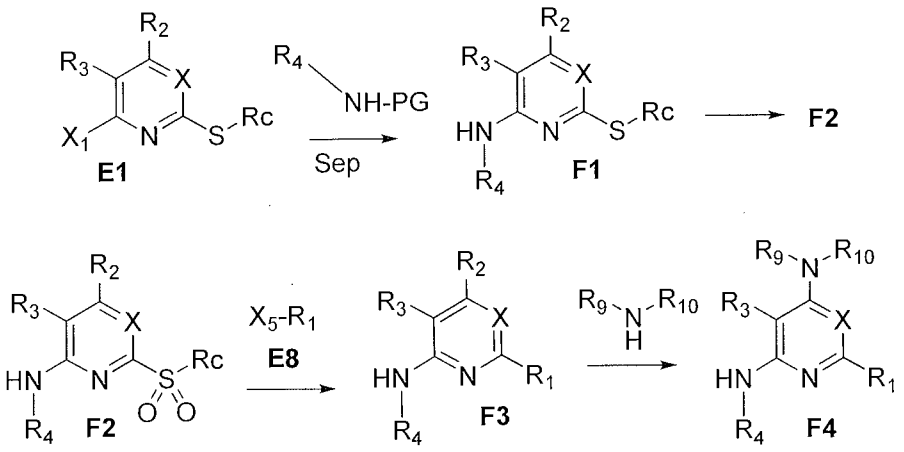


Alternatively, Compound **E7** may be prepared by reacting Compound **E6** with a substituted aryl, heteroaryl or heterocyclyl amine or amide (wherein the protecting group is absent) via a palladium catalyzed cross-coupling reaction using a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used).



Compound **E9** may be prepared directly by reacting Compound **E2** with a Compound **E8** (such as an R_1 substituent having an acidic proton group, wherein X_5 represents a reactive hydrogen atom) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^tAm, NaH, NaHMDS and the like). Compound **E9** may be carried forward in place to Compound **E6** to provide a Compound of Formula (I).

Scheme F Substituted Pyrimidine Compounds



Compound **F1** is prepared by reacting Compound **E1** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo and Rc represents C_{1-3}alkyl) with a substituted aryl, heteroaryl or heterocyclyl amine (wherein PG represents an optionally present protecting group monosubstituted on the amine) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS and the like) in a solvent (such as THF, DMF and the like) at a suitable temperature.

When R_3 is optionally halogen, the product Compound **F1** is obtained as a mixture of regioisomers, wherein the term "Sep" refers to isolating the desired Compound **F1** isomer to be carried forward from the mixture using separation techniques known to those of ordinary skill in the art.

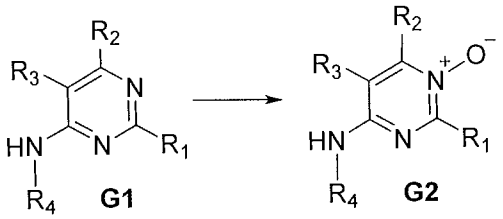
Alternatively, Compound **F1** is prepared by reacting Compound **E1** with a substituted aryl, heteroaryl or heterocyclyl amine or amide (wherein the protecting group is absent) via a palladium catalyzed cross-coupling reaction using a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2$(allyl), $PdCl_2$(ACN), $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used).

Compound **F2** is prepared by reacting Compound **F1** with an oxidizing agent (such as mCPBA, MPS and the like) in a solvent (such as CH_2Cl_2 and the like).

Compound **F2** may be reacted with a Compound **E8** (such as an R_1 substituent having an acidic proton group, wherein X_5 represents a reactive hydrogen atom) in the presence of a strong base (such as KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS and the like) to provide a Compound **F3**, representative of a Compound of Formula (I).

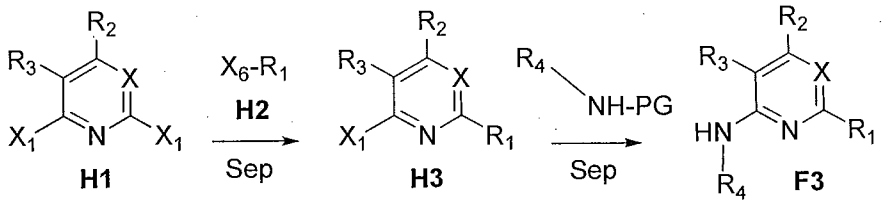
When R_2 is halogen, Compound **F3** may be treated with a substituted amine in a mixture with a solvent (wherein the solvent is selected from CH_3CN, DMSO, mixtures thereof and the like) to provide a Compound **F4**, representative of a Compound of Formula (III).

Scheme G Oxide Substituted Pyrimidine Compounds



Compound **G1** may be reacted with an oxidizing agent (such as mCPBA, MPS and the like) to provide a Compound **G2**, representative of a Compound of Formula (IV).

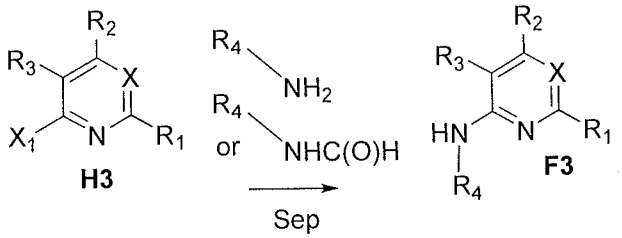
Scheme H Substituted Pyrimidine Compounds



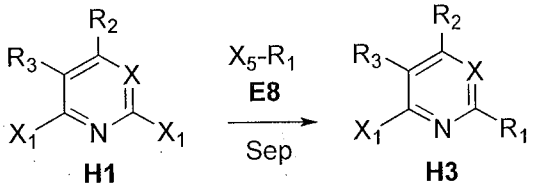
A Compound **H3** is prepared by reacting a Compound **H1** (wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) with a Compound **H2** (wherein R_1 is a substituted heteroaromatic or heterocyclic monocyclic or bicyclic ring system and X_6 represents a reactive group such as a boronic acid, boronate ester, trialkyltin, zinc chloride and the like attached to a carbon atom of R_1), in the presence of a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2$(allyl), $PdCl_2$(ACN), $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used).

When one or both of R_2 and R_3 are optionally halogen, the product Compound **H3** may be obtained as a mixture of regioisomers, wherein the term "Sep" refers to isolating the desired Compound **H3** isomer to be carried forward from the mixture using separation techniques known to those of ordinary skill in the art.

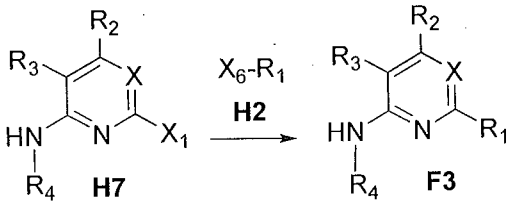
Compound **F3** is prepared by reacting Compound **H3** with various substituted aryl, heteroaryl or heterocyclyl amines in a solvent (wherein PG represents an optionally present protecting group monosubstituted on the amine; and, wherein the solvent is selected from EtOH, THF, DMF, mixtures thereof and the like), followed by separation and deprotection as needed.



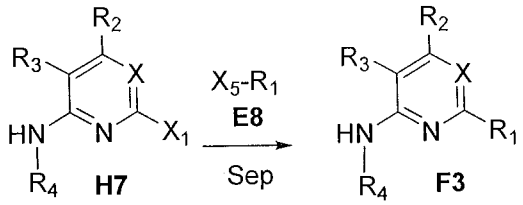
Alternatively, Compound **F3** is prepared by reacting a Compound **H3** with various substituted aryl, heteroaryl or heterocyclyl amines or amides in the presence of a mixture of a phosphino ligand:palladium source (wherein the palladium source is selected from $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$ and the like and the phosphino ligand is selected from PCy_3, Q-Phos, XPhos and the like; alternatively, a commercially available catalyst such as $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$ and the like may be used). When a Compound **H3** is reacted with an amide, the resulting intermediate product is hydrolyzed under basic conditions with a reagent (such as NaOH, KOH, LiOH and the like) at a suitable temperature, followed by separation as needed to obtain product Compound **F3**.



Alternatively, Compound **H3** may be prepared via a Heck reaction of Compound **H1** with Compound **E8**, followed by separation as needed.

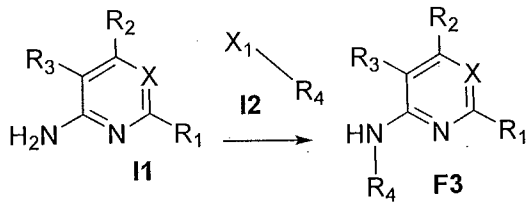


Alternatively, Compound **F3** is prepared by reacting Compound **H7** with a substituted Compound **H2** (wherein R_1 is a substituted heteroaromatic or heterocyclic monocyclic or bicyclic ring system and X_6 represents a reactive group such as a boronic acid, boronate ester, trialkyltin, zinc chloride and the like attached to a carbon atom of R_1).

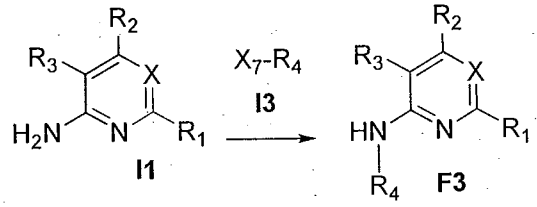


Alternatively, Compound **F3** may be prepared via a Heck reaction of Compound **H7** with Compound **E8** (wherein X_5 represents a reactive hydrogen group), followed by separation as needed.

Scheme I Substituted Pyrimidine Compounds



Compound **F3** is prepared by reacting a substituted Compound **I1** with a Compound **I2** (such as various substituted aryl, heteroaryl or heterocyclyl ring systems, wherein X_1 represents a halogen atom selected from bromo, chloro or iodo) in the presence of a transition metal catalyst (such as a catalyst containing a metal selected from copper, palladium and the like).



Compound **F3** is prepared by reacting a substituted Compound **I1** with a Compound **I3** (such as various substituted aryl, heteroaryl or heterocyclyl ring systems, wherein X_7 represents a ketone or aldehyde leaving group) in the presence of a borohydride (such as $NaCNBH_3$ or $NaBH(OAc)_3$ and the like).

Specific Synthetic Examples

To assist in understanding the scope of the compounds of Formula (I) or a form thereof described herein, the following Specific Examples are included. The experiments relating to the compounds of Formula (I) or a form thereof described herein should not, of course, be construed as specifically limiting the scope of the compounds of Formula (I) or a

form thereof described herein and such variations of the compounds of Formula (I) or a form thereof as described herein, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope as described herein and hereinafter claimed.

Other than in the working examples, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term "about". Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term "about" in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding techniques.

While the numerical ranges and parameters setting forth the characterization of the compounds of Formula (I) or a form thereof described herein are approximations, the numerical values set forth in the working examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

The compounds of Formula (I) or a form thereof provided herein are described in more detail with reference to the following non-limiting examples, which are offered to more fully illustrate the scope of the compounds of Formula (I) or a form thereof described herein, but are not to be construed as limiting the scope thereof. The examples illustrate the preparation of compounds of Formula (I) or a form thereof described herein, and the testing of these compounds of Formula (I) or a form thereof *in vitro* and/or *in vivo*. Those of skill in the art will understand that the synthesis techniques described in these examples represent techniques that fall within the practice of those having ordinary skill in the chemical arts, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those having skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific methods that are disclosed herein

while still obtaining a like or similar result without departing from the spirit and scope described herein.

The reagents and solvents were used as purchased (from a variety of vendors), except where noted. Where applicable, the term "Celite" is used as shown in the following examples to represent the tradename CELITE® (brand of diatomaceous earth). Where applicable, chromatographic separations were performed using techniques and equipment commonly available such as, for example, by using an ISCO CombiFlash® Rf system. Where applicable, NMR spectra were obtained using techniques and equipment commonly available such as, for example, by using a Bruker Avance III^{500} spectrometer with deuterated solvents such as, for example, DMSO-d_6 or residual solvent as standard. Where applicable, melting points were determined using techniques and equipment commonly available such as, for example, by using a SRS OptiMelt® MPA100 (values as obtained without correction/calibration). Where applicable, TLC analysis was performed using techniques and equipment commonly available such as, for example, by using Aldrich 254 nm glass-backed plates (60 Å, 250 μm), visualized using UV and I_2 stains. Where applicable, ESI mass spectra were obtained using techniques and equipment commonly available such as, for example, by using an ACQUITY UPLC® System, with values shown as $[M+H]^+$ or $[M-H]^-$, unless otherwise indicated. Where applicable, the structure of the product was obtained via a 2D NOESY (Nuclear Overhauser SpectroscopY) experiment.

The following abbreviations are provided to ensure the terms used herein are unambiguous to one skilled in the art:

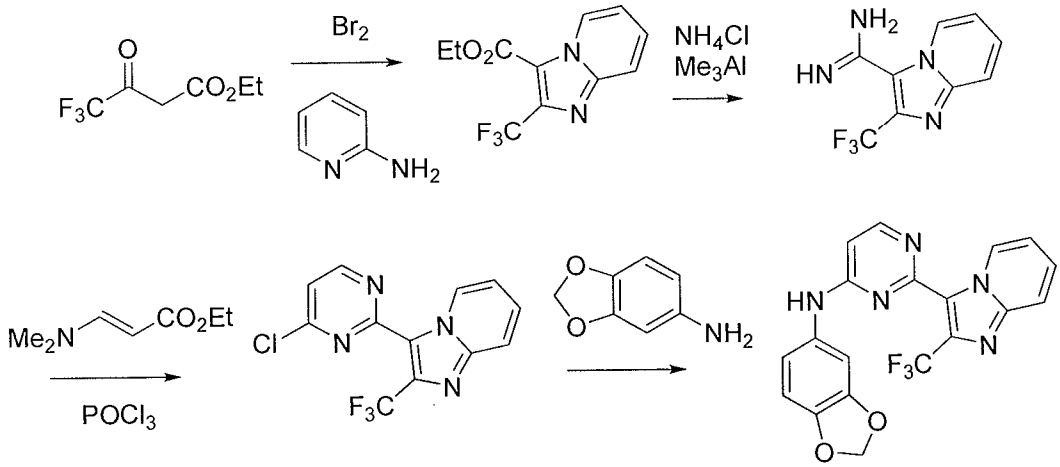
Abbreviation	Meaning
AcOH or HOAc	acetic acid
ACN or MeCN	acetonitrile
$AlMe_3$	trimethylaluminum
APC	allylpalladium (II) chloride dimer
Boc	*tert*-butoxycarbonyl
CsOAc	cesium acetate
DCM or CH_2Cl_2	dichloromethane
DME	dimethyl ether
DMF	dimethyl formamide
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine

Abbreviation	Meaning
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
HPLC	high performance liquid chromatography
h, hr, min, s	hour (h or hr), minute (min), second (s)
iPrMgCl*LiCl	isopropylmagnesium chloride lithium chloride complex
iPrOAc	isopropyl acetate
K_2CO_3	potassium carbonate
K_3PO_4	potassium phosphate
KOtBu or t-BuOK	potassium *tert*-butoxide
LC/MS, LCMS or LC-MS	liquid chromatographic mass spectroscopy
MeOH	methanol
$MeNH_2$ x HCl	methanamine hydrochloride
MS	mass spectroscopy
m.p.	melting point (shown in ^{o}Centigrade)
MPS	potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium hexamethyldisilazide
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NaOtAm	sodium *tert*-pentoxide
NaOMe	sodium methoxide
NaOEt	sodium ethoxide
NaOtBu	sodium *tert*-butoxide
NCS	N-chlorosuccinimide
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NIS	N-iodosuccinimide
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
Oxone	potassium peroxymonosulfate
PCl_5	phosphorus perchloride or phosphorus pentachloride
PCy_3	tricyclohexylphosphine
[Pd]	palladium
Pd/C^{o}	palladium on carbon

Abbreviation	Meaning
$Pd_2(dba)_3$ or Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$PdCl_2(ACN)$	bis(acetonitrile)dichloropalladium(II)
$PdCl_2(allyl)$	chloroallylpalladium(II) dimer
$[Pd(OAc)_2]_3$	palladium (II) acetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium
$POCl_3$	phosphorus oxychloride
PPh_3	triphenylphosphine
psi	pounds per square inch pressure
Pt/C	platinum on carbon
PTSA	p-toluenesulfonic acid
Q-Phos or QPhos	1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
RT	room temperature
TBSO or OTBS	*tert*-butyldimethylsilyloxy
TCDI	1,1'-thiocarbonyldiimidazole
t-Bu	tert-butyl
TEA, NEt_3, Et_3N	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TsOH X H_2O	p-toluenesulfonic acid monohydrate
UPLC	Ultra Performance Liquid Chromatography
Xphos or XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Example 1

N-(1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine (Cpd 28)



Step 1. To a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (9.0 g, 48.9 mmol) in CH_2Cl_2 (50 mL) was added bromine (2.5 mL, 49 mmol). The reaction mixture was stirred for 15 hours at room temperature, and then concentrated under dry nitrogen. To the crude material in ethanol (30 mL) was added pyridin-2-amine (5.2 g, 55 mmol). The reaction mixture was heated at 60°C for 3 hours. The ethanol was evaporated, and the remainder was partitioned between EtOAc and water. The organic layer was dried, filtered through a short plug of silica gel, then concentrated under reduced pressure, and purified by silica gel chromatography to provide ethyl 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate as a white solid (5.3 g, 42 %).

Step 2. To a suspension of NH_4Cl (2.67 g, 50 mmol) in toluene (20 mL) at 0°C was added $AlMe_3$ (2M solution in toluene, 25 mL, 50 mmol) over about a 5 minute period followed by gas evolution. The suspension was stirred at 0°C for 5 minutes, then warmed to room temperature. A solution of ethyl 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (2.58 g, 10 mmol) in toluene (50 mL) was added to the suspension. The reaction mixture was heated at 80°C for 72 hours and then cooled in an ice-bath, quenched with MeOH (100 mL) and NaOH (2 g, 50 mmol). The mixture was filtered through Celite, and concentrated to provide crude 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboximidamide as a brownish solid (2.3 g).

Step 3. A mixture of 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboximidamide (2.3 g, 10 mmol) and ethyl 3-(dimethylamino)acrylate (7.2 g, 50 mmol) in diphenyl ether (10

mL) was heated at 160°C for 1 hour. The mixture was cooled to room temperature and diluted with hexane (200 mL). The precipitate was filtered and washed with hexanes to provide 2-(2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl)pyrimidin-4(3H)-one as a light brown solid. The solid was dissolved in acetonitrile (10 mL) and to the mixture was added $POCl_3$ (1.9 mL, 20 mmol). The reaction mixture was heated to 100°C for 30 minutes, cooled in an ice-water bath, then diluted with dichloromethane (100 mL), and washed with an aqueous $NaHCO_3$ solution. The organic layer was dried, then filtered through Celite and purified by silica gel chromatography to provide 3-(4-chloropyrimidin-2-yl)-2-(trifluoromethyl)imidazo[1,2-a]pyridine as a light yellow solid material (1.09 g, 37% over 3 steps).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.61 (d, J = 6.9 Hz, 1H), 9.00 (d, J = 5.0 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 5.4 Hz, 1H), 7.69 (ddd, J = 8.7, 7.1, 1.3 Hz, 1H), 7.37 (td, J = 7.0, 1.1 Hz, 1H).

Step 4. To a solution of 3-(4-chloropyrimidin-2-yl)-2-(trifluoromethyl)imidazo[1,2-a]pyridine (75 mg, 0.25 mmol) and benzo[d][1,3]dioxol-5-amine (69 mg, 0. 5 mmol) in THF (1 mL) at 0°C was added KOtBu (1M solution in THF, 1 mL, 1 mmol). After 10 minutes, the reaction mixture was quenched with HOAc, then partitioned between EtOAc and water. The organic portion was dried, then concentrated, and the remainder was purified by silica gel chromatography to provide the title compound as a tan solid (58 mg, 58 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.70 (s, 1H), 9.43 (d, J = 6.6 Hz, 1H), 8.43 (d, J = 5.7 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.58 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.37 (br. s., 1H), 7.17 (td, J = 6.9, 0.9 Hz, 1H), 6.95 (dd, J = 8.2, 1.9 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 6.0 Hz, 1H), 6.03 (s, 2H); MS *m/z* 400 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 1 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
2	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (dt, J = 6.9, 0.9 Hz, 1H), 9.45 (br. s, 1H), 8.36 (d, J = 5.7 Hz, 1H), 7.60 (dt, J = 8.8, 0.9 Hz, 1H), 7.38 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.95 - 6.98 (m, 2H), 6.87 (dd, J = 4.4, 3.5 Hz, 1H), 6.54 (d, J = 6.0 Hz, 1H), 4.25 - 4.30 (m, 4H), 2.75 (s, 3H); MS *m/z* 360 $[M+H]^+$

Cpd	Name & Data
3	2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 (br. s, 1H), 9.81 (dt, J = 6.9, 1.1 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.63 (dt, J = 8.8, 1.1 Hz, 1H), 7.42 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.03 (td, J = 6.9, 1.3 Hz, 1H), 6.74 (d, J = 5.7 Hz, 1H), 2.78 (s, 3H); MS *m/z* 370 $[M+H]^+$
4	N-(4-methoxyphenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.84 (d, J = 6.6 Hz, 1H), 9.44 (br. s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 7.59 (dt, J = 8.8, 0.9 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.37 (ddd, J = 8.9, 6.9, 1.3 Hz, 1H), 6.97 - 7.00 (m, 2H), 6.95 (td, J = 6.9, 0.9 Hz, 1H), 6.52 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 2.73 (s, 3H); MS *m/z* 332 $[M+H]^+$
5	N-(4-chlorophenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.81 (d, J = 6.9 Hz, 1H), 9.78 (br. s, 1H), 8.45 (d, J = 5.7 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.44 (s, 2H), 7.40 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.01 (td, J = 6.9, 1.3 Hz, 1H), 6.64 (d, J = 6.0 Hz, 1H), 2.74 (s, 3H); MS *m/z* 336 $[M+H]^+$
6	2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-phenylpyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (dt, J = 6.9, 0.9 Hz, 1H), 9.65 (br. s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.59 - 7.64 (m, 3H), 7.36 - 7.43 (m, 3H), 7.11 (tt, J = 7.4, 0.9 Hz, 1H), 6.98 (ddd, J = 7.5, 5.5, 0.9 Hz, 1H), 6.63 (d, J = 6.0 Hz, 1H), 2.75 (s, 3H); MS *m/z* 302 $[M+H]^+$
7	2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.36 (d, J = 6.9 Hz, 1H), 8.59 (d, J = 5.7 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 9.1 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.60 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.21 (td, J = 6.9, 1.3 Hz, 1H), 6.92 (d, J = 5.7 Hz, 1H); MS *m/z* 424 $[M+H]^+$
8	N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.95 (br. s., 1H), 9.37 (d, J = 6.9 Hz, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 6.8 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 390 $[M+H]^+$
9	N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.75 (br. s, 1H), 9.41 (d, J = 6.6 Hz, 1H), 8.45 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 6.9 Hz, 2H), 6.77 (d, J = 5.7 Hz, 1H), 2.31 (s, 3H); MS *m/z* 370 $[M+H]^+$
10	N-(4-bromophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.97 (br. s, 1H), 9.37 (d, J = 6.9 Hz, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 8.0, 6.9 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 6.9 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 435 $[M+H]^+$

Cpd	Name & Data
11	N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.52 (dt, J = 7.3, 0.9 Hz, 1H), 8.38 (d, J = 6.0 Hz, 1H), 7.72 (dt, J = 9.1, 0.9 Hz, 1H), 7.30 - 7.37 (m, 3H), 7.11 (d, J = 8.8 Hz, 2H), 6.93 (td, J = 6.9, 1.3 Hz, 1H), 6.87 (br. s., 1H), 6.54 (d, J = 6.0 Hz, 1H), 6.46 (t, J = 73.8 Hz, 1H); MS *m/z* 422 $[M+H]^+$
12	N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.63 (dt, J = 7.3, 0.9 Hz, 1H), 8.40 (d, J = 6.0 Hz, 1H), 7.79 (dt, J = 9.1, 0.9 Hz, 1H), 7.41 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.24 - 7.33 (m, 2H), 7.00 (td, J = 6.9, 0.9 Hz, 1H), 6.94 - 6.98 (m, 2H), 6.91 (br. s, 1H), 6.50 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H); MS *m/z* 386 $[M+H]^+$
13	2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s., 1H), 9.56 - 9.72 (m, 1H), 8.60 (d, J = 5.4 Hz, 1H), 7.83 - 7.98 (m, 3H), 7.63 - 7.74 (m, 3H), 6.90 (d, J = 5.4 Hz, 1H); MS *m/z* 458 $[M+H]^+$
14	2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.72 - 9.82 (m, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.65 - 7.77 (m, 1H), 7.46 (dd, J = 9.0, 2.7 Hz, 2H), 7.39 (dd, J = 9.6, 2.0 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 6.84 (br. s, 1H), 6.64 (d, J = 6.0 Hz, 1H); MS *m/z* 474 $[M+H]^+$
15	N-(4-bromophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.96 (br. s, 1H), 9.60 (dd, J = 2.0, 0.8 Hz, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.92 (dd, J = 9.6, 0.8 Hz, 1H), 7.66 (dd, J = 9.6, 2.0 Hz, 1H), 7.61 - 7.64 (m, 2H), 7.50 - 7.55 (m, 2H), 6.81 (d, J = 6.0 Hz, 1H); MS *m/z* 469 $[M+H]^+$
16	2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.60 - 9.78 (m, 1H), 8.40 (dd, J = 6.0, 0.9 Hz, 1H), 7.66 (dd, J = 9.5, 0.6 Hz, 1H), 7.34 (dd, J = 8.8, 2.5 Hz, 2H), 7.31 (dd, J = 9.6, 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.76 (br. s, 1H), 6.54 (d, J = 6.0 Hz, 1H), 6.46 (t, J = 74.4 Hz, 1H); MS *m/z* 456 $[M+H]^+$
17	N-(4-chlorophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.59 - 9.75 (m, 1H), 8.41 (dd, J = 6.0, 0.9 Hz, 1H), 7.66 (dd, J = 9.6, 0.8 Hz, 1H), 7.23 - 7.36 (m, 5H), 6.74 (br. s, 1H), 6.55 (dd, J = 6.0, 1.3 Hz, 1H); MS *m/z* 425 $[M+H]^+$

Cpd	Name & Data
18	2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (br. s, 1H), 10.26 (s, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.88 (d, J = 11.0 Hz, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 6.0 Hz, 1H), 2.86 (s, 3H); MS *m/z* 438 $[M+H]^+$
19	N-(4-bromophenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.30 (s, 1H), 10.07 (br. s, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.87 - 7.96 (m, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 6.0 Hz, 1H), 2.83 (s, 3H); MS *m/z* 449 $[M+H]^+$
20	N-(4-methylphenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.28 (s, 1H), 9.83 (br. s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 6.70 (d, J = 6.0 Hz, 1H), 2.81 (s, 3H), 2.30 (s, 3H); MS *m/z* 384 $[M+H]^+$
21	2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methylphenyl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.78 (s, 1H), 9.63 (br. s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.94 (dd, J = 10.1, 5.4 Hz, 1H), 7.70 (ddd, J = 10.7, 7.9, 2.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.8 Hz, 1H), 2.30 (s, 3H); MS *m/z* 388 $[M+H]^+$
22	2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (br. s, 1H), 8.41 (d, J = 5.7 Hz, 1H), 7.94 (dd, J = 9.9, 5.2 Hz, 1H), 7.69 (ddd, J = 10.0, 7.8, 2.4 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.75 - 6.82 (m, 1H), 6.68 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H); MS *m/z* 404 $[M+H]^+$
23	2-[5chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.27 (d, J = 6.3 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.56 (br. s, 1H), 7.26 (dd, J = 8.5, 1.9 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.73 - 6.80 (m, 2H), 6.42 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H); MS *m/z* 433 $[M+H]^+$
24	2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.47 (br. s, 1H), 8.47 (d, J = 6.6 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.50 (dd, J = 8.8, 1.9 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 74.4 Hz, 1H), 6.90 (d, J = 6.3 Hz, 1H), 4.00 (s, 3H); MS *m/z* 469 $[M+H]^+$

Cpd	Name & Data
25	N-(4-bromophenyl)-2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.43 - 7.52 (m, J = 8.5 Hz, 3H), 6.87 (d, J = 6.0 Hz, 1H), 4.00 (s, 3H); MS *m/z* 482 $[M+H]^+$
26	N-(4-bromophenyl)-2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.75 (br. s., 1H), 9.55 (d, J = 3.2 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 7.83 (dd, J = 8.8, 5.0 Hz, 1H), 7.67 (d, J = 7.9 Hz, 2H), 7.57 (td, J = 9.1, 1.6 Hz, 1H), 7.31 - 7.46 (m, J = 7.6 Hz, 3H), 7.01 - 7.21 (m, 4H), 6.72 (d, J = 5.7 Hz, 1H); MS *m/z* 461 $[M+H]^+$
27	2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.88 (br. s, 1H), 9.49 - 9.61 (m, 1H), 8.37 (d, J = 6.0 Hz, 1H), 7.90 (dd, J = 9.9, 5.2 Hz, 1H), 7.66 - 7.75 (m, 3H), 7.39 - 7.49 (m, 3H), 7.14 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 6.3 Hz, 1H), 2.23 (s, 3H); MS *m/z* 396 $[M+H]^+$
29	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm9.63 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.84 (dt, J = 9.1, 0.9 Hz, 1H), 7.58 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.22 (br. s., 1H), 7.15 (td, J = 6.9, 1.3 Hz, 0H), 7.01 (dd, J = 8.5, 2.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 6.0 Hz, 1H), 4.20 - 4.29 (m, 4H); MS *m/z* 410 $[M+H]^+$
30	N-(6-methoxypyridin-3-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.53 (d, J = 6.9 Hz, 1H), 8.34 (d, J = 5.7 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.69 (dt, J = 9.1, 0.9 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.32 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 6.91 (td, J = 7.0, 1.3 Hz, 2H), 6.75 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 6.0 Hz, 1H), 3.90 (s, 3H); MS *m/z* 387 $[M+H]^+$
31	N^2,N^2-dimethyl-N^5-{2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-yl}pyridine-2,5-diamine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.55 (d, J = 6.9 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.51 (br. s, 1H), 7.32 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 6.92 (td, J = 6.9, 0.9 Hz, 1H), 6.81 (br. s, 0H), 6.51 (d, J = 9.1 Hz, 1H), 6.35 (d, J = 5.4 Hz, 1H), 3.08 (s, 6H); MS *m/z* 400 $[M+H]^+$
32	2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.66 (dd, J = 1.9, 0.9 Hz, 1H), 8.60 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.87 (dd, J = 9.6, 0.8 Hz, 1H), 7.74 (dd, J = 9.5, 1.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 6.0 Hz, 1H); MS *m/z* 503 $[M+H]^+$

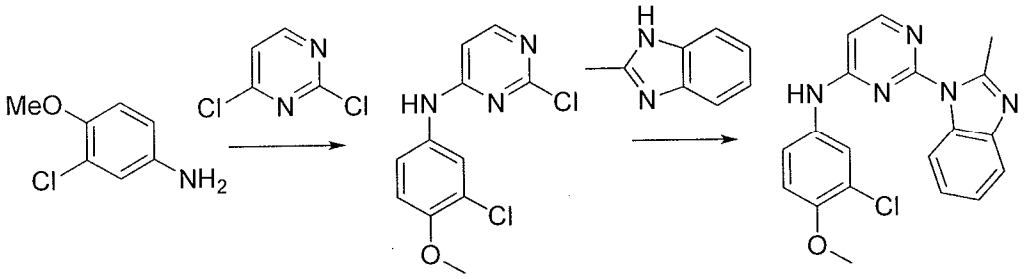
Cpd	Name & Data
33	2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.70 - 9.86 (m, 1H), 8.32 (d, J = 4.7 Hz, 1H), 7.60 (d, J = 9.5 Hz, 1H), 7.40 (dd, J = 9.6, 1.7 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.47 (br. s, 1H), 3.78 (s, 3H); MS *m/z* 465 $[M+H]^+$
34	N-(3-fluoro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.77 (s, 1H), 9.35 (d, J = 6.9 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 13.6 Hz, 1H), 7.53 (ddd, J = 9.1, 6.9, 1.3 Hz, 1H), 7.17 - 7.23 (m, 1H), 7.13 (td, J = 6.9, 1.1 Hz, 1H), 7.13 (td, J = 6.9, 0.9 Hz, 1H), 7.10 (t, J = 9.1 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H); MS *m/z* 404 $[M+H]^+$
35	N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.80 (s, 1H), 9.40 (d, J = 6.9 Hz, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.88 - 7.92 (m, 1H), 7.85 (dt, J = 9.1, 1.0 Hz, 1H), 7.59 (ddd, J = 9.1, 6.6, 1.3 Hz, 1H), 7.43 (dd, J = 8.8, 2.8 Hz, 1H), 7.18 (td, J = 6.9, 1.3 Hz, 1H), 7.15 (d, J = 9.1 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H), 3.85 (s, 3H); MS *m/z* 420 $[M+H]^+$
36	N-(3-chloro-4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 9.38 (d, J = 7.3 Hz, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.86 (dt, J = 9.1, 1.1 Hz, 1H), 7.59 (ddd, J = 9.1, 6.9, 1.3 Hz, 1H), 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.20 (td, J = 6.9, 1.3 Hz, 1H), 6.80 (d, J = 5.7 Hz, 1H), 2.30 (s, 3H); MS *m/z* 404 $[M+H]^+$
37	N-(4-ethoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.64 (br. s, 1H), 9.43 (br. s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 7.84 (dt, J = 9.1, 1.3 Hz, 1H), 7.57 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.16 (t, J = 6.5 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 6.0 Hz, 1H), 4.02 (q, J = 6.9 Hz, 2H), 1.34 (t, J = 6.9 Hz, 3H); MS *m/z* 400 $[M+H]^+$
38	N-[4-(propan-2-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.76 (s, 1H), 9.41 (d, J = 6.9 Hz, 1H), 8.45 (d, J = 6.0 Hz, 1H), 7.85 (dt, J = 9.1, 0.9 Hz, 1H), 7.58 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.16 (td, J = 6.9, 0.9 Hz, 1H), 6.77 (d, J = 6.0 Hz, 1H), 2.89 (spt, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 7H); MS *m/z* 398 $[M+H]^+$
39	N-[4-(1H-pyrazol-1-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.98 (s, 1H), 9.42 (d, J = 7.3 Hz, 1H), 8.51 (d, J = 5.7 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 7.86 (td, J = 9.1, 1.3 Hz, 1H), 7.76 - 7.84 (m, J = 3.5 Hz, 4H), 7.73 (d, J = 1.6 Hz, 1H), 7.59 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.20 (td, J = 6.9, 1.3 Hz, 1H), 6.84 (d, J = 6.0 Hz, 1H), 6.54 (t, J = 1.9 Hz, 1H); MS *m/z* 422 $[M+H]^+$

Cpd	Name & Data
45	N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.53 (br. s., 1H), 9.16 (d, J = 1.3 Hz, 1H), 8.81 (s, 1H), 8.38 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 4.7 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.70 (dd, J = 8.2, 2.5 Hz, 1H), 3.79 (s, 3H); MS *m/z* 387 $[M+H]^+$
46	2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.41 - 9.49 (m, 1H), 9.20 (br. s, 1H), 8.49 (dd, J = 6.0, 2.2 Hz, 1H), 8.02 - 8.12 (m, 1H), 7.83 - 7.92 (m, 2H), 7.58 (d, J = 8.5 Hz, 2H), 6.93 - 7.32 (m, 2H); MS *m/z* 425 $[M+H]^+$
47	N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.53 (dd, J = 4.9, 1.4 Hz, 1H), 9.25 (d, J = 1.3 Hz, 1H), 9.20 (br. s., 1H), 8.55 (d, J = 6.0 Hz, 1H), 8.15 (d, J = 4.7 Hz, 1H), 7.70 - 7.81 (m, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 6.0 Hz, 1H); MS *m/z* 391 $[M+H]^+$
48	2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.31 (br. s, 1H), 9.02 (d, J = 2.5 Hz, 1H), 8.65 (d, J = 5.7 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 10.4 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 9.8, 2.5 Hz, 1H), 6.95 (d, J = 6.0 Hz, 1H), 3.66 (s, 3H); MS *m/z* 454 $[M+H]^+$
49	2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.65 (br. s, 1H), 8.96 - 9.06 (m, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.76 (d, J = 9.8 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.36 (dd, J = 9.6, 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H); MS *m/z* 470 $[M+H]^+$
50	N-(4-methoxyphenyl)-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.04 (br. s, 1H), 8.97 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.75 - 7.79 (m, 3H), 7.38 (dd, J = 9.1, 2.2 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 6.0 Hz, 1H), 3.59 (s, 3H), 3.33 (s, 3H); MS *m/z* 416 $[M+H]^+$
51	N-[4-(difluoromethoxy)phenyl]-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.90 (br. s, 1H), 8.98 (d, J = 1.9 Hz, 1H), 8.50 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.37 (dd, J = 9.8, 2.5 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.19 (t, J = 74.4 Hz, 1H), 6.78 (d, J = 5.7 Hz, 1H), 3.61 (s, 3H); MS *m/z* 452 $[M+H]^+$
53	N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.74 (dd, J = 4.9, 1.4 Hz, 1H), 9.44 (d, J = 1.6 Hz, 1H), 9.30 (br. s., 1H), 8.72 (d, J = 6.0 Hz, 1H), 8.32 (d, J = 4.7 Hz, 1H), 7.89 - 8.00 (m, 2H), 7.42 - 7.52 (m, 2H), 7.07 (dd, J = 6.0, 1.6 Hz, 1H), 7.20 (t, J = 74.4 Hz, 1H); MS *m/z* 423 $[M+H]^+$

Cpd	Name & Data
54	2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.58 (ddd, J = 5.7, 1.9, 0.9 Hz, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.97 (ddd, J = 9.8, 5.4, 0.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.73 (ddd, J = 9.9, 7.7, 2.5 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 6.0 Hz, 1H); MS *m/z* 442 $[M+H]^+$
55	N-[4-(difluoromethoxy)phenyl]-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.75 (dd, J = 5.5, 2.0 Hz, 1H), 9.10 (br. s, 1H), 8.51 (d, J = 5.7 Hz, 1H), 7.84 (ddd, J = 9.8, 5.4, 0.9 Hz, 1H), 7.71 - 7.76 (m, 2H), 7.60 (ddd, J = 10.0, 7.6, 2.5 Hz, 1H), 7.22 - 7.26 (m, 2H), 6.99 (t, J = 74.1 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 440 $[M+H]^+$
56	N-[4-(trifluoromethyl)phenyl]-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 10.03 (br. s, 1H), 8.48 (d, J = 6.9 Hz, 1H), 8.21 - 8.36 (m, 1H), 8.00 - 8.15 (m, 1H), 7.65 - 7.73 (m, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.06 - 7.12 (m, 1H), 7.03 (t, J = 6.8 Hz, 1H); MS *m/z* 424 $[M+H]^+$
60	N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.49 (d, J = 6.6 Hz, 1H), 8.03 - 8.31 (m, 2H), 7.30 - 7.55 (m, 3H), 7.00 - 7.12 (m, 2H), 6.79 - 6.87 (m, 3H), 3.76 (s, 3H); MS *m/z* 386 $[M+H]^+$
62	N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.58 (d, J = 3.8 Hz, 1H), 9.23 (d, J = 1.6 Hz, 1H), 8.95 (br. s., 1H), 8.48 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 4.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 6.0 Hz, 1H), 2.37 (s, 3H); MS *m/z* 371 $[M+H]^+$
118	2-(imidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.10 (s, 1H), 9.92 (d, J = 7.3 Hz, 1H), 8.51 (app. s, 1H), 8.48 (d, J = 5.7 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.75 - 7.86 (m, 3H), 7.46 (ddd, J = 9.1, 6.6, 0.9 Hz, 1H), 7.14 (td, J = 6.9, 1.1 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H); MS *m/z* 356 $[M+H]^+$

Example 2

N-(3-chloro-4-methoxyphenyl)-2-(2-methyl-1*H*-benzimidazol-1-yl)pyrimidin-4-amine (Cpd 40)



Step1. 3-Chloro-4-methoxyaniline (2.07 g, 13.1 mmol), 2,4-dichloropyrimidine (1.95 g, 13.1 mmol) and triethylamine (2.1 mL, 15 mmol) were mixed in isopropanol (10 mL). The mixture was heated at 100°C for 13 hours, then partially concentrated, diluted with water, and made basic with K_2CO_3. The precipitate was filtered, then washed with water, followed by hexane. The major isomer, 2-chloro-N-(3-chloro-4-methoxyphenyl)pyrimidin-4-amine (2.07 g, 59 %) was recrystallized from methanol as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.99 (br. s, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.73 (br. s., 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 5.7 Hz, 1H), 3.85 (s, 3H).

Step 2. 2-Chloro-N-(3-chloro-4-methoxyphenyl)pyrimidin-4-amine (84 mg, 0.31 mmol), 2-methyl-1H-benzo[d]imidazole (82 mg, 0.62 mmol) and K_2CO_3 (86 mg, 0.62 mmol) were mixed in DMF (2 mL). The reaction mixture was heated at 120°C for 3 days, then cooled, partitioned between water and EtOAc, and purified by silica gel chromatography to provide the title compound as a white solid (29 mg, 26%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.94 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 8.03 - 8.10 (m, 1H), 7.82 - 7.90 (m, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.40 - 7.45 (m, 1H), 7.20 - 7.29 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 5.7 Hz, 1H), 3.86 (s, 3H), 2.79 (s, 3H); MS *m/z* 366 $[M+H]^+$.

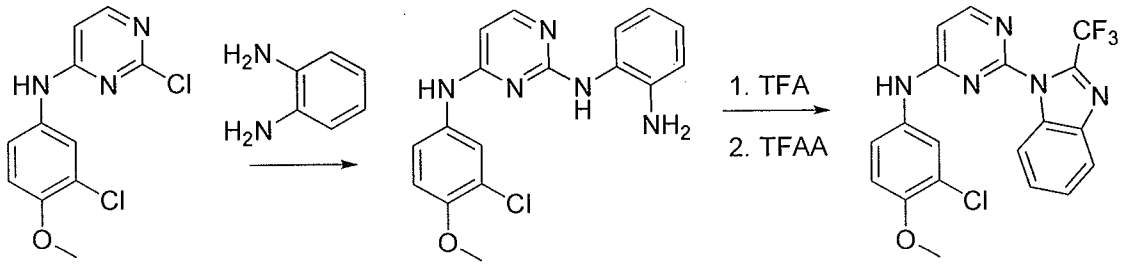
Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 2 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
1	N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.79 (br. s., 1H), 8.36 (d, J = 5.4 Hz, 1H), 7.95 - 8.17 (m, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.42 - 7.54 (m, 2H), 7.17 - 7.33 (m, 2H), 6.96 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 5.0 Hz, 1H), 3.76 (s, 3H), 2.77 (s, 3H); MS *m/z* 332 $[M+H]^+$

Cpd	Name & Data
41	2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.37 (s, 1H), 8.55 (d, J = 5.7 Hz, 1H), 8.01 - 8.06 (m, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.61 - 7.65 (m, 1H), 7.26 (app. quind, J = 7.3, 1.4 Hz, 2H), 6.91 (d, J = 5.7 Hz, 1H), 2.81 (s, 3H); MS *m/z* 370 $[M+H]^+$
61	N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.32 (1H, d, J = 5.5 Hz), 8.06 (1H, d, J = 8 Hz), 7.59 (3H, d, J = 8 Hz), 7.26 (2H, m), 7.14 (2H, d, J = 8 Hz), 7.0 (1H, t, J = 74 Hz), 6.69 (1H, d, J = 6 Hz), 2.82 (3H, s); MS *m/z* 368 $[M+H]^+$

Example 3

N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]pyrimidin-4-amine (Cpd 42)



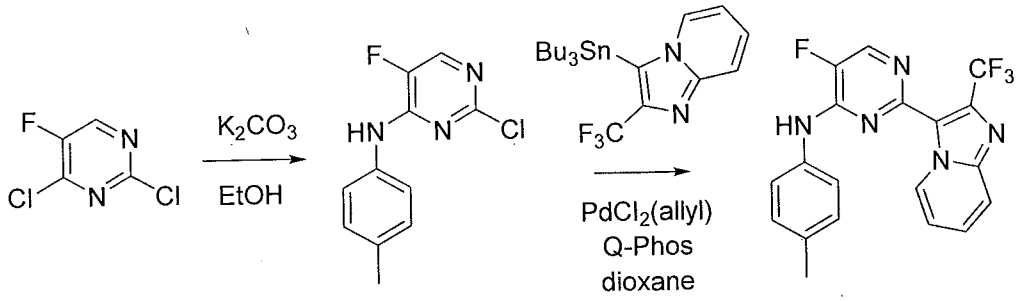
A mixture of 2-chloro-N-(3-chloro-4-methoxyphenyl)pyrimidin-4-amine (280 mg, 1.03 mmol) and benzene-1,2-diamine (540 mg, 5 mmol) in isopropanol (5 mL) was heated in a microwave oven at 160°C for 10 minutes. The reaction mixture was diluted with water, extracted with EtOAc, then filtered through a short plug of silica gel, and concentrated to provide a first crude intermediate N^2-(2-aminophenyl)-N^4-(3-chloro-4-methoxyphenyl)pyrimidine-2,4-diamine. The first crude intermediate was dissolved in dichloromethane (5 mL), then trifluoroacetic anhydride was added in two portions (0.5 mL each). The reaction mixture was washed with an aqueous $NaHCO_3$ solution, and purified by silica gel chromatography to provide a second crude intermediate N-(2-(4-(3-chloro-4-methoxyphenylamino)-pyrimidin-2-ylamino)phenyl)-2,2,2-trifluoroacetamide.

To a solution of the second crude intermediate (71 mg, 0.16 mmol) in acetonitrile (2 mL) was added trifluoroacetic acid (0.5 mL). The mixture was heated in a microwave oven at 180°C for 1 hour and 45 minutes after which UPLC showed complete conversion. The final product was purified by silica gel chromatography to provide the title compound as a white solid (40 mg, 59%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 - 10.18 (m, 1H), 8.45 (d, J = 5.7 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.83 - 7.90 (m, 1H), 7.52 - 7.56 (m, J = 8.2, 8.2, 1.3 Hz, 1H), 7.50 (td, J = 7.9, 1.3 Hz, 1H), 7.43 (dd, J = 9.0, 2.7 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H); MS *m/z* 420 $[M+H]^+$.

Example 4

5-fluoro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine (Cpd 43)



Step1: A mixture of 2,4-dichloro-5-fluoropyrimidine (1.00 g, 5.99 mmol), 4-toluidine (642 mg, 5.99 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) in EtOH (10 mL) was stirred for 18 hours at 50°C. The mixture was filtered through Celite and purified by column chromatography to yield 2-chloro-5-fluoro-N-*p*-tolylpyrimidin-4-amine (1.19 g, 84%).

Step2: A mixture of 2-chloro-5-fluoro-N-p-tolylpyrimidin-4-amine (165 mg, 0.69 mmol), 3-(tributylstannyl)-2-(trifluoromethyl)imidazo[1,2-a]pyridine (300 mg, 0.63 mmol), Q-Phos (13.5 mg, 0.019 mmol) and $PdCl_2$(allyl) (6.9 mg, 0.019 mmol) in dioxane (1.5 mL) was stirred for 2 hours at 90°C. The mixture was purified by column chromatography to yield the title compound (213 mg, 80%).

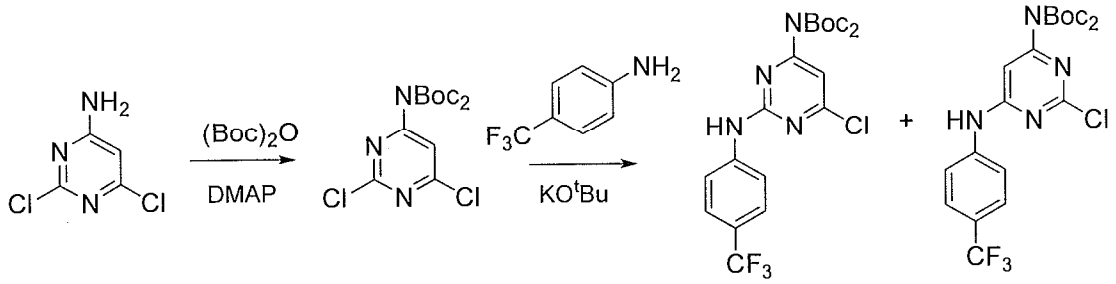
^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.24 - 9.29 (1H, m) 8.29 (1H, d, *J*=2.84 Hz) 7.66 - 7.71 (1H, m) 7.46 (2H, d, *J*=8.51 Hz) 7.31 (1H, ddd, *J*=9.14, 6.62, 1.26 Hz) 7.14 (2H, d, *J*=8.20 Hz) 6.82 - 6.89 (2H, m) 2.30 (3H, s); MS *m/z* 388.2 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 4 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
44	5-chloro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.34 - 9.42 (1H, m) 8.51 (1H, s) 7.80 (1H, dd, *J*=9.14, 0.95 Hz) 7.49 (2H, d, *J*=8.51 Hz) 7.41 (1H, ddd, *J*=8.99, 6.78, 1.26 Hz) 7.20 - 7.27 (3H, m) 6.91 (1H, td, *J*=6.94, 1.26 Hz) 2.42 (3H, s); MS *m/z* 404.2 $[M+H]^+$

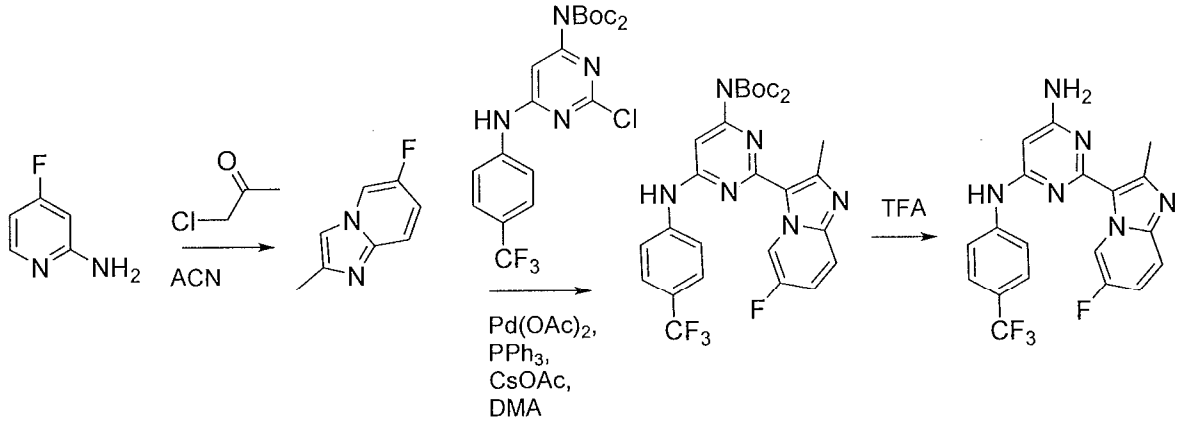
Example 5

2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 68)



Step 1. A mixture of 2,6-dichloropyrimidine-4-amine (3.78 g, 23.05 mmol) and DMAP (cat.) in dichloromethane (20 mL) was treated with di-*tert*-butyldicarbonate (11.05 g, 50.71 mmol) at 0°C. After addition, the resulting mixture was stirred at ambient temperature overnight. The mixture was poured into ice-water (120 mL) and extracted with dichloromethane (150 mL). The organic phase was separated, washed with brine (100 mL), dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by filtering through a pad of silica gel (100 g) to afford di-*tert*-butyl (2,6-dichloropyrimidin-4-yl)imidodicarbonate as an oil (7.55 g, 90%).

Step 2. A solution of di-*tert*-butyl (2,6-dichloropyrimidin-4-yl)imidodicarbonate (1.75 g, 4.81 mmol) and 4-trifluoromethylaniline (775.0 mg, 4.81 mmol) in THF (10 mL) was treated with potassium *tert*-butoxide solution (1M in THF, 9.62 mL, 9.62 mmol) at -78°C. The mixture was allowed to stir and warm to 0°C over 20 minutes. The mixture was then poured into ice-water (120 mL) and extracted with dichloromethane (150 mL). The organic phase was separated, washed with brine (100 mL), dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (by eluting with hexane then 2% ethyl acetate-hexane) to afford di-*tert*-butyl 6-chloro-2-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (750.0 mg, 32% yield), and (by eluting with 4% ethyl acetate-hexane) di-*tert*-butyl 2-chloro-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (1.08 g, 46%).



Step 3. 4-Fluoropyridin-2-amine (8.57 g, 76.44 mmol) and chloroacetone (12.99 g, 71.67 mmol) were pre-mixed and stirred in a 250 mL round bottom flask at 0°C for 15 minutes. The resulting mixture was diluted with acetonitrile (50 mL) and refluxed for overnight. The acetonitrile was evaporated, and ethyl ether (200 mL) was added to produce a precipate, which was collected by filtration. The solid was partitioned between dichloromethane (300 mL) and a saturated $NaHCO_3$ solution (250 mL). The organic layer was separated, dried over $MgSO_4$, then filtered and concentrated under the reduced pressure. The residual material was separated by silica gel column chromatography (1: 1 ethyl acetate-hexane) to afford 6-fluoro-2-methylimidazo[1,2-*a*]pyridine (5.20 g, 46%) as a glassy solid.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.95 - 7.99 (m, 1H), 7.46 (dd, J = 5.04, 9.77 Hz, 1H), 7.34 (s, 1H), 6.99 - 7.06 (m, 1H), 2.44 (d, J = 0.63 Hz, 3H); MS *m/z* 151.0 (100) $[M+H]^+$.

Step 4. A mixture of 6-fluoro-2-methylimidazo[1,2-*a*]pyridine (445.0 mg, 2.97 mmol), di-*tert*-butyl 2-chloro-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (1.0 g, 5.78 mmol), palladium (II) acetate (33.4 mg, 0.149 mmol), triphenylphosphine (46.7 mg, 0.178 mmol), cesium acetate (1.14 g, 5.94 mmol) and DMA (5 mL) was degassed by three cycles of vacuum pumping and N_2 purging, and then was heated to 100°C for 1 hour. The solution was cooled and poured into water (50 mL), and this mixture was extracted with dichloromethane. The extract was dried over $MgSO_4$, then filtered and concentrated under the reduced pressure. The residual material was triturated with ethyl ether to afford di-*tert*-butyl 2-(6-fluoro-2-methylimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (706.0 mg, 83%).

Step 5. A solution of di-*tert*-butyl 2-(6-fluoro-2-methylimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (140 mg, 0.24 mmol)

in dichloromethane (2 mL) was treated with TFA (0.4 mL) at 0°C. The resulting mixture was stirred at ambient temperature for 4 hours. The solvent was concentrated under reduced pressure, and the residual material was partitioned between ethyl acetate and a saturated $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$, then filtered and evaporated. The residual material was triturated with ethyl ether to afford the title compound as a white solid (87.0 mg, 87%). m.p. 209-211 °C.

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 10.40 (dd, J = 2.21, 5.36 Hz, 1H), 8.88 (s, 1H), 8.11 - 8.27 (m, 1H), 7.78 - 7.85 (m, 1H), 7.74 (d, J = 8.83 Hz, 2H), 7.69 (d, J = 8.83 Hz, 2H), 6.47 (br. s., 2H), 6.03 (s, 1H), 2.93 (s, 3H); MS *m/z* 403.5 (100) $[M+H]^+$, 404.4 (30).

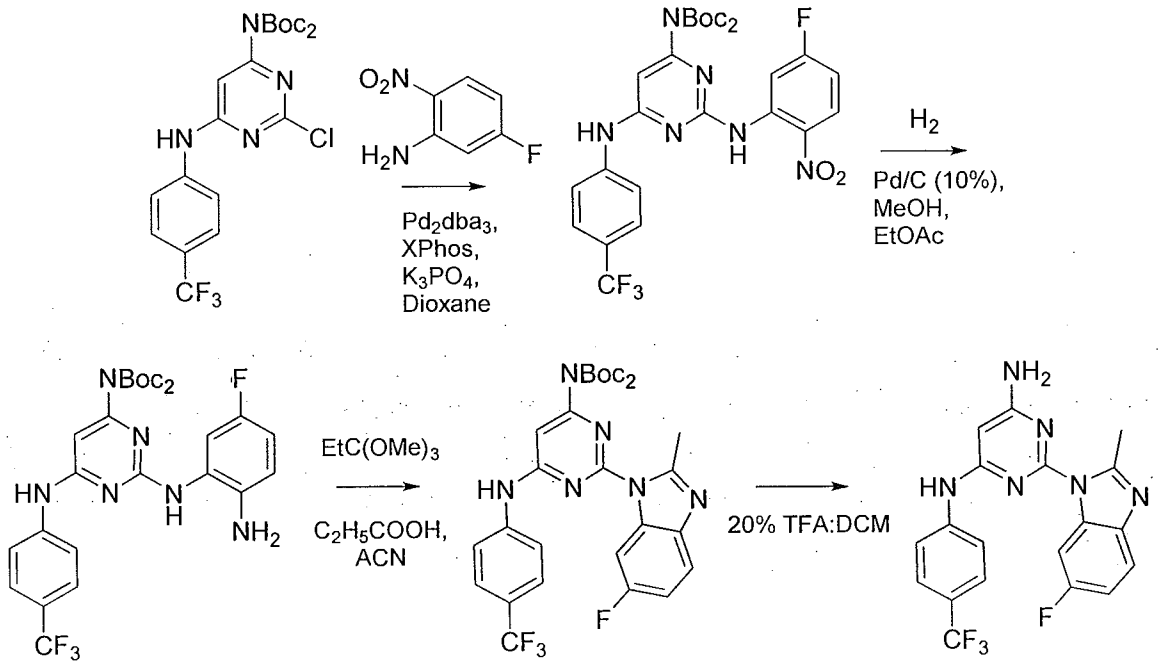
Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 5 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
65	N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.67 (ddd, J = 1.10, 1.26, 7.09 Hz, 1H), 8.40 (s, 1H), 7.73 (td, J = 1.10, 9.14 Hz, 1H), 7.59 - 7.66 (d, J = 9.1 Hz, 2H), 7.51 (ddd, J = 1.26, 6.94, 9.14 Hz, 1H), 7.15 - 7.23 (d, J = 9.1 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 7.05 - 7.12 (m, 1H), 6.11 (br. s., 2H), 5.96 (s, 1H); MS *m/z* 437.3 $[M+H]^+$
66	2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine m.p. 203-205 °C; MS *m/z* 439.4 $[M+H]^+$
67	N-[4-(trifluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine m.p. 199-202 °C; MS *m/z* 455.3 $[M+H]^+$
69	N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 10.41 (dd, J = 2.21, 5.36 Hz, 1H), 8.57 (s, 1H), 8.19 (s, 1H), 7.71 - 7.89 (m, 1H), 7.53 (d, J = 9.77 Hz, 2H), 7.20 - 7.26 (d, J = 9.77 Hz, 2H), 6.81 – 7.11 (t, J = 75.00 Hz, 1H), 6.36 (br, s., 2H), 5.91 (s, 1H), 2.91 (s, 3H); m.p. 136-138 °C; MS *m/z* 401.5 $[M+H]^+$
75	2-(2-cyclopropyl-6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 (dd, J = 2.21, 5.99 Hz, 1H), 9.28 (s, 1H), 7.70 - 7.87 (m, 1H), 7.58 (dd, J = 5.52, 9.62 Hz, 1H), 7.41 (ddd, J = 2.68, 7.72, 9.77 Hz, 1H), 6.98 – 7.28 (t, J = 75.00 Hz, 1H), 7.24 - 7.32 (m, 1H), 7.18 - 7.24 (m, 1H), 6.73 (s, 2H), 5.72 (s, 1H), 3.42 - 3.56 (m, 1H), 0.89 - 1.11 (m, 4H); m.p. 198-200 °C; MS *m/z* 445.5 $[M+H]^+$

Cpd	Name & Data
84	[3-(4-amino-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridin-2-yl]methanol ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 9.36 - 9.77 (m, 1 H), 7.90 - 7.97 (m, 2 H), 7.59 - 7.69 (m, 1 H), 7.50 - 7.55 (m, 2 H), 7.- 7.45 (m, 1 H), 6.55 - 6.58 (m, 1 H), 4.86 (s, 2 H); MS *m/z* 419.1 $[M+H]^+$
100	2-(6-fluoro-2-methylimidazo[1,2-a]pyrimidin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.45 (dd, J = 2.84, 5.67 Hz, 1H), 9.46 (s, 1H), 8.76 (d, J = 2.84 Hz, 1H), 7.72 (d, J = 8.51 Hz, 2H), 7.64 (d, J = 8.51 Hz, 2H), 6.82 (s, 2H), 5.79 (s, 1H), 2.84 (s, 3H); m.p. 256-258 °C; MS *m/z* 404.3 $[M+H]^+$

Example 6

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 71)



Step 1: A mixture of 5-fluoro-2-nitroaniline (156.2 mg, 1.00 mmol),), di-*tert*-butyl 2-chloro-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (480.0 mg, 0.98 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (56.1 mg, 0.1 mmol), tris(dibenzylideneacetone) dipalladium(0) (53.8 mg, 0.05 mmol) and potassium phosphate (625.0 mg, 2.95 mmol) in dioxane (2 mL) was degassed by three cycles of vacuum pumping and N_2 purging, and then was heated to 100°C for 2 hours. The solution was cooled and poured into water (10 mL), and this mixture was extracted with ethyl acetate (15 mL). The extract was dried over $MgSO_4$, then filtered and evaporated. The residual material was

separated by column chromatography (eluting with 1:1 dichloromethane:hexane, then 1:2 ethyl acetate:dichloromethane) to afford di-*tert*-butyl 2-(5-fluoro-2-nitrophenylamino)-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (483.0 mg, 81%).

Step 2: A pressure reaction vessel charged with di-*tert*-butyl 2-(5-fluoro-2-nitrophenylamino)-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (483.0 mg), Pd/C (10%, wet, 48.0 mg) and 1:1 ethyl acetate:methanol (5 mL) was placed on a Parr shaker. The mixture was degassed by three cycles of vacuum pumping and N_2 purging. The vessel was pressurized to 40 psi hydrogen and shaken for 2 hours. The charcoal was removed by filtration, and the solvent was evaporated to give di-tert-butyl 2-(2-amino-5-fluorophenylamino)-6-(4-(trifluoromethyl)phenylamino)-pyrimidin-4-yliminodicarbonate. The residual material was used in the next step without further purification. MS *m/z* 579.6 (100) $[M+H]^+$, 580.6 (40).

Step 3: A mixture of di-tert-butyl 2-(2-amino-5-fluorophenylamino)-6-(4-(trifluoromethyl)-phenylamino)pyrimidin-4-yliminodicarbonate (365.0 mg, 0.63 mmol), triethyl orthoacetate (306.0 mg, 1.89 mmol), *p*-toluenesulfonic acid (5.0 mg, 0.025 mmol) and ethanol (2.0 mL) was heated to reflux for 2 hours. After cooling, the mixture was partitioned between dichloromethane (20 mL) and a saturated $NaHCO_3$ solution (10 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, then filtered and evaporated. The residual oil was triturated with ethyl ether to afford di-*tert*-butyl 2-(6-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (316.0 mg, 83%). MS *m/z* 603.6 (100) $[M+H]^+$, 604.6 (40).

Step 4: A solution of the product (316.0 mg, 0.52 mmol) in dichloromethane (3 mL) was treated with TFA (1 mL) at 0°C. The resulting mixture was stirred at ambient temperature for 4 hours. The solvent was evaporated, and the residual material was triturated with ethyl ether to afford the title compound as a white solid (152.0 mg, 73%). m.p. 253 – 255°C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.72 (s, 1H), 8.00 (d, J = 8.51 Hz, 2H), 7.52 - 7.69 (m, 3H), 7.45 (dd, J = 1.89, 9.14 Hz, 1H), 7.01 - 7.24 (m, 3H), 6.20 (s, 1H), 2.66 (s, 3H); MS *m/z* 403.3 (100) $[M+H]^+$.

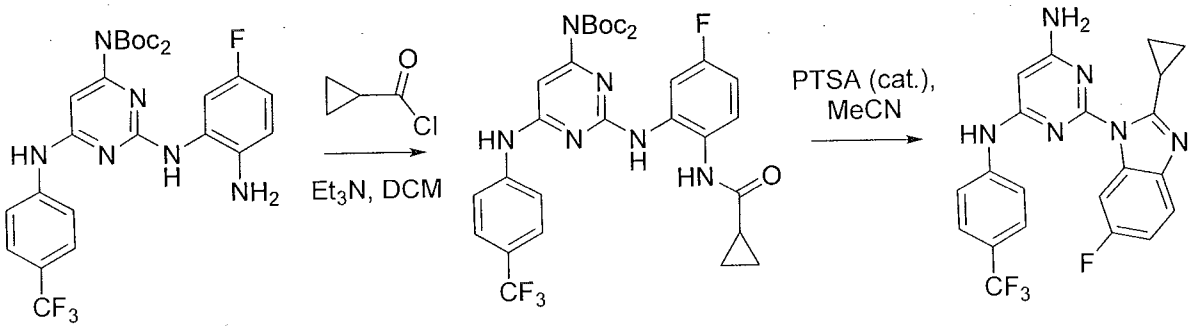
Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 6 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
93	2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.76 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 8.5, 1.9 Hz, 1H), 7.02 (br. s., 2H), 5.90 (s, 1H), 2.83 (s, 3H); MS *m/z* 419.8 $[M+H]^+$
72	N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.25 (s, 1H), 7.99 (dd, *J* = 2.21, 10.09 Hz, 1H), 7.56 (dd, *J* = 5.04, 8.83 Hz, 1H), 7.48 (d, *J* = 8.83 Hz, 2H), 7.00 – 7.30 (t, J = 75.00 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.07 (dt, *J* = 2.36, 9.06 Hz, 1H), 6.84 (br. s., 2H), 5.74 (s, 1H), 2.80 (s, 3H); m.p. 168-170 °C; MS *m/z* 401.5 $[M+H]^+$
76	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.47 (s, 1H), 7.96 (d, *J* = 9.14 Hz, 1H), 7.66 (d, *J* = 12.93 Hz, 1H), 7.57 (dd, *J* = 5.04, 8.20 Hz, 1H), 7.00 – 7.28 (t, J = 70.00 Hz, 1H), 7.27 - 7.39 (m, 1H), 7.23 (d, *J* = 8.51 Hz, 1H), 7.08 (t, *J* = 8.20 Hz, 1H), 6.94 (br. s., 2H), 5.80 (s, 1H), 2.50 (br. s., 3H); m.p. 182-183 °C; MS *m/z* 419.4 $[M+H]^+$
77	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.47 (br. s., 1H), 7.90 (d, *J* = 9.14 Hz, 1H), 7.50 - 7.74 (m, 2H), 7.29 (d, *J* = 5.04 Hz, 1H), 7.00 – 7.28 (t, J = 70.00 Hz, 1H), 7.22 (d, *J* = 8.20 Hz, 1H), 7.09 (d, *J* = 7.88 Hz, 1H), 6.93 (br. s., 2H), 5.80 (s, 1H), 3.27 (m,2H), 1.28 (t, *J* = 6.62 Hz, 3H); m.p. 156-158 °C; MS *m/z* 433.5 $[M+H]^+$
81	2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.64 (s, 1H), 7.89 (dd, *J* = 2.52, 10.09 Hz, 1H), 7.70 (d, *J* = 8.20 Hz, 2H), 7.58 - 7.66 (m, 3H), 7.05 - 7.13 (m, 1H), 6.98 (br. s., 2H), 5.88 (s, 1H), 3.28 (q, *J* = 7.46 Hz, 2H), 1.28 (t, *J* = 7.57 Hz, 3H); m.p. 201-203 °C; MS *m/z* 417.2 $[M+H]^+$
96	2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.11 (br. s, 1H), 8.27 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 13.9, 1.6 Hz, 1H), 7.65 (t, J = 8.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 8.5, 1.9 Hz, 1H), 6.57 (br. s., 2H), 6.07 (s, 1H), 2.87 (s, 3H); MS *m/z* 437.8 $[M+H]^+$

Cpd	Name & Data
97	2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.56 (br. s, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 6.6, 2.2 Hz, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.23 (dd, J = 8.5, 2.2 Hz, 1H), 7.20 (dd, J = 6.6, 2.2 Hz, 2H), 6.94 (t, J = 74.7 Hz, 1H), 6.35 (br. s., 2H), 5.91 (s, 1H), 2.85 (s, 3H); MS *m/z* 418.0 $[M+H]^+$
98	2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.94 (br. s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.82 (dd, J = 14.3, 1.4 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.42 (dd, J = 8.7, 1.1 Hz, 1H), 7.27 (dd, J = 8.7, 2.0 Hz, 1H), 7.10 (br. s, 2H), 5.93 (s, 1H), 2.83 (s, 3H); MS *m/z* 437.8 $[M+H]^+$
99	2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (br. s, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 8.00 - 8.03 (m, 2H), 7.65 - 7.67 (m, 2H), 7.64 (dd, J = 8.8, 2.2 Hz, 1H), 7.42 (t, J = 75.0 Hz, 1H), 6.79 (br. s., 2H), 6.38 (s, 1H), 3.32 (s, 3H); MS *m/z* 417.8 $[M+H]^+$
144	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.25 (s, 1H), 7.84 - 8.12 (m, 1H), 7.60 (dd, *J* = 5.04, 8.51 Hz, 1H), 7.49 (d, *J* = 8.83 Hz, 2H), 7.01 – 7.31 (t, J = 75.00 Hz, 1H), 7.15 (d, *J* = 8.20 Hz, 2H), 7.04 - 7.13 (m, 1H), 6.84 (br. s., 2H), 5.76 (s, 1H), 3.28 (q, *J* = 7.25 Hz, 2H), 1.28 (t, *J* = 7.41 Hz, 3H); m.p. 166-168 °C; MS *m/z* 415.4 $[M+H]^+$

Example 7

2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 82)



Step 1: To a solution of di-tert-butyl 2-(2-amino-5-fluorophenylamino)-6-(4-(trifluoromethyl)-phenylamino)pyrimidin-4-yliminodicarbonate (212.0 mg, 0.37 mmol), triethylamine (42.0 mg, 0.41 mmol) in dichloromethane (2 mL) was added cyclopropanecarbonyl chloride (38.3 mg, 0.37 mmol) at 0°C. The mixture was stirred at ambient temperature for 3 hours, then partitioned between dichloromethane and water. The

organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated to give di-*tert*-butyl 2-(2-(cyclopropanecarboxamido)-5-fluorophenylamino)-6-(4-(trifluoromethyl)phenylamino)-pyrimidin-4-yliminodicarbonate. The residual solid was used directly in the next step without further purification.

Step 2: A mixture of crude di-*tert*-butyl 2-(2-(cyclopropanecarboxamido)-5-fluorophenylamino)-6-(4-(trifluoromethyl)phenylamino)-pyrimidin-4-yliminodicarbonate, p-toluenesulfonic acid (7.0 mg, 0.037 mmol) and acetonitrile (3 mL) was heated in a microwave oven at 180°C for 30 minutes. The mixture was partitioned between ethyl acetate and a saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:1 dichloromethane:hexane, then 1:5 MeOH:50% ethyl acetate in dichloromethane) to afford the title compound (103.0mg, 65% for two steps). m.p. 203 – 206°C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.49 - 9.59 (m, 1H), 7.70 (td, J = 1.00, 13.24 Hz, 1H), 7.64 (d, J = 8.57 Hz, 2H), 7.49 (d, J = 8.57 Hz, 2H), 7.36 - 7.42 (m, 1H), 6.91 - 6.97 (m, 1H), 6.88 (br. s, 2H), 5.77 (s, 1H), 2.88 - 3.01 (m, 1H), 0.97 - 1.05 (m, 2H), 0.86 - 0.95 (m, 2H); MS *m/z* 429.2 (100) $[M+H]^+$, 430.2 (20).

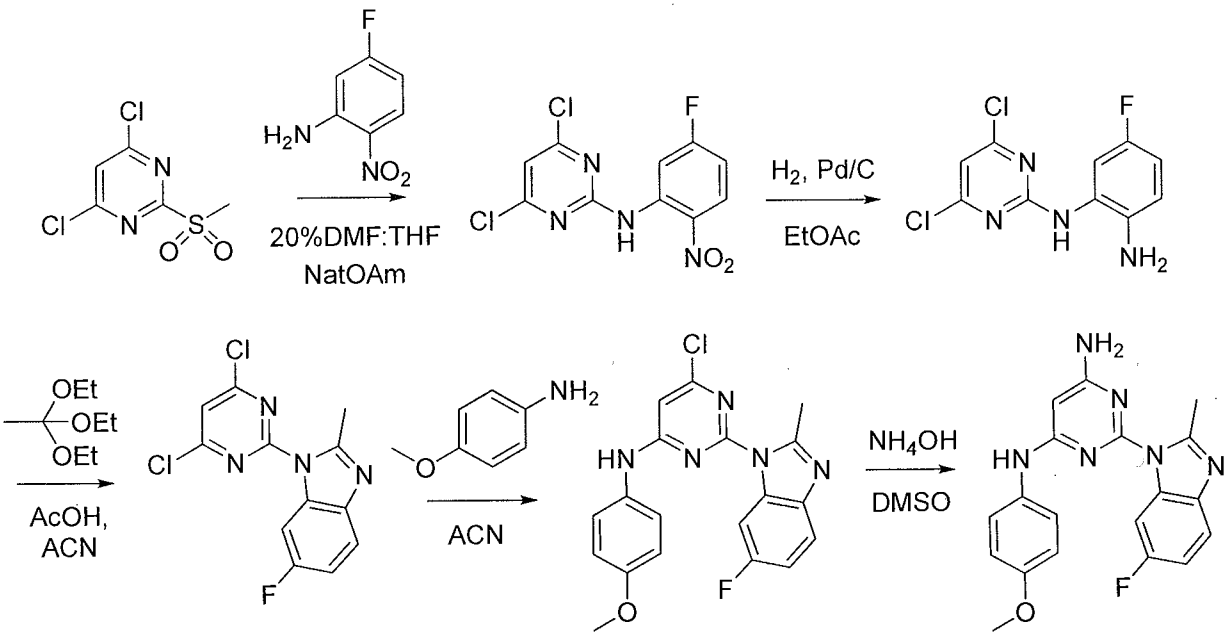
Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 7 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
78	2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 7.70 - 7.95 (m, 2H), 7.52 (dd, J = 5.04, 8.83 Hz, 1H), 7.28 (d, J = 2.52 Hz, 1H), 6.98 – 7.26 (t, J = 70.00 Hz, 1H), 7.22 (m, 1H), 7.03 - 7.09 (m, 1H), 6.98 (br. s, 2H), 5.82 (s, 1H), 3.07 (m, 1H), 1.10 - 1.15 (m, 2H), 1.01 - 1.08 (m, 2H); m.p. 186-188 °C; MS *m/z* 445.5 $[M+H]^+$
83	2-(2-cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (s, 1H), 7.96 (d, J = 5.04, 8.83 Hz, 1H), 7.79 (d, J = 8.51 Hz, 2H), 7.61 (d, J = 8.51 Hz, 2H), 7.34 (dd, J = 2.52, 9.46 Hz, 1H), 6.93 - 7.09 (m, 3H), 5.78 - 5.93 (m, 1H), 3.02 (s, 1H), 1.13 - 1.19 (m, 2H), 1.04 - 1.08 (m, 2H); MS *m/z* 429.2 $[M+H]^+$

Cpd	Name & Data
143	2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.30 (s, 1H), 7.83 - 7.90 (m, 1H), 7.54 (d, J = 8.83 Hz, 3H), 7.00 – 7.30 (t, J = 75.00 Hz, 1H), 7.11 - 7.18 (m, 2H), 7.02 - 7.10 (m, 1H), 6.83 - 6.92 (m, 2H), 5.78 (s, 1H), 3.08 - 3.20 (m, 1H), 1.09 - 1.14 (m, 2H), 0.99 - 1.07 (m, 2H); m.p. 175-177 °C; MS *m/z* 427.2 $[M+H]^+$
145	N-[4-(difluoromethoxy)phenyl]-2-[2-(difluoromethyl)-6-fluoro-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.32 (s, 1H), 8.36 (dd, J = 1.89, 10.09 Hz, 1H), 7.95 – 8.16 (t, J = 52.5 Hz, 1H), 7.85 (dd, J = 5.04, 8.83 Hz, 1H), 7.44 (d, J = 8.83 Hz, 2H), 7.04 – 7.34 (t, J = 75.00 Hz, 1H), 7.27 (dt, J = 2.36, 9.06 Hz, 1H), 7.20 (d, J = 8.83 Hz, 2H), 6.98 (br. s., 2H), 5.76 (s, 1H); m.p. 114-115 °C; MS *m/z* 437.4 $[M+H]^+$
149	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.70 (s, 1H), 7.92 - 7.97 (m, 1H), 7.81 (d, J = 8.51 Hz, 2H), 7.60 (d, J = 8.51 Hz, 2H), 7.50 - 7.55 (m, 1H), 7.19 (ddd, J = 1.58, 5.04, 7.25 Hz, 2H), 7.00 (br. s., 2H), 5.90 (s, 1H), 2.94 - 3.03 (m, 1H), 1.15 (m, 2H), 1.05 (m, 2H); m.p. 199-201 °C; MS *m/z* 411.3 $[M+H]^+$
150	2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.66 (s, 1H), 8.09 - 8.20 (m, 1H), 7.73 (d, J = 8.51 Hz, 2H), 7.67 - 7.71 (m, 1H), 7.63 (d, J = 8.51 Hz, 2H), 7.26 - 7.31 (m, 2H), 6.97 (br. s., 2H), 5.87 (s, 1H), 5.04 (s, 2H), 3.25 (s, 3H); m.p. 212-213 °C; MS *m/z* 415.4 $[M+H]^+$
151	2-[2-(propan-2-yl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (s, 1H), 7.85 - 7.91 (m, 1H), 7.74 (d, J = 8.83 Hz, 2H), 7.61 - 7.65 (m, 1H), 7.59 (d, J = 8.83 Hz, 2H), 7.17 - 7.25 (m, 2H), 6.95 (s, 2H), 5.90 (s, 1H), 3.96 - 4.08 (m, 1H), 1.29 (d, J = 6.94 Hz, 6H); m.p. 216-218 °C; MS *m/z* 413.4 $[M+H]^+$
152	2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.71 (s, 1H), 8.36 - 8.52 (m, 1H), 7.89 – 8.11 (t, J = 55.00 Hz, 1H), 7.80 - 7.87 (m, 1H), 7.68 (m. 4H), 7.35 - 7.48 (m, 2H), 6.92 - 7.20 (m, 2H), 5.91 (s, 1H); m.p. 187-188 °C; MS *m/z* 421.4 $[M+H]^+$

Example 8

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine (Cpd 265)



Step 1: To a mixture of 5-fluoro-2-nitroaniline (8.16 g, 35.93 mmol), 4,6-dichloro-2-(methylsulfonyl)pyrimidine (5.06 g, 32.67 mmol), THF (50 mL) and DMF (12 mL) was added sodium *tert*-pentoxide (2.5 M in THF, 28.6mL, 71.5 mmol) dropwise at -78°C. The mixture was stirred at -78°C for 30 minutes, then ice/water (300 mL) was added to form a precipitate. The solid was collected by filtration, then washed with water and hexane to afford 4,6-dichloro-N-(5-fluoro-2-nitrophenyl)pyrimidin-2-amine (9.32 g, 95%).

Step 2: A 250 mL flask charged with 4,6-dichloro-N-(5-fluoro-2-nitrophenyl)pyrimidin-2-amine (6.35 g, 21.03 mmol), Pd/C (10%, wet, 635.0 mg) and ethyl acetate (50 mL) was degassed by three cycles of vacuum pumping and N_2 purging, and then filled with hydrogen from a hydrogen balloon. The mixture was stirred at ambient temperature for 16 hours. The charcoal was removed by filtration, and the solvent was evaporated. The residual material was washed with hexane to afford N^1-(4,6-dichloropyrimidin-2-yl)-5-fluorobenzene-1,2-diamine as a white solid (5.55 g, 97%).

Step 3: A mixture of N^1-(4,6-dichloropyrimidin-2-yl)-5-fluorobenzene-1,2-diamine (2.57 g, 9.47 mmol), triethyl orthoacetate (6.06 g, 37.87 mmol), acetic acid (6 mL) and acetonitrile (30 mL) was stirred at ambient temperature for 18 hours. A saturated $NaHCO_3$ solution was added to the mixture portionwise at 0°C, with resultant bubbling of the mixture.

The solution was added to the mixture until the bubbling ceased. The product was then extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was washed with hexane to afford 1-(4,6-dichloropyrimidin-2-yl)-6-fluoro-2-methyl-1H-benzo[d]imidazole as a brownish solid (2.41 g, 86%).

Step 4: A mixture of 1-(4,6-dichloropyrimidin-2-yl)-6-fluoro-2-methyl-1H-benzo[d]imidazole (150.0 mg, 0.51 mmol), 4-methoxyaniline (125.0 mg, 1.01 mmol) and acetonitrile (1 mL) was stirred at 80°C for 18 hours. After cooling, ethyl ether was added to the mixture to form 6-chloro-2-(6-fluoro-2-methyl-1H-benzo[d]imidazol-1-yl)-N-(4-methoxyphenyl)pyrimidin-4-amine as a precipitate, which was isolated by filtration.

Step 5: To 6-chloro-2-(6-fluoro-2-methyl-1H-benzo[d]imidazol-1-yl)-N-(4-methoxyphenyl)-pyrimidin-4-amine was added DMSO (2 mL) and NH_4OH (27%, 0.1 mL). The reaction mixture was sealed, placed in a microwave oven and heated at 170°C for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water (2 x 20 mL) and brine, then dried over $MgSO_4$ and filtered through a silica gel pad (10 g). The solvent was evaporated, and the residual material was triturated with dichloromethane to afford the title compound as a white solid (161.0 mg, 88%). m.p. 193 - 195°C.

^{1}H NMR (500 MHz, Acetone-d_6)□ δ ppm 8.74 (s, 1H), 8.11 (dd, J = 2.52, 10.40 Hz, 1H), 7.52 (dd, J = 5.20, 8.67 Hz, 1H), 7.34 - 7.43 (d, J = 9.14 Hz, 2H), 7.01 (d, J = 2.84 Hz, 1H), 6.94 (d, J = 9.14 Hz, 2H), 6.49 (br. s., 2H), 5.76 (s, 1H), 3.79 (s, 3H), 2.84 (s, 3H); MS *m/z* 365.0 (100) $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 8 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
52	2-{[6-{[4-(difluoromethoxy)phenyl]amino}-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}ethanol ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.17 (1H, dd, J = 7.2, 1.5 Hz), 7.59 (1H, dd, J = 7.2, 1.5 Hz), 7.51 (2H, d, J = 9 Hz), 7.28 (1H, m), 7.13 (2H, d, J = 9 Hz), 6.78 (1H, t, J = 75 Hz), 5.81 (1H, s), 3.75 (2H, t, J = 6 Hz), 3.53 (2H, br), 2.89 (3H, s); MS *m/z* 427.1 $[M+H]^+$

Cpd	Name & Data
57	2-{[2-(2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.13 (1H, d, J = 7.5 Hz), 7.71 (2H, d, J = 7.5 Hz), 7.6 (1H, dd, J = 9, 1 Hz), 7.56 (2H, d, J = 9 Hz), 7.27 (1H, m), 7.13 (2H, d, J = 9 Hz), 5.91 (1H, s), 3.76 (2H, t, J = 6 Hz), 3.55 (2H, br), 2.89 (3H, s); MS *m/z* 429.2 $[M+H]^+$
58	N^4-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)-N^6-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (Methanol-d_4) δ ppm 8.15 (1H, d, J = 8 Hz), 7.67 (2H, d, J =8.5 Hz), 7.59 (1H, d, J = 8 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.26 (1H, m), 5.87 (1H, s), 3.58 (4H, br), 3.38 (3H, s).2.87 (3H, s); MS *m/z* 443.1 $[M+H]^+$
59	N^4-[4-(difluoromethoxy)phenyl]-N^6-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.06 (1H, d, J = 7 Hz), 7.47 (1H, m), 7.38 (2H, d, J = 9 Hz), 7.15 (1H, m), 7.00 (2H, d, J = 9 Hz), 5.68 (1H, s), 3.28 (3H, s), 2.76 (3H, s); MS *m/z* 441.1 $[M+H]^+$
63	2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.13 (1H, m), 7.73 (2H, d, J = 8.5 Hz), 7.61 (1H, m), 7.58 (2H, d, J = 8.5 Hz), 7.29 (2H, m), 5.95 (1H, s), 2.89 (3H, s); MS *m/z* 385.1 $[M+H]^+$
64	2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.19 (1H, dd, J = 11, 7.5 Hz), 7.67 (2H, d, J = 8.5 Hz), 7.6 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 11, 7.5 Hz), 5.93 (1H, s), 2.9 (3H, s); MS *m/z* 421.1 $[M+H]^+$
73	2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.61 (1H, dd, J = 8, 1.5 Hz), 8.39 (1H, d, J = 4 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.28 (1H, dd, J = 8, 4 Hz), 5.91 (1H, s), 2.97 (3H, s); MS *m/z* 386.2 $[M+H]^+$
74	2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.04 (1H, dd, J = 11, 7.5 Hz), 7.54 (1H, dd, J = 13.5, 1.5 Hz), 7.44 (1H, t, J = 8.5 Hz), 7.32 (1H, dd, J = 11, 7.5 Hz), 7.24 (1H, dd, J = 13.5, 1.5 Hz), 5.81 (1H, s), 2.78 (3H, s); MS *m/z* 439.1 $[M+H]^+$
79	N-[4-(trifluoromethyl)phenyl]-2-(2,5,6-trimethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (s, 1H), 7.91 (s, 1H), 7.77 (d(AB), J = 8.8 Hz, 2H), 7.63 (d(AB), J = 7.9 Hz, 2H), 7.34 (s, 1H), 6.92 (br. s., 2H), 5.85 (s, 1H), 2.79 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H); MS *m/z* 413.0 $[M+H]^+$

Cpd	Name & Data
80	N-[3-fluoro-4-(trifluoromethyl)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.90 (s, 1H), 8.05 - 8.10 (m, 1H), 7.89 (d, J = 14.2 Hz, 1H), 7.65 (t, J = 8.7 Hz, 1H), 7.57 - 7.62 (m, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.20 - 7.28 (m, 2H), 7.05 (br. s, 1H), 5.91 (s, 1H), 2.82 (s, 3H); MS *m/z* 403.1 $[M+H]^+$
85	2-(6-bromo-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.73 (d(AB), J = 8.2 Hz, 2H), 7.65 (d(AB), J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 6.97 - 7.07 (m, 2H), 5.87 (s, 1H), 2.83 (s, 3H); MS *m/z* 463.0 $[M+H]^+$
86	2-(2,6-dimethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (s, 1H), 7.88 (s, 1H), 7.74 (d(AB), J = 8.5 Hz, 2H), 7.61 (d(AB), J = 8.5 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 8.2, 1.3 Hz, 1H), 6.93 (br. s., 2H), 5.84 (s, 1H), 2.77 (s, 3H), 2.34 (s, 3H); MS *m/z* 339.0 $[M+H]^+$
87	2-(6-ethyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 7.89 (s, 1H), 7.77 (d(AB), J = 8.5 Hz, 2H), 7.61 (d(AB), J = 8.8 Hz, 2H), 7.52 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 8.2, 1.3 Hz, 1H), 6.95 (br. s., 2H), 5.86 (s, 1H), 2.81 (s, 3H), 2.64 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H); MS *m/z* 413.0 $[M+H]^+$
88	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 7.85 (dd, J = 9.6, 2.0 Hz, 1H), 7.68 - 7.73 (d(AB), J = 8.5 Hz, 2H), 7.61 - 7.68 (d(AB), J = 8.8 Hz, 2H), 7.14 (td, J = 10.4, 2.2 Hz, 1H), 7.04 (br. s., 2H), 5.89 (s, 1H), 2.83 (s, 3H); MS *m/z* 421 $[M+H]^+$
89	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 7.80 - 7.84 (m, J = 9.5, 2.2 Hz, 1H), 7.80 (dd, J = 14.0, 1.1 Hz, 1H), 7.66 (t, J = 8.7 Hz, 1H), 7.38 (dd, J = 8.5, 1.3 Hz, 1H), 7.16 (dd, J = 10.4, 2.2 Hz, 1H), 7.11 - 7.16 (m, 2H), 5.91 (s, 1H); MS *m/z* 439 $[M+H]^+$
90	2-{[2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (br. s., 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.70 (d(AB), J = 7.9 Hz, 2H), 7.64 (d(AB), J = 8.8 Hz, 2H), 7.15 (td, J = 10.3, 2.4 Hz, 1H), 5.96 (br. s, 1H), 4.83 (br. s, 1H), 3.59 (q, J = 5.7 Hz, 2H), 3.38 - 3.51 (m, 2H), 2.85 (s, 3H); MS *m/z* 465.0 $[M+H]^+$

Cpd	Name & Data
91	2-(6-ethenyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 8.4, 1.4 Hz, 1H), 6.98 (br. s., 1H), 6.75 (dd, J = 17.7, 11.0 Hz, 1H), 5.87 (s, 1H), 5.64 (dd, J = 17.7, 0.6 Hz, 1H), 5.13 (dd, J = 11.0, 0.9 Hz, 1H), 2.82 (s, 1H); MS *m/z* 399 $[M+H]^+$
92	2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.37 (1H, dd, J = 9, 3 Hz), 8.3 (1H, m), 7.72 (2H, d, J = 8.5 Hz), 7.6 (2H, d, J = 8.5 Hz), 5.96 (1H, s), 1.33 (2H, m), 1.19 (2H, m); MS *m/z* 430.1 $[M+H]^+$
94	2-(6-fluoro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.52 (1H, dd, J = 9, 3 Hz), 8.33 (1H, dd, m), 7.65 (2H, d, J = 9 Hz), 7.60 (2H, d, J = 9 Hz), 5.95 (1H, s), 3.00 (3H, s); MS *m/z* 404.2 $[M+H]^+$
101	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.19 (1H, dd, J = 11, 7.5 Hz), 7.53 (1H, dd, J = 13, 2.5 Hz), 7.44 (1H, dd, J = 10, 7.5 Hz), 7.23 (2H, m), 5.86 (1H, s), 2.89 (3H, s); MS *m/z* 437.1 $[M+H]^+$
102	N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (Methanol-d_4) δ ppm 8.18 (1H, dd, J = 11.5, 7.5 Hz), 7.44 (2H, d, J = 9 Hz), 7.40 (1H, dd, J = 11.5, 7.5 Hz), 7.14 (2H, d, 9 Hz), 6.77 (1H, t, J = 75 Hz), 5.79 (1H, s), 2.87 (1H, s); MS *m/z* 419.1 $[M+H]^+$
103	2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.38 (1H, dd, J = 9, 3 Hz), 8.29 (1H, m), 7.5 (2H, d, J = 9 Hz), 7.14 (2H, d, J = 7 Hz), 6.78 (1H, t, J = 75 Hz), 3.4 (1H, m), 1.3 (2H, m), 1.17 (2H, m); MS *m/z* 428.1 $[M+H]^+$
104	2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.77 (d, *J*=2.21 Hz, 1H), 8.43 (d, *J*=2.21 Hz, 1H), 7.60 (d, *J*=6.94 Hz, 4H), 5.91 (s, 1H) 3.05 (s, 3H); MS *m/z* 420.1 $[M+H]^+$
105	2-(6-chloro-2-ethyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.66 (d, *J*=2.52 Hz, 1H), 8.38 (d, *J*=2.21 Hz, 1H), 7.62 (dd, *J*=19.50, 9.50 Hz, 4H), 5.92 (s, 1H), 3.48 (q, *J*=7.60 Hz, 2H), 1.39 (t, *J*=7.41 Hz, 3H); MS *m/z* 434.1 $[M+H]^+$

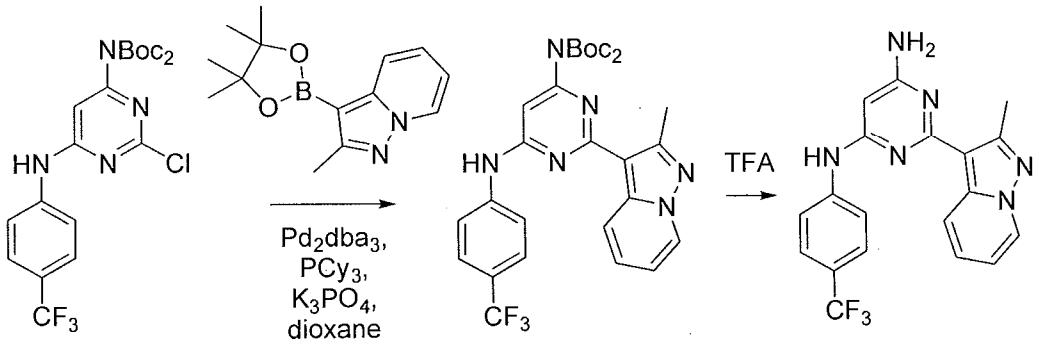
Cpd	Name & Data
146	2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(methylsulfanyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.45 - 8.50 (1H, s) 8.25 - 8.30 (1H, m) 7.55 - 7.59 (1H, m) 7.50 (2H, s) 7.32 (2H, s) 7.17 - 7.25 (2H, m) 6.24 - 6.33 (2H, m) 5.92 (1H, s) 2.51 (3H, s) 2.07 (3H, s); MS *m/z* 363.2 $[M+H]^+$
147	2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.72 - 8.80 (1H, s) 7.66 - 7.76 (3H, m) 7.46 (3H, d, *J*=0.63 Hz) 7.08 (2 H, s) 6.18 - 6.28 (2H, m) 5.97 (1H,s) 1.30 (3H, s) 1.10 (2H, s) 0.61 (2H, d, *J*=2.21 Hz); MS *m/z* 425.2 $[M+H]^+$
148	N-[4-(difluoromethoxy)phenyl]-2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ □ppm 8.49 (1H, s) 8.16 - 8.20 (1H, m) 7.55 - 7.60 (3H, m) 7.15 - 7.23 (4H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.27 (2H, br. s.) 5.92 (1H, s) 3.32 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=6.90 Hz); MS *m/z* 423.3 $[M+H]^+$
153	2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.66 (s, 1H), 7.96 - 8.10 (m, 1H), 7.73 (d, *J* = 8.83 Hz, 2H), 7.58 - 7.64 (m, 3H), 7.18 - 7.26 (m, 2H), 6.96 (br. s, 2H), 5.88 (s, 1H), 3.22 - 3.29 (m, 2H), 1.29 (t, *J* = 7.41 Hz, 3H); m.p. 183-185 ; MS *m/z* 415.4 (100) $[M+H]^+$, 416.4 (30)
156	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.49 (1H, s) 8.16 - 8.20 (1H, m) 7.55 - 7.60 (3H, m) 7.15 - 7.23 (4H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.27 (2H, br. s.) 5.92 (1H, s) 3.32 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=6.90 Hz); MS *m/z* 397.2 $[M+H]^+$
157	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.71 (1H, s) 8.13 - 8.18 (1H, m) 7.68 - 7.75 (1H, m) 7.57 - 7.62 (1H, m) 7.26 - 7.35 (2H, m) 7.16 - 7.25 (2H, m) 6.94 (1H, t, *J*=73.80 Hz) 6.36 (2H, s) 5.98 (1H, s) 3.33 (2H, q, *J*=7.60 Hz) 1.35 (3H, t, *J*=7.90 Hz); MS *m/z* 415.2 $[M+H]^+$
182	2-[2-(methylsulfanyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (br. s., 1H) 8.38 (d, *J*=7.88 Hz, 1H), 7.83 (d, *J*=8.51 Hz, 2H), 7.66 (d, *J*=8.51 Hz, 2H), 7.56 (d, *J*=7.57 Hz, 1H), 7.23 (td, *J*=7.57, 1.26 Hz, 1H), 7.13 - 7.19 (m, 1H), 6.41 (br. s., 2H), 6.02 (s, 1H), 2.63 (s, 3 H); MS *m/z* 418.3 $[M+H]^+$
196	2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.13 (1H, m), 7.58 (1H, m), 7.3-7.25 (4H, m), 7.13 (1H, d, J = 8 Hz), 5.81 (1H, s), 2.86 (3H, s), 2.31 (3H, s); MS *m/z* 331.1 $[M+H]^+$
197	N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.13 (1H, m), 7.58 (1H, m), 7.33 (2H, d, J = 9 Hz), 7.27 (2H, m), 6.94 (2H, d, J = 9 Hz), 5.72 (1H, s), 3.81 (3H, s), 2.86 (3H, s); MS *m/z* 347.1 $[M+H]^+$

Cpd	Name & Data
198	N-[4-(dimethylamino)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.12 (1H, m), 7.58 (1H, m), 7.27 (2H, m), 7.22 (2H, d, J = 9 Hz), 6.81 (2H, d, J = 9 Hz), 5.67 (1H, s), 2.92 (6H, s), 2.86 (3H, s); MS *m/z* 360.4 $[M+H]^+$
205	N-(1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.04 (1H, s), 8.20-8.17 (1H, m), 7.61-7.58 (1H, m), 7.27-7.21 (2H, m), 7.15 (1H, d, J = 1.8 Hz), 6.91 (1H, d, J = 8.2 Hz), 6.86 (1H, dd, J = 8.2, 1.8 Hz), 6.76 (2H, br s), 6.03 (2H, s), 5.72 (1H, s), 2.84 (3H, s); m.p. 166-167; MS *m/z* 359.1 $[M+H]^+$
206	N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.40 (1H, s), 8.13 (1H, dd, J = 7.0, 1.2 Hz), 7.71 (1H, d, J = 2.1 Hz), 7.61 (1H, dd, J = 7.0, 1.2 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.28-7.20 (3H, m), 6.88 (2H, br s), 5.79 (1H, s), 2.83 (3H, s); m.p.: 141-142; MS *m/z* 397.1 $[M+H]^+$
207	N-(3-fluoro-4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.19 (1H, s), 8.18-8.15 (1H, m), 7.62-7.59 (1H, m), 7.50 (1H, dd, J = 13.6, 2.2 Hz), 7.28-7.13 (4H, m), 6.82 (2H, br s), 5.76 (1H, s), 3.85 (3H, s), 2.84 (3H, s); m.p.: 233-234; MS *m/z* 365.2 $[M+H]^+$
208	N-(6-methoxypyridin-3-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.10 (1H, s), 8.24 (1H, d, J = 2.6 Hz), 8.14 (1H, dd, J = 8.4, 1.2 Hz), 7.84 (1H, dd, J = 8.8, 2.7 Hz), 7.59 (1H, dd, J = 8.4, 1.5 Hz), 7.27-7.20 (2H, m), 6.85 (1H, d, J = 8.8 Hz), 6.80 (2H, br s), 5.69 (1H, s), 3.87 (3H, s), 2.80 (3H, s); m.p.: 118-119; MS *m/z* 348.2 $[M+H]^+$
209	N-(4-chlorophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.11 (1H, m), 7.58 (1H, m), 7.45 (2H, d, J = 9 Hz), 7.28-7.23 (4H, m), 5.83 (1H, s), 2.85 (3H, s); MS *m/z* 351.6 $[M+H]^+$
210	4-{[6-amino-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.1 (1H, m), 7.75 (2H, d, J = 9 Hz), 7.61 (3H, m), 7.28 (2H, m), 5.95 (1H, s), 2.88 (3H, s); MS *m/z* 342.3 $[M+H]^+$
211	2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-nitrophenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.16 (2H, m), 8.12 (1H, m), 7.79 (2H, m), 7.62 (1H, m), 7.29 (2H, m), 5.99 (1H, s), 2.90 (3H, s); MS *m/z* 362.3 $[M+H]^+$
212	N-(4-bromophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.11 (1H, m), 7.59 (1H, m), 7.42 (4H, m), 7.27 (2H, m), 5.84 (1H, s), 2.86 (3H, s); MS *m/z* 397.0 $[M+H]^+$
221	2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.11 (1H, m), 7.57 (1H, m), 7.54 (2H, d, 9 Hz), 7.24 (2H, m), 7.19 (2H, d, J = 9 Hz), 5.84 (1H, S), 2.85 (3H, s); MS *m/z* 401.0 $[M+H]^+$

Cpd	Name & Data
234	N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.11 (1H, m), 7.57 (1H, m), 7.45 (2H, d, 7 Hz), 7.25 (2H, m), 7.09 (2H, d, J = 9 Hz), 5.48 (1H, S), 2.85 (3H, s); MS *m/z* 383.1 $[M+H]^+$
235	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Methanol-d_4) δ ppm 8.10 (1H, m), 7.58-7.54 (2H, m), 7.27-7.14 (4H, m), 5.47 (1H, s), 2.85 (3H, s); MS *m/z* 401.0 $[M+H]^+$
263	N-(4-chlorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.59 (s, 1H), 8.05 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.47 - 7.61 (m, 4H), 7.31 - 7.42 (m, 2H), 6.92 - 7.08 (m, 1H), 6.37 (br. s., 1H), 5.93 (s, 1H), 2.77 - 2.88 (m, 3H); m.p.: 183-185; MS *m/z* 369.0 $[M+H]^+$
264	2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.37 (br. s., 1H), 8.10 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.52 (dd, *J* = 5.04, 8.83 Hz, 1H), 7.34 (d, *J* = 8.20 Hz, 2H), 7.18 (d, *J* = 8.20 Hz, 2H), 6.94 - 7.07 (m, 1H), 6.27 (br. s., 2H), 5.82 - 5.96 (m, 1H), 2.85 (s, 3H), 2.32 (s, 3H); m.p.: 210-212; MS *m/z* 349.0 $[M+H]^+$
266	N-[4-(dimethylamino)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.11 - 8.16 (m, 1H), 8.07 - 8.10 (m, 1H), 7.47 - 7.56 (m, 1H), 7.23 (d, *J* = 9.77 Hz, 2H), 6.94 - 7.05 (m, 1H), 6.79 (d, *J* = 8.83 Hz, 2H), 6.09 - 6.25 (br, s, 2H), 5.67 (s, 1H), 2.94 (s, 6H), 2.85 (s, 3H); m.p.: 122-125; MS *m/z* 378.0 $[M+H]^+$
267	N-(4-chloro-3-fluorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.80 (s, 1H), 8.03 (dd, *J* = 2.52, 10.09 Hz, 1H), 7.67 (dd, *J* = 2.36, 11.82 Hz, 1H), 7.54 (dd, *J* = 5.04, 8.51 Hz, 1H), 7.44 (t, *J* = 8.67 Hz, 1H), 7.27 - 7.37 (m, 1H), 6.95 - 7.09 (m, 1H), 6.46 (br. s., 2H), 5.99 (s, 1H), 2.85 (s, 3H); m.p.: 225-227; MS *m/z* 387.0 $[M+H]^+$
268	2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.37 - 8.52 (m, 1H), 8.14 (dd, *J* = 2.68, 10.25 Hz, 1H), 7.55 (dd, *J* = 5.20, 8.67 Hz, 1H), 7.40 (br. s., 1H), 7.22 - 7.30 (m, 2H), 7.00 - 7.11 (m, 1H), 6.94 (d, *J* = 6.62 Hz, 1H), 6.27 - 6.40 (s, 2H), 5.91 - 6.06 (s, 1H), 2.89 (s, 3H), 2.34 (s, 3H); m.p.: 203-205; MS *m/z* 349.0 $[M+H]^+$
269	N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.62 (s, 1H), 8.04 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.56 (d, *J* = 1.89 Hz, 1H), 7.53 (dd, *J* = 5.04, 8.83 Hz, 1H), 7.21 - 7.29 (m, 2H), 6.97 - 7.05 (m, 1H), 6.38 (br. s., 2H), 5.91 (s, 1H), 2.83 (s, 3H); m.p.: 212-215; MS *m/z* 415.0 $[M+H]^+$

Example 9

2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 154)



A mixture of 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (53 mg, 0.205 mmol), di-*tert*-butyl 2-chloro-6-(4-(trifluoromethyl)phenylamino)pyrimidin-4-yliminodicarbonate (110 mg, 0.225 mmol), tris(dibenzylideneacetone) dipalladium(0) (18 mg, 0.02 mmol) tricyclohexylphosphine (14 mg, 0.051 mmol), and potassium phosphate (87.0 mg, 0.41 mmol) in dioxane (3.5 mL) and water (0.1 mL) was degassed by purging with argon, and then was heated at 85°C for 3 hours. The solution was cooled and filtered via plug of Celite. The filtrate was concentrated and purified by silica gel column chromatography giving tert-butyl 3,3-dimethylbutanoyl(2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-6-(4-(trifluoromethyl)phenylamino)-pyrimidin-4-yl)carbamate (25mg, 21%) as a clear oil, which was dissolved in dichloromethane (1 mL) and treated with TFA (0.1 mL) at 0°C. The resulting mixture was stirred at room temperature for 4 hours. The solvent was concentrated, and the residual material was partitioned between ethyl acetate and a saturated $NaHCO_3$ solution. The organic layer was separated, dried over Na_2SO_4, then filtered and evaporated. The residual material was triturated with ethyl ether to afford the title compound as a yellow solid (8 mg, 50%).

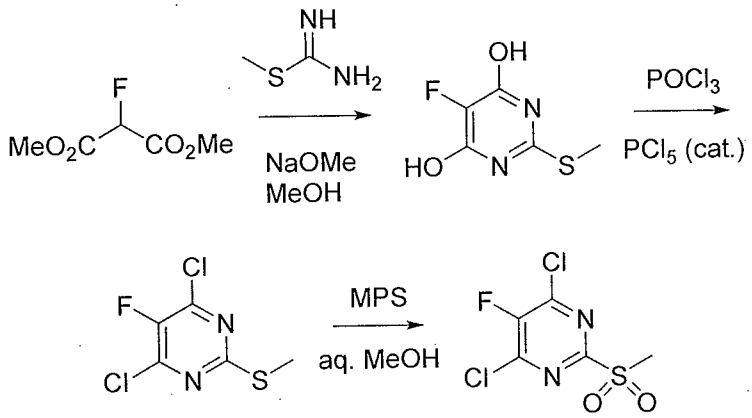
^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.55 (d, J = 8.8 Hz, 1H), 8.42 (br. s., 1H), 8.37 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.13 (ddd, J = 8.4, 7.3, 0.8 Hz, 1H), 6.77 (td, J = 6.6, 1.6 Hz, 1H), 5.82 (br. s., 2H), 5.77 (s, 1H), 2.66 (s, 3H); MS *m/z* 385.3 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 9 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
70	N-[4-(trifluoromethyl)phenyl]-2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.54 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz), 5.86 (1H, s), 5.60 (2H, v br), 3.73 (3H, s), 2.53 (3H, s), 2.50 (3H, s); m.p. 270-271 °C; MS *m/z* 363.0 $[M+H]^+$

Example 10

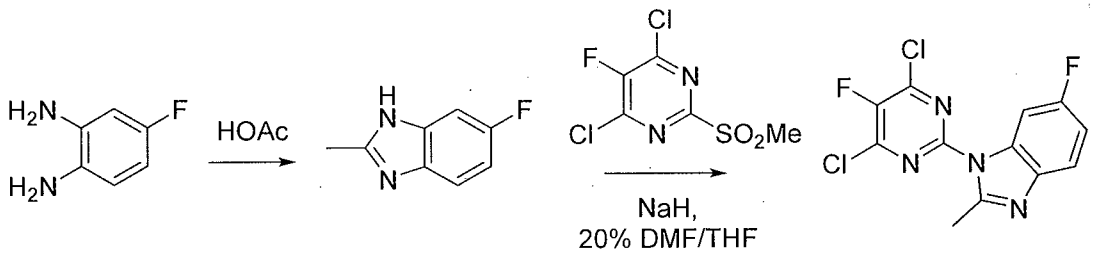
5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine (Cpd 179)



Step 1. To a solution of methyl carbamimidothioate-$(H_2SO_4)_{1/2}$ salt (45.90 g, 0.33 mol) and dimethyl 2-fluoromalonate (45.03 g, 0.30 mol) in MeOH (450 mL) at 0°C was slowly added sodium methoxide (4.37 M in MeOH, 226 mL, 0.99 mol). The mixture was stirred for 16 hours at room temperature. The solution was concentrated under reduced pressure. The resulting slurry was diluted with water (50 mL) and acidified to about pH 2 by using a 6N HCl solution. The resulting precipitate was collected, washed with water and dried under vacuum to give 5-fluoro-2-(methylthio)pyrimidine-4,6-diol (46.85 g, 88%).

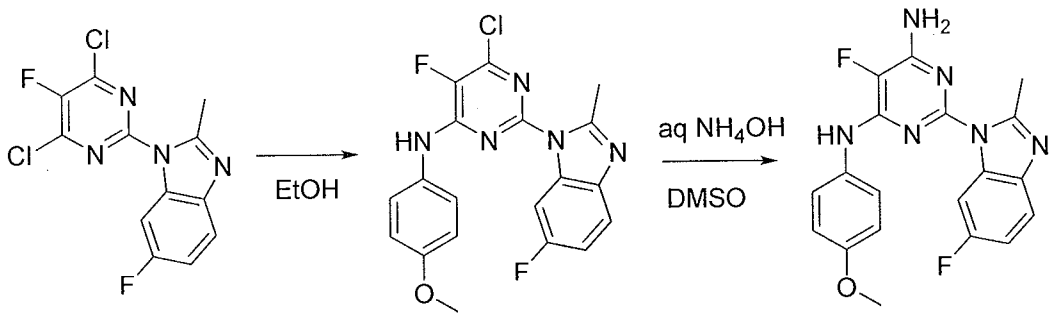
To a solution of 5-fluoro-2-(methylthio)pyrimidine-4,6-diol (13.2 g, 74.9 mmol) in $POCl_3$ (60 mL) was added a catalytic amount of PCl_5 (60 mg). The mixture was heated at 100°C for 16 hours and then concentrated under reduced pressure. To the mixture was carefully added ice water (150 mL). The resulting precipitate was removed by filtration, washed with water, then dried under nitrogen to give 4,6-dichloro-5-fluoro-2-(methylthio)pyrimidine (13.5 g, 85%).

To a solution of 4,6-dichloro-5-fluoro-2-(methylthio)pyrimidine (12.4 g, 58.8 mmol) in MeOH (150 mL) was added potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (108.7 g, 176.4 mmol) and water (70 mL). The mixture was stirred for 6 hours at room temperature. The salt was removed by filtration, then washed with MeOH until no more product was observed. The combined organic mixture was concentrated then ice water was added to the mixture to provide a precipitate, which was filtered and washed by water. The solid was dried under nitrogen to yield 4,6-dichloro-5-fluoro-2-(methylsulfonyl)pyrimidine as a white solid (14.6 g, 99%).



Step 2. A solution of 4-fluorobenzene-1,2-diamine (3.78 g, 30 mmol) in acetic acid (10.0 mL) was microwaved for 1 hour at 180°C. The mixture was concentrated under reduced pressure and triturated with ether to yield 6-fluoro-2-methyl-1H-benzo[d]imidazole as a brownish solid (4.31 g, 88%).

To a solution of 6-fluoro-2-methyl-1H-benzo[d]imidazole (2.31 g, 15.4 mmol) in THF (50 mL) and DMF (10 mL) at -78°C was added 60% NaH (648 mg, 16.2 mmol). The mixture was stirred for about 10 minutes at room temperature. To the mixture at -78°C was added 4,6-dichloro-5-fluoro-2-(methylsulfonyl)pyrimidine (3.74 g, 15.3 mmol) in one portion, then the mixture was stirred at -78°C for 15 minutes. The reaction mixture was quenched with a 1M HCl solution (18 mL) and a crude mixture was extracted with EtOAc (200 mL). The organic layer was concentrated under reduced pressure, and purified by column chromatography (5~30% EtOAc/hexanes) to give 1-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoro-2-methyl-1H-benzo[d]imidazole as a white solid (1.83 g, 38%).



Step 3. The mixture of 1-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoro-2-methyl-1H-benzo[d]-imidazole (63 mg, 0.2 mmol) and 4-methoxyaniline (49 mg, 0.4 mmol) in EtOH (1 mL) was stirred for 1 hour at 60°C. The precipitate was obtained by adding water (10 mL). The product (6-chloro-5-fluoro-2-(6-fluoro-2-methyl-1H-benzo[d]imidazol-1-yl)-N-(4-methoxyphenyl)-pyrimidin-4-amine) was removed by filtration and washed with water several times. The resulting crude 6-chloro-5-fluoro-2-(6-fluoro-2-methyl-1H-benzo[d]imidazol-1-yl)-N-(4-methoxyphenyl)pyrimidin-4-amine was used in the next step without further purification.

To the crude product in DMSO (5 mL) was added 14 M aqueous NH_4OH (3 mL). The suspended mixture was heated for 18 hours at 100°C until all the starting material was consumed. After cooling to room temperature, water (10 mL) was added to the mixture to form a precipitate. The precipitate was isolated by filtration and washed with water several times. The resulting product was dried under nitrogen to give the title compound as an off-white solid (72 mg, 94%).

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.30 (1H, br. s.) 7.94 (1H, dd, *J*=9.93, 2.36 Hz) 7.48 - 7.56 (3H, m) 6.93 - 7.05 (3H, m) 6.48 (2H, br. s.) 3.83 (3H, s) 2.75 (3H, s); MS *m/z* 383.2 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 10 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
95	5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.60 (1H, s) 8.02 (1H, dd, *J*=7.25, 2.21 Hz) 7.86 (2H, d, *J*=8.51 Hz) 7.65 (2H, d, *J*=8.51 Hz) 7.56 - 7.60 (1H, m) 7.29 (2 H, s) 7.17 - 7.26 (2H, m) 2.75 (3H, s); MS *m/z* 403.2 $[M+H]^+$

Cpd	Name & Data
106	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.39 (1H, s) 7.97 (1H, d, *J*=7.88 Hz) 7.59 - 7.64 (2H, m) 7.42 (1H, d, *J*=7.25 Hz) 7.01 - 7.11 (4H, m) 6.83 (1H, t, *J*=74.56 Hz) 6.40 (2H, br. s.) 2.63 (3H, s); MS *m/z* 401.1 $[M+H]^+$
107	2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.69 (1H, br. s.) 7.91 (1H, d, *J*=7.88 Hz) 7.85 (2H, d, *J*=8.51 Hz) 7.53 (2H, d, *J*=8.51 Hz) 7.47 (1H, d, *J*=6.94 Hz) 7.02 - 7.13 (2H, m) 6.54 (2H, br. s.) 3.14 (2H, q, *J*=7.36 Hz) 1.20 (3H, t); MS *m/z* 417.1 $[M+H]^+$
108	5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (1H, br. s.) 8.13 (1H, dd, *J*=9.46, 5.04 Hz) 7.98 (2H, d, *J*=8.51 Hz) 7.71 (2H, d, *J*=8.51 Hz) 7.31 (1H, dd, *J*=9.62, 2.36 Hz) 6.96 - 7.04 (1H, m) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 421.1 $[M+H]^+$
109	5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (1H, br. s.) 7.89 - 8.00 (3H, m) 7.71 (2H, d, *J*=8.51 Hz) 7.56 (1H, dd, *J*=8.83, 5.04 Hz) 7.02 - 7.08 (1H, m) 6.76 (2H, br. s.) 2.82 (3H, s); MS *m/z* 421.1 $[M+H]^+$
110	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.01 (1H, dd, *J*=10.40, 2.21 Hz) 7.81 (1H, br. s.) 7.68 - 7.72 (2H, m) 7.65 (1H, dd, *J*=8.83, 5.04 Hz) 7.26 - 7.31 (2H, m) 7.12 - 7.18 (1H, m) 6.87 (1H, t, *J*=74.56 Hz) 5.87 (2H, br. s.) 2.87 (3H, s); MS *m/z* 419.1 $[M+H]^+$
111	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.73 (1H, s) 7.93 (1H, dd, *J*=9.93, 2.36 Hz) 7.80 (1H, dd, *J*=12.93, 2.52 Hz) 7.51 - 7.59 (2H, m) 7.36 (1 H, t, *J*=8.99 Hz) 7.01 - 7.08 (1H, m) 6.98 (1H, t, *J*=73.77 Hz) 6.71 (2H, br. s.) 2.81 (3H, s); MS *m/z* 437.1 $[M+H]^+$
112	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.19 (1H, dd, *J*=9.46, 5.04 Hz) 7.94 (1H, br. s.) 7.79 (1H, dd, *J*=12.93, 2.52 Hz) 7.35 - 7.50 (3H, m) 7.09 - 7.16 (1H, m) 6.87 (1H, t, *J*=73.77 Hz) 5.91 (2H, s) 2.90 (3H, s); MS *m/z* 437.2 $[M+H]^+$
113	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.19 (1H, dd, *J*=9.46, 5.04 Hz) 7.81 (1H, br. s.) 7.67 - 7.74 (2H, m) 7.42 (1H, dd, *J*=9.46, 2.84 Hz) 7.25 - 7.32 (2H, m) 7.07 - 7.16 (1H, m) 6.88 (1H, t, *J*=74.56 Hz) 5.84 (2H, s) 2.88 (3H, s); MS *m/z* 419.1 $[M+H]^+$

Cpd	Name & Data
114	2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.91 (1H, s) 8.57 - 8.58 (1H, m) 8.39 (1H, d, *J*=2.21 Hz) 7.93 (2H, d, *J*=8.51 Hz) 7.75 (2H, d, *J*=8.51 Hz) 6.83 (2H, br. s.) 2.93 (3H, s); MS *m/z* 438.3 $[M+H]^+$
115	2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.47 (1H, br. s.) 8.41 (1H, d, *J*=2.21 Hz) 8.23 (1H, d, *J*=2.52 Hz) 7.55 (2H, d, *J*=8.83 Hz) 7.11 (2H, d, *J*=9.14 Hz) 6.85 (1H, t, *J*=74.10 Hz) 6.55 (2H, br. s.) 2.74 (3H, s); MS *m/z* 436.2 $[M+H]^+$
116	2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.77 (1H, s) 8.56 (1H, d, *J*=2.21 Hz) 7.73 (1H, dd, *J*=12.61, 2.52 Hz) 7.50 - 7.56 (1H, m) 7.39 (1H, t, *J*=8.99 Hz) 7.00 (1H, t, *J*=73.61 Hz) 6.79 (2H, br. s.) 2.91 (3H, s); MS *m/z* 454.1 $[M+H]^+$
117	2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.90 (1H, s) 8.22 - 8.34 (2 H, m) 7.99 (2H, d, *J*=8.20 Hz) 7.71 (2H, d, *J*=8.20 Hz) 6.84 (2H, br. s.) 3.20 - 3.29 (1H, m) 1.26 - 1.34 (2H, m) 1.06 - 1.12 (2H, m); MS *m/z* 448.1 $[M+H]^+$
119	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.71 (1H, br. s.) 8.12 (1H, d, *J*=8.51 Hz) 7.87 (1H, dd, *J*=13.08, 2.68 Hz) 7.52 - 7.62 (2H, m) 7.34 (1H, t, *J*=8.99 Hz) 7.17 - 7.27 (2H, m) 6.98 (1H, t, *J*=73.93 Hz) 6.65 (2H, br. s.) 2.81 (3H, s); MS *m/z* 419.3 $[M+H]^+$
120	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (1H, br. s.) 8.06 (2H, d, *J*=8.51 Hz) 8.00 (1H, dd, *J*=7.25, 1.26 Hz) 7.67 (2H, d, *J*=8.51 Hz) 7.50 - 7.56 (1H, m) 7.14 - 7.25 (2H, m) 6.70 (2H, br. s.) 2.96 - 3.05 (1H, m) 1.20 - 1.26 (2H, m) 1.00 - 1.06 (2H, m); MS *m/z* 429.2 $[M+H]^+$
121	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.40 (1H, s) 7.86 (1H, dd, *J*=7.72, 1.73 Hz) 7.63 - 7.70 (2H, m) 7.36 (1H, d, *J*=9.14 Hz) 6.98 - 7.08 (4H, m) 6.64 - 6.97 (1H, m) 6.41 (2H, s) 2.83 - 2.91 (1H, m) 1.01 - 1.07 (2H, m) 0.80 - 0.87 (2H, m); MS *m/z* 427.2 $[M+H]^+$

Cpd	Name & Data
122	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.73 (1H, s) 7.96 - 8.03 (2H, m) 7.50 - 7.60 (2H, m) 7.32 (1H, t, *J*=8.83 Hz) 7.20 (2H, dtd, *J*=19.70, 7.33, 7.33, 1.26 Hz) 6.80 - 7.13 (2H, m) 6.66 (2H, s) 2.97 - 3.05 (1H, m) 1.23 (2H, dd, *J*=5.04, 2.84 Hz) 1.01 - 1.08 (2H, m); MS *m/z* 445.2 $[M+H]^+$
123	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.52 - 8.56 (1H, s) 8.04 - 8.09 (1H, m) 7.76 (2H, d, *J*=9.14 Hz) 7.57 - 7.61 (1H, m) 7.19 (4H, d, *J*=8.83 Hz) 6.97 (1H, m) 6.49 - 6.58 (2H, s) 3.25 (2H, d, *J*=7.57 Hz) 1.29 - 1.34 (3H, m); MS *m/z* 415.3 $[M+H]^+$
124	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.72 (1H, s) 8.05 - 8.09 (1H, m) 7.87 (1H, dd, *J*=12.93, 2.52 Hz) 7.59 - 7.63 (1H, m) 7.54 (1H, ddd, *J*=8.91, 2.60, 1.42 Hz) 7.33 (1H, t, *J*=8.83 Hz) 7.18 - 7.27 (2H, m) 6.98 (1H, t, *J*=74.70 Hz) 6.64 (2H, s) 3.28 (2H, q, *J*=7.36 Hz) 1.35 (3H, t, *J*=7.90 Hz); MS *m/z* 433.3 $[M+H]^+$
125	2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.69 - 8.75 (1H, m) 7.97 - 8.04 (1H, m) 7.76 - 7.83 (2H, m) 7.55 - 7.61 (2H, m) 7.30 - 7.37 (1H, m) 6.59 - 6.69 (2H, m) 2.68 (3H, s); MS *m/z* 439.2 $[M+H]^+$
126	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.72 - 8.76 (1H, m) 8.12 - 8.18 (1H, m) 7.74 - 7.80 (1H, m) 7.45 - 7.55 (2H, m) 7.34 - 7.40 (1H, m) 6.90 - 7.05 (1H, m) 6.69 - 6.78 (2H, m) 2.82 (3H, s); MS *m/z* 455.2 $[M+H]^+$
127	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 - 8.90 (1H, m) 7.93 - 7.99 (2H, m) 7.77 - 7.82 (1H, m) 7.72 (2H, s) 6.90 - 6.97 (1H, m) 6.73 - 6.84 (2H, m) 2.83 (3H, s); MS *m/z* 439.2 $[M+H]^+$
128	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.71 - 8.79 (1H, m) 7.74 - 7.82 (2H, m) 7.48 - 7.55 (1H, m) 7.33 - 7.40 (1H, m) 6.83 - 7.15 (3H, m) 6.70 - 6.79 (2H, m) 2.82 (3H, s); MS *m/z* 455.2 $[M+H]^+$

Cpd	Name & Data
129	2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.89 (1H, s) 7.95 (2H, d, *J*=8.51 Hz) 7.66 - 7.77 (3H, m) 6.90 - 6.98 (1H, m) 6.79 (2H, br. s.) 3.30 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=7.41 Hz); MS *m/z* 453.2 $[M+H]^+$
130	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.75 (1H, s) 7.72 - 7.81 (2H, m) 7.51 (1H, ddd, *J*=8.91, 2.60, 1.42 Hz) 7.35 (1H, t, *J*=8.83 Hz) 6.81 - 7.14 (2H, m) 6.74 (2H, br. s.) 3.28 (2H, q, *J*=7.25 Hz) 1.34 (3H, t, *J*=7.41 Hz); MS *m/z* 469.2 $[M+H]^+$
131	N-[4-(difluoromethoxy)phenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.59 (1H, s) 7.79 (1H, ddd, *J*=9.85, 2.44, 0.95 Hz) 7.69 - 7.74 (2H, m) 7.20 - 7.24 (2H, m) 6.81 - 7.13 (2H, m) 6.65 (2H, br. s.) 2.78 (3H, s); MS *m/z* 437.2 $[M+H]^+$
132	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.59 (1H, s) 7.75 (1H, ddd, *J*=9.77, 2.21, 0.95 Hz) 7.68 - 7.72 (2H, m) 7.18 - 7.25 (2H, m) 6.81 - 7.13 (2H, m) 6.65 (2 H, s) 3.25 (2H, q, *J*=7.57 Hz) 1.28 - 1.33 (3H, m); MS *m/z* 451.2 $[M+H]^+$
133	N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, br. s.) 8.15 (1H, dd, *J*=11.82, 7.72 Hz) 7.68 - 7.74 (2H, m) 7.46 (1H, dd, *J*=10.72, 7.57 Hz) 7.21 - 7.26 (2H, m) 7.05 (2H, t, *J*=76.30 Hz) 6.65 (2H, s) 2.78 (3H, s); MS *m/z* 437.3 $[M+H]^+$
134	5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.87 (1H, br. s.) 7.99 (2H, d, *J*=8.51 Hz) 7.92 (1H, d, *J*=8.20 Hz) 7.69 (2H, d, *J*=8.51 Hz) 7.19 (1H, td, *J*=8.20, 5.04 Hz) 7.01 (1H, dd, *J*=10.72, 7.25 Hz) 6.74 (2H, br. s.) 2.83 (3H, s); MS *m/z* 421.2 $[M+H]^+$
135	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, s) 7.92 (1H, d, *J*=9.14 Hz) 7.72 - 7.78 (2H, m) 6.80 - 7.24 (5H, m) 6.59 (2H, br. s.) 2.79 (3H, s); MS *m/z* 418.2 $[M+H]^+$
136	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.74 (1H, s) 7.93 (1H, d, *J*=7.57 Hz) 7.85 (1H, dd, *J*=12.93, 2.52 Hz) 7.51 - 7.57 (1H, m) 7.34 (1H, t, *J*=8.99 Hz) 6.82 - 7.23 (3H, m) 6.69 (2H, s) 2.86 (3H, s); MS *m/z* 437.2 $[M+H]^+$

Cpd	Name & Data
137	5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.88 (1H, br. s.) 8.47 (1H, dd, *J*=8.04, 1.73 Hz) 8.40 - 8.44 (1H, m) 7.92 - 8.00 (2H, m) 7.72 (2H, d, *J*=8.51 Hz) 7.18 - 7.23 (1H, m) 6.70 - 6.80 (2H, m) 2.90 (3H, s); MS *m/z* 404.2 $[M+H]^+$
138	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.58 (1H, s) 8.46 (1H, dd, *J*=8.20, 1.58 Hz) 8.40 (1H, dd, *J*=4.73, 1.58 Hz) 7.70 - 7.76 (2H, m) 7.21 - 7.25 (2H, m) 7.15 - 7.19 (1H, m) 6.99 (2H, s) 6.56 - 6.66 (2H, m) 2.86 (3H, s); MS *m/z* 402.2 $[M+H]^+$
139	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.75 (1H, br. s.) 8.45 - 8.50 (1H, m) 8.42 (1H, dd, *J*=4.73, 1.58 Hz) 7.80 (1H, dd, *J*=12.61, 2.52 Hz) 7.53 (1H, dt, *J*=9.06, 1.93 Hz) 7.37 (1H, t, *J*=8.83 Hz) 7.20 (1H, dd, *J*=8.20, 4.73 Hz) 6.83 - 7.16 (2H, m) 6.72 (2H, br. s.) 2.89 (3H, s); MS *m/z* 420.2 $[M+H]^+$
140	2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.88 (1H, s) 8.05 (2H, d, *J*=8.51 Hz) 7.81 (1H, dd, *J*=8.20, 0.63 Hz) 7.67 (2H, d, *J*=8.51 Hz) 7.16 (1H, td, *J*=8.12, 4.89 Hz) 6.95 - 7.02 (1H, m) 6.74 (2H, s) 2.96 - 3.03 (1H, m) 1.24 - 1.29 (2H, m) 1.03 - 1.08 (2H, m); MS *m/z* 447.2 $[M+H]^+$
141	2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.59 (1H, s) 7.77 - 7.84 (3H, m) 7.16 - 7.20 (2H, m) 7.12 - 7.16 (1H, m) 6.81 - 7.11 (2H, m) 6.61 (2H, s) 3.01 (1H, tt, *J*=8.28, 4.97 Hz) 1.20 - 1.24 (2H, m) 1.03 (2H, dq, *J*=8.32, 3.43 Hz); MS *m/z* 445.2 $[M+H]^+$
142	2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.77 (1H, s) 7.99 (1H, dd, *J*=12.93, 2.52 Hz) 7.83 (1H, dd, *J*=8.20, 0.95 Hz) 7.57 (1H, ddd, *J*=9.06, 2.60, 1.58 Hz) 7.33 (1H, t, *J*=8.99 Hz) 7.18 (1H, td, *J*=8.12, 4.89 Hz) 6.83 - 7.13 (2H, m) 6.72 (2 H, s) 3.01 (1H, tt, *J*=8.28, 4.97 Hz) 1.23 - 1.30 (2H, m) 1.08 (2H, dq, *J*=8.32, 3.43 Hz); MS *m/z* 463.2 $[M+H]^+$
155	2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.62 (1H, s) 8.23 - 8.32 (2H, m) 7.72 - 7.78 (2H, m) 7.18 - 7.24 (2H, m) 6.98 (1H, t, *J*=75.30 Hz) 6.71 (2H, br. s.) 3.27 (1H, tt, *J*=8.28, 4.97 Hz) 1.25 (2H, dd, *J*=4.89, 3.00 Hz) 1.05 (2H, dd, *J*=8.20, 3.15 Hz); MS *m/z* 446.2 $[M+H]^+$

Cpd	Name & Data
158	2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.82 (1H, d, *J*=1.58 Hz) 8.11 (1H, d, *J*=8.20 Hz) 7.92 - 7.99 (2H, m) 7.69 (2H, d, *J*=8.51 Hz) 7.58 (1H, d, *J*=2.21 Hz) 7.19 (1H, dd, *J*=8.83, 2.21 Hz) 6.70 (2H, br. s.) 2.82 (3H, s); MS *m/z* 437.2 $[M+H]^+$
159	2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.42 (1H, s) 7.95 - 8.00 (1H, m) 7.55 - 7.62 (2H, m) 7.43 (1H, d, *J*=1.58 Hz) 7.01 - 7.10 (3H, m) 6.84 (1H, t, *J*=75.30 Hz) 6.44 (2H, br. s.) 2.64 (3H, s); MS *m/z* 435.2 $[M+H]^+$
160	2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.83 (1H, br. s.) 8.19 (1H, d, *J*=1.58 Hz) 7.94 (2H, d, *J*=8.20 Hz) 7.70 (3H, d, *J*=8.51 Hz) 7.55 (1H, d, *J*=8.51 Hz) 7.21 - 7.27 (1H, m) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 437.2 $[M+H]^+$
161	2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, s) 8.17 - 8.22 (1H, m) 7.70 - 7.77 (2H, m) 7.55 (1H, d, *J*=8.20 Hz) 7.20 - 7.26 (3H, m) 6.97 (1H, t, *J*=74.70 Hz) 6.62 (2H, br. s.) 2.80 (3H, s); MS *m/z* 435.2 $[M+H]^+$
162	2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (1H, br. s.) 8.08 (1H, dd, *J*=8.67, 5.20 Hz) 7.97 (2H, d, *J*=8.20 Hz) 7.64 - 7.73 (2H, m) 7.33 (1H, d, *J*=6.62 Hz) 6.98 - 7.04 (1H, m) 6.72 (2H, br. s.) 3.29 (2H, q, *J*=7.36 Hz) 1.34 (3H, t, *J*=8.20 Hz); MS *m/z* 435.3 $[M+H]^+$
163	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.56 (1H, s) 8.09 (1H, dd, *J*=9.46, 5.04 Hz) 7.69 - 7.75 (2H, m) 7.31 (1H, dd, *J*=9.30, 2.68 Hz) 7.18 - 7.24 (2H, m) 6.81 - 7.14 (2H, m) 6.57 (2H, br. s.) 3.22 - 3.29 (2H, m) 1.27 - 1.34 (3H, m); MS *m/z* 433.3 $[M+H]^+$
164	2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.85 (1H, s) 7.96 (2H, d, *J*=8.51 Hz) 7.89 (1H, dd, *J*=10.09, 2.52 Hz) 7.70 (2H, d, *J*=8.51 Hz) 7.59 (1H, dd, *J*=8.51, 5.04 Hz) 7.01 - 7.09 (1H, m) 6.75 (2H, br. s.) 3.29 (2H, q, *J*=7.46 Hz) 1.33 (3H, t, *J*=14.80 Hz); MS *m/z* 435.3 $[M+H]^+$
165	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.56 (1H, s) 7.90 (1H, dd, *J*=10.40, 2.52 Hz) 7.68 - 7.75 (2H, m) 7.56 (1H, dd, *J*=8.83, 5.04 Hz) 7.18 - 7.26 (2H, m) 6.81 - 7.12 (2H, m) 6.61 (2H, br. s.) 3.25 (2H, q, *J*=7.46 Hz) 1.26 - 1.34 (3H, m); MS *m/z* 433.3 $[M+H]^+$

Cpd	Name & Data
172	5-methyl-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.19 (1H, s) 8.14 (1H, dt, *J*=8.20, 0.95 Hz) 7.87 (2H, d, *J*=8.51 Hz) 7.64 (2H, d, *J*=8.51 Hz) 7.55 - 7.60 (1H, m) 7.22 (1H, ddd, *J*=8.04, 7.09, 1.26 Hz) 7.15 (1H, ddd, *J*=8.28, 7.17, 1.26 Hz) 6.31 (2H, br. s.) 2.80 (3H, s) 2.22 (3H, s); MS *m/z* 399.2 $[M+H]^+$
183	5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[6-(trifluoromethyl)pyridin-3-yl]pyrimidine-4,6-diamine ^{1}H NMR (Methanol-d_4) δ ppm 8.92 (1H, d, J = 2.5 Hz), 8.34 (1H, dd, J = 8.5, 2.4 Hz), 7.81 (1H, dd, J = 9.8, 2.5 Hz), 7.75 (1H, d, J = 8.7 Hz), 7.54 (1H, dd, J = 8.7, 5 Hz), 7.06 (1H, td, J = 9.2, 2.5 Hz), 2.82 (3H, s); MS *m/z* 422.3 $[M+H]^+$
184	5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.37 (br. s., 1H), 7.94 (dd, J = 10.4, 2.5 Hz, 1H), 7.50 - 7.58 (m, 3H), 7.20 (d, J = 8.2 Hz, 2H), 7.01 (ddd, J = 9.8, 8.8, 2.5 Hz, 1H), 6.52 (br. s., 2H), 2.78 (s, 3H), 2.34 (s, 3H); MS *m/z* 367.2 $[M+H]^+$
185	N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.58 (br. s., 7H), 7.93 (dd, J = 10.2, 2.7 Hz, 1H), 7.70 - 7.76 (m, 2H), 7.54 (dd, J = 8.7, 5.2 Hz, 1H), 7.37 - 7.42 (m, 2H), 7.03 (ddd, J = 9.8, 8.8, 2.5 Hz, 1H), 6.63 (br. s., 2H), 2.79 (s, 3H); MS *m/z* 387.2 $[M+H]^+$
189	5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.43 (br. s., 1H), 7.97 (dd, J = 10.1, 2.5 Hz, 1H), 7.54 (dd, J = 8.8, 5.0 Hz, 1H), 7.32 - 7.37 (m, 1H), 7.23 - 7.31 (m, 2H), 7.03 (ddd, J = 9.5, 8.7, 2.8 Hz, 1H), 6.68 - 6.75 (m, 1H), 6.57 (br. s., 2H), 3.77 (s, 3H), 2.81 (s, 3H); MS *m/z* 383.2 $[M+H]^+$
190	N-(3-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.63 (br. s., 1H), 7.96 (dd, J = 10.1, 2.5 Hz, 1H), 7.91 (t, J = 2.0 Hz, 1H), 7.62 (ddd, J = 8.3, 2.0, 0.8 Hz, 1H), 7.55 (dd, J = 8.8, 5.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.14 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.04 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 6.68 (br. s., 2H), 2.82 (s, 3H); MS *m/z* 387.2 $[M+H]^+$
191	5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.21 (br. s., 1H), 8.49 (dd, J = 10.2, 2.7 Hz, 1H), 8.32 - 8.42 (m, 2H), 8.10 (dd, J = 8.7, 5.2 Hz, 1H), 7.91 (dd, J = 9.1, 0.9 Hz, 2H), 7.59 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 7.21 (br. s., 2H), 3.34 (s, 3H); MS *m/z* 437.2 $[M+H]^+$

Cpd	Name & Data
192	4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.79 (br. s., 1H), 7.80 - 7.86 (m, 2H), 7.78 (dd, J = 10.1, 2.5 Hz, 1H), 7.61 (dt, J = 8.8, 2.5 Hz, 2H), 7.42 (dd, J = 8.8, 5.0 Hz, 1H), 6.91 (ddd, J = 9.5, 8.5, 2.6 Hz, 1H), 6.65 (br. s., 2H), 2.67 (s, 3H); MS *m/z* 378.2 $[M+H]^+$
193	methyl 4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzoate ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.82 (br. s., 1H), 7.99 - 8.04 (m, 2H), 7.96 (dd, J = 10.1, 2.5 Hz, 1H), 7.85 - 7.90 (m, 2H), 7.56 (dd, J = 8.8, 5.0 Hz, 1H), 7.05 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 6.73 (br. s., 2H), 3.88 (s, 3H), 2.83 (s, 3H); MS *m/z* 411.2 $[M+H]^+$
194	5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.36 (1H, br. s.) 8.19 (1H, d, *J*=8.51 Hz) 7.64 (1H, s) 7.57 (1H, d, *J*=7.57 Hz) 7.46 (1H, dd, *J*=8.20, 2.21 Hz) 7.16 - 7.26 (3H, m) 6.94 (1H, d, *J*=7.57 Hz) 6.49 (2H, br. s.) 2.81 (3H, s) 2.33 (3H, s); MS *m/z* 439.2 $[M+H]^+$
195	5-fluoro-N-(3-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.42 (1H, br. s.) 8.13 - 8.18 (1H, m) 7.58 (1H, d, *J*=7.25 Hz) 7.40 (1H, t, *J*=2.21 Hz) 7.16 - 7.32 (4H, m) 6.67 - 6.71 (1H, m) 6.52 (2H, br. s.) 3.75 (3H, s) 2.82 (3H, s); MS *m/z* 365.2 $[M+H]^+$
199	5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.35 (1H, br. s.) 8.13 (1H, d, *J*=8.20 Hz) 7.54 - 7.61 (3H, m) 7.12 - 7.24 (4H, m) 6.45 (2H, br. s.) 2.78 (3H, s) 2.33 (3H, s); MS *m/z* 349.2 $[M+H]^+$
200	5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.28 (1H, br. s.) 8.12 (1H, d, *J*=8.20 Hz) 7.52 - 7.60 (3H, m) 7.12 - 7.24 (2H, m) 6.93 - 6.98 (2H, m) 6.41 (2H, br. s.) 3.82 (3H, s) 2.76 (3H, s); MS *m/z* 365.2 $[M+H]^+$
201	N-(4-chlorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, br. s.) 8.07 - 8.14 (1H, m) 7.73 - 7.80 (2H, m) 7.58 (1H, d, *J*=6.94 Hz) 7.35 - 7.42 (2H, m) 7.15 - 7.26 (2H, m) 6.56 (2H, br. s.) 2.79 (3H, s); MS *m/z* 369.2 $[M+H]^+$
202	4-{[6-amino-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.92 (1H, br. s.) 8.08 - 8.13 (1H, m) 7.97 - 8.03 (2H, m) 7.71 - 7.77 (2H, m) 7.56 - 7.62 (1H, m) 7.24 (2H, quind, *J*=7.33, 7.33, 7.33, 7.33, 1.58 Hz) 6.73 (2H, br. s.) 2.80 - 2.83 (3H, m); MS *m/z* 360.2 $[M+H]^+$

Cpd	Name & Data
203	N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.33 (1H, br. s.) 8.15 (1H, d, *J*=6.62 Hz) 7.56 (1H, d, *J*=7.25 Hz) 7.28 (1H, d, *J*=2.21 Hz) 7.16 - 7.25 (2H, m) 7.09 (1H, dd, *J*=8.51, 2.21 Hz) 6.85 (1H, d, *J*=8.51 Hz) 6.45 (2H, br. s.) 6.02 (2H, s) 2.79 (3H, s); MS *m/z* 379.2 $[M+H]^+$
204	5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.63 (1H, br. s.) 8.11 (1H, d, *J*=7.57 Hz) 7.80 - 7.89 (2H, m) 7.57 (1H, d, *J*=7.88 Hz) 7.31 - 7.38 (2H, m) 7.15 - 7.26 (2H, m) 6.58 (2H, br. s.) 2.79 (3H, s); MS *m/z* 419.1 $[M+H]^+$
213	2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.40 (1H, br. s.) 8.15 (1H, dd, *J*=11.98, 7.88 Hz) 7.49 - 7.55 (2H, m) 7.44 (1H, dd, *J*=10.72, 7.57 Hz) 7.21 (2H, d, *J*=8.20 Hz) 6.55 (2H, br. s.) 2.79 (3H, s) 2.35 (3H, s); MS *m/z* 385.2 $[M+H]^+$
214	2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.30 (1H, br. s.) 8.12 (1H, dd, *J*=11.98, 7.88 Hz) 7.46 - 7.51 (2H, m) 7.41 (1H, dd, *J*=10.72, 7.57 Hz) 6.93 - 6.98 (2H, m) 6.48 (2H, br. s.) 3.81 (3H, s) 2.75 (3H, s); MS *m/z* 401.3 $[M+H]^+$
215	N-(4-chlorophenyl)-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.61 (1H, br. s.) 8.15 (1H, dd, *J*=11.82, 7.72 Hz) 7.68 - 7.73 (2H, m) 7.38 - 7.50 (3 H, m) 6.66 (2H, br. s.) 2.80 (3H, s); MS *m/z* 405.2 $[M+H]^+$
216	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.53 (1H, s) 8.13 - 8.17 (1H, m) 7.73 - 7.79 (2H, m) 7.64 - 7.69 (1H, m) 7.19 - 7.30 (4H, m) 6.82 - 7.13 (1H, m) 6.54 (2H, br. s.) 5.02 (2H, s) 3.28 (3H, s); MS *m/z* 431.3 $[M+H]^+$
217	5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.36 (1H, br. s.) 8.18 (1H, dd, *J*=6.78, 1.73 Hz) 7.66 (1H, dd, *J*=6.62, 1.89 Hz) 7.54 - 7.60 (2H, m) 7.17 - 7.30 (4H, m) 6.46 (2H, br. s.) 4.99 - 5.04 (2H, m) 3.28 (3H, s) 2.34 (3H, s); MS *m/z* 379.3 $[M+H]^+$

Cpd	Name & Data
218	5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.31 (1H, br. s.) 8.14 - 8.19 (1H, m) 7.65 (1H, dd, *J*=6.78, 1.73 Hz) 7.53 - 7.59 (2H, m) 7.25 (2H, quind, *J*=7.41, 7.41, 7.41, 7.41, 1.58 Hz) 6.93 - 6.99 (2H, m) 6.43 (2H, br. s.) 4.97 - 5.02 (2H, m) 3.82 (3H, s); MS *m/z* 395.3 $[M+H]^+$
219	N-(4-chlorophenyl)-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.58 (1H, br. s.) 8.12 - 8.17 (1H, m) 7.73 - 7.79 (2H, m) 7.65 - 7.70 (1H, m) 7.37 - 7.41 (2H, m) 7.24 - 7.32 (2H, m) 6.58 (2H, br. s.) 5.03 (2H, s) 3.29 (3H, s); MS *m/z* 399.2 $[M+H]^+$
220	5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.83 (1H, br. s.) 8.11 - 8.18 (1H, m) 7.96 - 8.03 (2H, m) 7.66 - 7.73 (3H, m) 7.25 - 7.33 (2H, m) 6.68 (2H, br. s.) 5.05 (2H, s) 3.29 (3H, s); MS *m/z* 433.2 $[M+H]^+$
222	1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.91 (1H, s) 8.63 (1H, d, *J*=1.58 Hz) 7.92 - 7.99 (2H, m) 7.74 (3H, t, *J*=8.51 Hz) 7.61 (1H, dd, *J*=8.20, 1.58 Hz) 6.84 (2H, br. s.) 2.90 (3H, s); MS *m/z* 428.3 $[M+H]^+$
223	1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.58 - 8.63 (2H, m) 7.68 - 7.75 (3H, m) 7.57 - 7.62 (1H, m) 7.22 - 7.27 (2H, m) 6.84 - 7.16 (1H, m) 6.68 (2H, br. s.) 2.87 (3H, s); MS *m/z* 426.3 $[M+H]^+$
224	1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.61 (1H, s) 8.42 (1H, br. s.) 7.71 (1H, d, *J*=8.20 Hz) 7.49 - 7.60 (3H, m) 7.24 (2H, d, *J*=7.88 Hz) 6.58 (2H, br. s.) 2.87 (3H, s) 2.36 (3H, s); MS *m/z* 374.3 $[M+H]^+$
225	1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.62 (1H, s) 8.37 (1H, s) 7.71 (1H, d, *J*=8.20 Hz) 7.49 - 7.60 (3H, m) 6.98 - 7.03 (2H, m) 6.57 (2H, br. s.) 3.84 (3H, s) 2.84 (3H, s); MS *m/z* 390.3 $[M+H]^+$
226	1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.60 (1H, s) 8.28 (1H, dd, *J*=8.51, 0.63 Hz) 8.00 (1H, dd, *J*=1.58, 0.63 Hz) 7.70 - 7.77 (2H, m) 7.55 (1H, dd, *J*=8.51, 1.58 Hz) 7.19 - 7.25 (2H, m) 6.98 (1H, t, *J*=75.00 Hz) 6.63 (2H, br. s.) 2.83 (3H, s); MS *m/z* 426.3 $[M+H]^+$

Cpd	Name & Data
227	1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.42 (1H, br. s.) 8.31 (1H, s) 7.99 (1H, s) 7.50 - 7.57 (3H, m) 7.20 (2H, d, *J*=8.20 Hz) 6.55 (2H, br. s.) 2.83 (3H, s) 2.34 (3H, s); MS *m/z* 374.3 $[M+H]^+$
228	1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.33 - 8.39 (1H, m) 8.29 (1H, d, *J*=8.51 Hz) 7.98 (1H, s) 7.49 - 7.56 (3H, m) 6.95 - 7.00 (2H, m) 6.51 (2H, br. s.) 3.83 (3H, s) 2.81 (3H, s); MS *m/z* 390.4 $[M+H]^+$
229	1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.90 (1H, s) 8.28 (1H, d, *J*=8.51 Hz) 8.02 (1H, s) 7.97 (2H, d, *J*=8.51 Hz) 7.71 (2H, d, *J*=8.20 Hz) 7.58 (1H, dd, *J*=8.51, 1.58 Hz) 6.78 (2H, br. s.) 2.87 (3H, s); MS *m/z* 428.3 $[M+H]^+$
230	1-{4-amino-6-[(4-chlorophenyl)amino]-5-fluoropyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.64 (1H, br. s.) 8.28 (1H, dd, *J*=8.51, 0.63 Hz) 8.01 (1H, d, *J*=1.58 Hz) 7.70 - 7.76 (2H, m) 7.57 (1H, dd, *J*=8.51, 1.58 Hz) 7.36 - 7.43 (2H, m) 6.67 (2H, br. s.) 2.84 (3H, s); MS *m/z* 394.2 $[M+H]^+$
231	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.02 (1H, d, *J*=2.84 Hz) 8.62 (1H, br. s.) 8.19 (1H, dd, *J*=8.83, 2.52 Hz) 7.71 - 7.77 (3H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.68 (2H, s) 2.88 (3H, s); MS *m/z* 446.2 $[M+H]^+$
232	5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.03 (1H, d, *J*=2.84 Hz) 8.45 (1H, br. s.) 8.18 (1H, dd, *J*=8.83, 2.21 Hz) 7.74 (1H, d, *J*=8.83 Hz) 7.53 - 7.59 (2H, m) 7.18 (2H, d, *J*=7.88 Hz) 6.61 (2H, br. s.) 2.87 (3H, s) 2.32 (3H, s); MS *m/z* 394.2 $[M+H]^+$
233	5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.03 (1H, d, *J*=1.89 Hz) 8.38 (1H, br. s.) 8.17 (1H, dd, *J*=8.83, 2.21 Hz) 7.73 (1H, d, *J*=8.83 Hz) 7.52 - 7.60 (2H, m) 6.92 - 6.99 (2H, m) 6.57 (2H, br. s.) 3.80 (3H, s) 2.54 (3H, s); MS *m/z* 410.2 $[M+H]^+$
236	5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.04 (1H, d, *J*=2.52 Hz) 8.90 (1H, br. s.) 8.21 (1H, dt, *J*=8.83, 1.42 Hz) 7.99 (2H, dd, *J*=8.35, 3.31 Hz) 7.77 (1H, d, *J*=8.83 Hz) 7.70 (2H, d, *J*=8.51 Hz) 6.83 (2H, br. s.) 2.92 (3H, s); MS *m/z* 448.2 $[M+H]^+$

Cpd	Name & Data
237	N-(4-chlorophenyl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.62 (1H, br. s.) 7.79 (1H, dd, *J*=10.25, 2.05 Hz) 7.69 - 7.74 (2H, m) 7.37 - 7.44 (2H, m) 6.92 (1H, td, *J*=10.25, 2.21 Hz) 6.67 (2H, br. s.) 2.79 - 2.80 (3H, m); MS *m/z* 405.2 $[M+H]^+$
238	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.69 (1H, s) 7.75 - 7.85 (3H, m) 7.36 (2H, d, *J*=8.20 Hz) 6.92 (1H, td, *J*=10.25, 2.52 Hz) 6.69 (2H, br. s.) 2.79 (3H, s); MS *m/z* 456.1 $[M+H]^+$
240	N-(1,3-benzodioxol-5-yl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.37 (1H, br. s.) 7.80 (1H, dd, *J*=9.46, 1.89 Hz) 7.20 (1H, d, *J*=2.21 Hz) 7.05 (1H, dd, *J*=8.35, 2.05 Hz) 6.84 - 6.92 (2H, m) 6.55 (2H, br. s.) 6.02 (2H, s) 2.79 (3H, s); MS *m/z* 416.2 $[M+H]^+$
241	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.41 (1H, br. s.) 7.80 (1H, dd, *J*=9.93, 2.36 Hz) 7.50 - 7.56 (2H, m) 7.20 (2H, d, *J*=8.20 Hz) 6.90 (1H, td, *J*=10.25, 2.52 Hz) 6.56 (2H, br. s.) 2.79 (3H, s) 2.34 (3H, s); MS *m/z* 386.2 $[M+H]^+$
242	2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.34 (1H, br. s.) 7.76 - 7.83 (1H, m) 7.47 - 7.55 (2H, m) 6.94 - 7.00 (2H, m) 6.89 (1H, td, *J*=10.25, 2.21 Hz) 6.52 (2H, br. s.) 3.82 (3H, s) 2.76 (3H, s); MS *m/z* 402.2 $[M+H]^+$
243	2-(5,7-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.86 (1H, br. s.) 8.15 (1H, dd, *J*=11.66, 7.88 Hz) 7.91 - 7.98 (2H, m) 7.72 (2H, d, *J*=8.51 Hz) 7.48 (1H, dd, *J*=10.72, 7.57 Hz) 6.78 (2H, br. s.) 2.83 (3H, s); MS *m/z* 439.3 $[M+H]^+$
244	5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.82 (1H, br. s.) 8.00 (2H, d, *J*=8.51 Hz) 7.65 - 7.73 (3H, m) 7.45 (1H, d, *J*=8.51 Hz) 6.83 - 6.89 (1H, m) 6.67 (2H, br. s.) 3.64 - 3.69 (3H, m) 2.78 (3H, s); MS *m/z* 434.2 $[M+H]^+$
245	N-(4-chlorophenyl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, br. s.) 7.74 - 7.79 (2H, m) 7.68 (1H, d, *J*=2.52 Hz) 7.44 (1H, d, *J*=8.51 Hz) 7.35 - 7.41 (2H, m) 6.85 (1H, dd, *J*=8.83, 2.52 Hz) 6.57 (2H, br. s.) 3.69 (3H, s) 2.75 (3H, s); MS *m/z* 399.2 $[M+H]^+$

Cpd	Name & Data
246	5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.64 (1H, s) 7.84 - 7.89 (2H, m) 7.69 (1H, d, *J*=2.21 Hz) 7.44 (1H, d, *J*=8.83 Hz) 7.34 (2H, d, *J*=8.20 Hz) 6.85 (1H, dd, *J*=8.51, 2.52 Hz) 6.58 (2H, br. s.) 3.68 (3H, s) 2.75 (3H, s); MS *m/z* 449.2 $[M+H]^+$
247	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.52 (1H, s) 7.74 - 7.79 (2H, m) 7.69 (1H, d, *J*=2.52 Hz) 7.43 (1H, d, *J*=8.51 Hz) 7.17 - 7.23 (2H, m) 6.81 - 7.12 (2H, m) 6.53 (2H, br. s.) 3.69 (3H, s) 2.74 (3H, s); MS *m/z* 432.2 $[M+H]^+$
248	5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.34 (1H, br, s) 7.70 (1H, d, *J*=2.52 Hz) 7.56 - 7.60 (2H, m) 7.42 (1H, d, *J*=8.83 Hz) 7.17 (2H, d, *J*=8.20 Hz) 6.83 (1H, dd, *J*=8.83, 2.52 Hz) 6.45 (2H, br. s.) 3.65 (3H, s) 2.75 (3H, s) 2.33 (3H, s); MS *m/z* 380.2 $[M+H]^+$
249	5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.27 (1H, br. s.) 7.70 (1H, d, *J*=2.52 Hz) 7.54 - 7.60 (2H, m) 7.38 - 7.43 (1H, m) 6.92 - 6.97 (2H, m) 6.82 (1H, dd, *J*=8.51, 2.52 Hz) 6.41 (2H, br. s.) 3.82 (3H, s) 3.67 (3H, s) 2.72 (3H, s); MS *m/z* 396.2 $[M+H]^+$
250	N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.32 (1H, br. s.) 7.71 (1H, d, *J*=2.52 Hz) 7.42 (1H, d, *J*=8.51 Hz) 7.30 - 7.33 (1H, m) 7.09 (1H, dd, *J*=8.35, 2.05 Hz) 6.81 - 6.87 (2H, m) 6.44 (2H, br. s.) 6.01 (2H, s) 3.72 (3H, s) 2.74 (3H, s); MS *m/z* 409.2 $[M+H]^+$
254	5-fluoro-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.45 - 8.49 (1H, m) 8.44 (1H, d, *J*=1.89 Hz) 8.31 (1H, d, *J*=9.14 Hz) 8.11 (1H, dd, *J*=8.98, 2.36 Hz) 7.54 - 7.57 (2H, m) 7.21 (2H, d, *J*=8.20 Hz) 6.59 (2H, br. s.) 2.85 (3H, s) 2.34 (3H, s); MS *m/z* 394.2 $[M+H]^+$
255	5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.43 (1H, d, *J*=1.89 Hz) 8.40 (1H, br. s.) 8.30 (1H, d, *J*=9.14 Hz) 8.10 (1H, dd, *J*=8.99, 2.36 Hz) 7.52 - 7.57 (2H, m) 6.96 - 7.01 (2H, m) 6.55 (2H, br. s.) 3.83 (3H, s) 2.83 (3H, s); MS *m/z* 410.2 $[M+H]^+$
256	2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.25 (1H, s) 7.53 - 7.59 (2H, m) 7.42 (1H, d, *J*=1.58 Hz) 7.24 (1H, d, *J*=8.83 Hz) 6.93 - 6.99 (2H, m) 6.61 (1H, dd, *J*=8.20, 2.21 Hz) 6.33 (2H, s) 4.30 (2H, br. s.) 3.81 (3H, s) 2.67 (3H, s); MS *m/z* 380.3 $[M+H]^+$

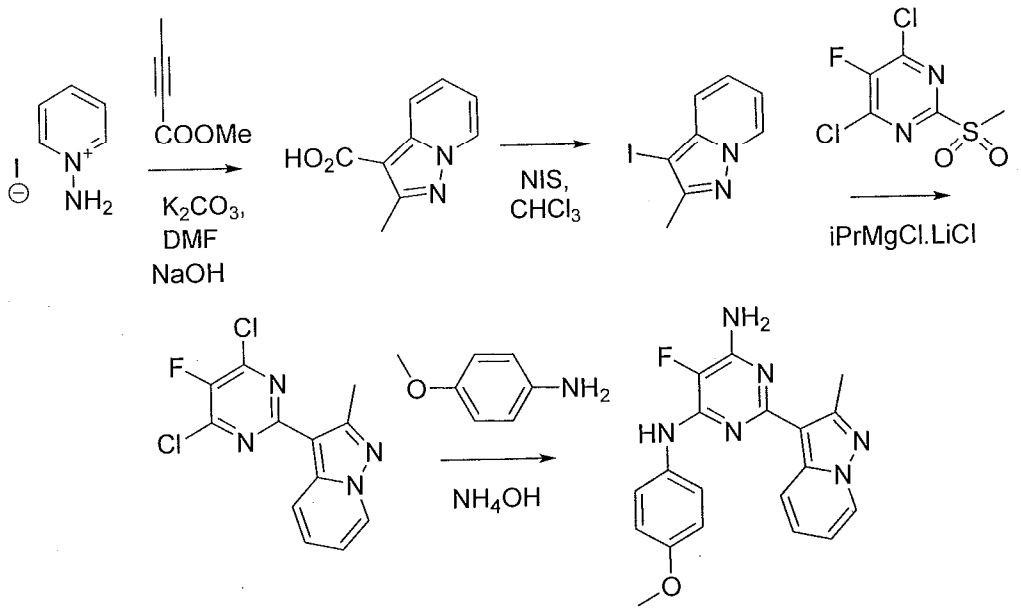
Cpd	Name & Data
257	2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.48 (1H, br. s.) 7.75 - 7.82 (2H, m) 7.42 (1H, d, *J*=2.21 Hz) 7.25 (1H, d, *J*=8.20 Hz) 7.17 - 7.22 (2H, m) 6.96 (1H, t, *J*=75.00 Hz) 6.64 (1H, dd, *J*=8.51, 2.21 Hz) 6.44 (2H, br. s.) 4.36 (2H, s) 2.68 (3H, s); MS *m/z* 416.2 $[M+H]^+$
258	2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.15 (1H, br. s.) 7.39 - 7.46 (2H, m) 7.28 (1H, d, *J*=2.21 Hz) 7.09 (1H, d, *J*=8.20 Hz) 7.04 (2H, d, *J*=8.20 Hz) 6.47 (1H, dd, *J*=8.51, 2.21 Hz) 6.22 (2H, br. s.) 4.16 (2H, s) 2.54 (3H, s) 2.18 (3H, s); MS *m/z* 364.3 $[M+H]^+$
259	N-(4-chlorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.60 (1H, br. s.) 8.13 (1H, dd, *J*=9.46, 5.04 Hz) 7.71 - 7.78 (2H, m) 7.36 - 7.43 (2H, m) 7.29 (1H, dd, *J*=9.30, 2.36 Hz) 6.99 (1H, td, *J*=9.30, 2.52 Hz) 6.60 (2H, br. s.) 2.80 (3H, s); MS *m/z* 387.2 $[M+H]^+$
260	N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.76 (1H, br. s.) 8.13 (1H, dd, *J*=8.83, 5.04 Hz) 7.86 (1H, dd, *J*=11.98, 2.52 Hz) 7.54 - 7.59 (1H, m) 7.45 - 7.51 (1H, m) 7.30 (1H, dd, *J*=9.30, 2.36 Hz) 7.02 (1H, td, *J*=9.22, 2.68 Hz) 6.69 (2H, br. s.) 2.84 (3H, s); MS *m/z* 405.2 $[M+H]^+$
261	N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.74 (1H, br. s.) 8.11 (1H, dd, *J*=7.57, 1.89 Hz) 7.90 (1H, dd, *J*=11.98, 2.52 Hz) 7.58 (2H, td, *J*=7.88, 2.21 Hz) 7.47 (1H, t, *J*=8.67 Hz) 7.18 - 7.28 (2H, m) 6.65 (2H, br. s.) 2.82 (3H, s); MS *m/z* 387.2 $[M+H]^+$
262	N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.77 (1H, br. s.) 7.93 (1H, dd, *J*=10.09, 2.21 Hz) 7.83 (1H, dd, *J*=11.82, 2.36 Hz) 7.53 - 7.59 (2H, m) 7.46 - 7.51 (1H, m) 7.05 (1H, td, *J*=9.14, 2.52 Hz) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 405.2 $[M+H]^+$
270	2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.36 (1H, br. s.) 8.07 - 8.11 (1H, m) 7.54 - 7.62 (3H, m) 7.15 - 7.24 (4H, m) 6.46 (2H, br. s.) 3.26 (2H, q, *J*=7.46 Hz) 2.33 (3H, s) 1.30 - 1.33 (3H, m); MS *m/z* 363.3 $[M+H]^+$
271	2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.15 (1H, br. s.) 7.93 - 7.97 (1H, m) 7.39 - 7.46 (3H, m) 6.99 - 7.10 (2H, m) 6.78 - 6.83 (2H, m) 6.28 (2H, s) 3.68 (3H, s) 3.10 (2H, q, *J*=7.36 Hz) 1.14 - 1.17 (3H, m); MS *m/z* 379.3 $[M+H]^+$

Cpd	Name & Data
272	2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.67 (1H, s) 8.04 - 8.10 (1H, m) 7.80 - 7.87 (2H, m) 7.58 - 7.64 (1H, m) 7.33 (2H, d, *J*=8.20 Hz) 7.14 - 7.26 (2H, m) 6.60 (2H, s) 3.26 (2H, q, *J*=7.36 Hz) 1.31 - 1.34 (3H, m); MS *m/z* 433.2 $[M+H]^+$
273	N-(1,3-benzodioxol-5-yl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.32 (1H, br. s.) 8.08 - 8.13 (1H, m) 7.58 (1H, d, *J*=7.57 Hz) 7.28 (1H, d, *J*=1.89 Hz) 7.15 - 7.24 (2H, m) 7.07 (1H, dd, *J*=8.67, 2.05 Hz) 6.85 (1H, d, *J*=8.51 Hz) 6.40 - 6.48 (2H, m) 6.01 (2H, s) 3.25 (2H, q, *J*=7.57 Hz) 1.30 - 1.33 (3H, m); MS *m/z* 393.2 $[M+H]^+$
274	N-(4-chlorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.57 (1H, br. s.) 8.03 - 8.09 (1H, m) 7.72 - 7.79 (2H, m) 7.60 (1H, d, *J*=7.57 Hz) 7.34 - 7.40 (2H, m) 7.16 - 7.26 (2H, m) 6.56 (2H, br. s.) 3.26 (2H, q, *J*=7.57 Hz) 1.33 (3H, t, *J*=7.57 Hz); MS *m/z* 383.4 $[M+H]^+$
275	N-(4-chloro-3-fluorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.75 (1H, br. s.) 8.06 (1H, d, *J*=6.94 Hz) 7.90 (1H, dd, *J*=11.98, 2.52 Hz) 7.62 (1H, dd, *J*=6.94, 1.58 Hz) 7.54 - 7.58 (1H, m) 7.42 - 7.49 (1H, m) 7.18 - 7.29 (2H, m) 6.65 (2H, br. s.) 3.29 (2H, q, *J*=7.36 Hz) 1.36 (3H, t, *J*=7.41 Hz); MS *m/z* 401.4 $[M+H]^+$
276	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.36 (1H, br. s.) 8.02 - 8.06 (1H, m) 7.61 - 7.67 (2H, m) 7.46 - 7.53 (1H, m) 7.12 - 7.23 (4H, m) 6.47 (2H, br. s.) 3.01 - 3.10 (1H, m) 2.32 (3H, s) 1.16 - 1.21 (2H, m) 0.98 (2H, dq, *J*=8.47, 3.38 Hz); MS *m/z* 375.4 $[M+H]^+$
277	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.29 (1H, br. s.) 8.04 (1H, d, *J*=8.83 Hz) 7.58 - 7.65 (2H, m) 7.46 - 7.51 (1H, m) 7.10 - 7.21 (2H, m) 6.89 - 6.96 (2H, m) 6.43 (2H, br. s.) 3.81 (3H, s) 3.02 - 3.10 (1H, m) 1.13 - 1.18 (2H, m) 0.96 (2H, dq, *J*=8.35, 3.42 Hz); MS *m/z* 391.3 $[M+H]^+$
278	2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.65 (1H, s) 7.98 - 8.03 (1H, m) 7.87 - 7.93 (2H, m) 7.49 - 7.54 (1H, m) 7.31 (2H, d, *J*=8.20 Hz) 7.12 - 7.24 (2H, m) 6.60 (2H, br. s.) 2.98 - 3.05 (1H, m) 1.17 - 1.23 (2H, m) 0.95 - 1.02 (2H, m); MS *m/z* 445.3 $[M+H]^+$

Cpd	Name & Data
279	N-(4-chlorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.59 (1H, br. s.) 7.97 - 8.04 (1H, m) 7.80 - 7.86 (2H, m) 7.47 - 7.55 (1H, m) 7.32 - 7.38 (2H, m) 7.12 - 7.23 (2H, m) 6.58 (2H, br. s.) 2.96 - 3.05 (1H, m) 1.17 - 1.25 (2H, m) 0.97 - 1.04 (2H, m); MS *m/z* 395.3 $[M+H]^+$
280	N-(4-chloro-3-fluorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.77 (1H, br. s.) 7.96 - 8.06 (2H, m) 7.60 (1H, dd, *J*=7.88, 2.52 Hz) 7.53 (1H, d, *J*=6.94 Hz) 7.45 (1H, t, *J*=8.67 Hz) 7.16 - 7.25 (2H, m) 6.68 (2H, br. s.) 2.96 - 3.03 (1H, m) 1.21 - 1.26 (2H, m) 1.02 - 1.07 (2H, m); MS *m/z* 413.3 $[M+H]^+$
281	5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine 1H NMR (500 MHz, Acetone-d_6) δ ppm 8.39 (1H, br. s.) 8.15 (1H, dd, J=8.51, 5.04 Hz) 7.53 - 7.58 (2H, m) 7.27 (1H, dd, J=9.62, 2.36 Hz) 7.19 (2H, d, J=8.20 Hz) 6.92 - 7.00 (1H, m) 6.51 (2H, br. s.) 2.79 (3H, s) 2.34 (3H, s); MS *m/z* 367.3 $[M+H]^+$
282	5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.30 (1H, br. s.) 8.14 (1H, dd, *J*=9.30, 4.89 Hz) 7.51 - 7.58 (2H, m) 7.26 (1H, dd, *J*=9.46, 2.52 Hz) 6.91 - 7.00 (3H, m) 6.44 (2H, br. s.) 3.83 (3H, s) 2.76 (3H, s); MS *m/z* 383.3 $[M+H]^+$
283	5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.66 (1H, s) 8.12 (1H, dd, *J*=8.67, 4.89 Hz) 7.80 - 7.86 (2H, m) 7.35 (2H, d, *J*=8.20 Hz) 7.29 (1H, dd, *J*=8.83, 2.52 Hz) 6.97 (1H, td, *J*=9.30, 2.52 Hz) 6.62 (2H, s) 2.79 (3H, s); MS *m/z* 437.3 $[M+H]^+$
284	2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 7.86 (2H, d, *J*=8.51 Hz) 7.53 (2H, d, *J*=8.51 Hz) 7.28 (1H, d, *J*=2.21 Hz) 7.13 (1H, d, *J*=8.51 Hz) 6.50 (1H, dd, *J*=8.51, 2.21 Hz) 6.42 (2H, br. s.) 4.26 (2H, s) 2.56 (3H, s) MS *m/z* 418.3 $[M+H]^+$

Example 11

5-fluoro-N-(4-methoxyphenyl)-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine (Cpd 239)



Step 1. To a mixture of 1-aminopyridinium iodide (9.59 g, 43.2 mmol) and methyl but-2-ynoate (5.2mL, 51.83 mmol) in DMF (50 mL) at 0°C was added K_2CO_3 (11.94g, 86.4 mmol). The reaction mixture was warmed to room temperature and stirred for 3 days until UPLC showed complete conversion to product. The reaction mixture was partitioned between water and EtOAc. The organic phase was concentrated, then MeOH (50 mL) and NaOH (6 mL, 50% in H_2O) were added and the reaction mixture was heated at 70°C for 1 hour. The MeOH was evaporated and the remaining mixture was acidified with 1N HCl to about pH 4. A crude 2-methylpyrazolo[1,5-a]pyridine-3-carboxylic acid was isolated on a filter and dried under vacuum, then dissolved in MeOH (50 mL) and $CHCl_3$ (100 mL) and N-iodosuccinimide (7.3g, 32.4 mmol) were added in one portion. The reaction mixture was stirred for 20 minutes at room temperature. The MeOH was evaporated and the remainder was washed three times with an aqueous $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography to give 3-iodo-2-methylpyrazolo[1,5-a]pyridine (4.2 g, 38% for 3 steps) as an off-white solid.

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.51 (dt, J = 6.8, 1.3 Hz, 1H), 7.41 (dt, J = 8.8, 1.3 Hz, 1H), 7.31 (ddd, J = 8.8, 6.8, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.3 Hz, 1H), 2.42 (s, 3H); MS *m/z* 298.1 $[M+H]^+$.

Step 2. To a solution of 3-iodo-2-methylpyrazolo[1,5-a]pyridine (340 mg,1.32 mmol) in dry THF (10 mL) at 0°C was added an isopropylmagnesium chloride lithium chloride complex solution (iPrMgCl.LiCl) (1.5 mL, 1.97 mL). The reaction mixture was stirred at 0°C for 30 minutes and 4,6-dichloro-5-fluoro-2-(methylsulfonyl)pyrimidine (484 mg, 1.97 mmol) in dry THF (20 mL) was added. The reaction mixture was stirred at 0°C for 1 hour, and the reaction was quenched with water. The crude product was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, then dried over Na_2SO_4, concentrated, and triturated in CH_3CN (10 mL). The resulting precipitate was filtered and dried providing 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-2-methylpyrazolo[1,5-a]pyridine (270 mg, 68%) isolated as a tan solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.79 (d, J = 6.9 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H), 7.61 (ddd, J = 8.8, 6.9, 0.9 Hz, 1H), 7.13 (td, J = 6.9, 1.1 Hz, 1H), 2.70 (s, 3H). MS *m/z* 298.1 $[M+H]^+$.

Step 3. 3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-2-methylpyrazolo[1,5-a]pyridine (65 mg, 0.21 mmol) and 4-methoxyaniline (52 mg, 0.42 mmol) were mixed in EtOH (1 mL) and heated in a sealed tube at 100°C until UPLC showed complete conversion (3 hours). After the starting materials were consumed, the reaction was cooled to room temperature and diluted with water (5 mL) to precipitate the product. The product was collected by filtration, washed with water and subsequently washed with hexanes. The crude product, without drying, was dissolved in iPrOAc (2 mL), then saturated ammonia in water (150 μL) was added. The reaction mixture was heated at 100°C in a sealed tube for 24 hours until UPLC showed complete consumption of starting material. A crude product was precipitated by addition of water (10 mL), then filtered and purified by chromatography on silica gel to provide the title compound (26 mg, 34 % in two steps).

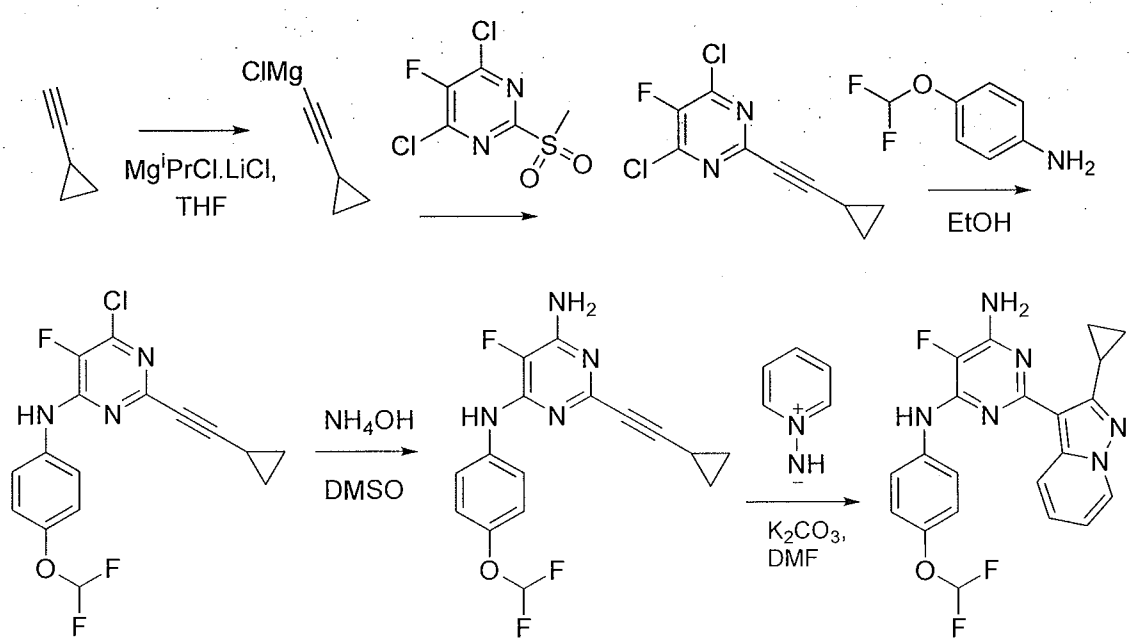
^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.54 (dt, J = 8.9, 1.2 Hz, 1H), 8.47 (dt, J = 6.9, 1.1 Hz, 1H), 7.93 (br. s., 1H), 7.59 (dd, J = 6.6, 2.2 Hz, 2H), 7.21 (ddd, J = 9.0, 6.8, 0.9 Hz, 1H), 6.98 (dd, J = 6.6, 2.2 Hz, 2H), 6.87 (td, J = 6.8, 1.3 Hz, 1H), 5.96 (br. s., 2H), 2.84 (s, 3H), 2.70 (s, 3H); MS *m/z* 383.2 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 11 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
173	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.55 (dt, J = 8.9, 1.2 Hz, 1H), 8.49 (dt, J = 6.9, 1.0 Hz, 1H), 8.20 (br. s., 1H), 7.76 - 7.81 (m, 2H), 7.20 - 7.27 (m, 3H), 6.98 (t, J = 75 Hz, 1H) 6.89 (td, J = 6.9, 1.4 Hz, 1H), 6.08 (br. s, 2H), 2.72 (s, 3H); MS *m/z* 401.2 $[M+H]^+$
177	5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.44 (dt, J = 9.1, 1.1 Hz, 1H), 8.37 (dt, J = 6.9, 0.9 Hz, 1H), 8.39 (br. s., 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.13 (ddd, J = 9.1, 6.7, 1.3 Hz, 1H), 6.77 (td, J = 6.8, 1.6 Hz, 1H), 6.09 (br. s., 2H), 2.62 (s, 3H); MS *m/z* 403.4 $[M+H]^+$
178	5-fluoro-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.76 - 8.81 (m, 1H), 8.70 (br. s., 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.68 (dd, J = 10.1, 4.7 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.45 (t, J = 9.8 Hz, 1H), 6.52 (br. s., 2H); MS *m/z* 475.3 $[M+H]^+$

Example 12

2-(2-cyclopropylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine (Cpd 180)



Step 1. To a solution of cyclopropylacetylene (777.0 mg, 9.82 mmol) in THF (5 mL) at -78°C was added an isopropylmagnesium chloride lithium chloride complex solution (9.0 mL, 1.3 M in THF) dropwise. The mixture was warmed to 0°C and stirred for 30 minutes. To the mixture at -78°C was added 4,6-dichloro-5-fluoro-2-(methylsulfonyl)pyrimidine (4.80 g, 19.6 mmol), then the mixture was warmed to 0°C and stirred for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:9 ethyl acetate-hexane) to afford 4,6-dichloro-2-(cyclopropylethynyl)-5-fluoropyrimidine (1.17 g, 45%).

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 1.53 - 1.67 (m, 1H), 0.98 - 1.10 (m, 2H), 0.83 - 0.94 (m, 2H); MS *m/z* 231.1 (100) $[M+H]^+$.

Step 2. A mixture of 4,6-dichloro-2-(cyclopropylethynyl)-5-fluoropyrimidine (241.0 mg, 1.04 mmol) and 4-difluoromethoxy aniline (707.0 mg, 4.45 mmol) in EtOH (2 mL) was stirred at reflux for 1 hour. After cooling, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:20 and 1:10 ethyl acetate-hexane) to afford 6-chloro-2-(cyclopropylethynyl)-N-(4-(difluoromethoxy)phenyl)-5-fluoropyrimidin-4-amine (258.0 mg, 70%); MS *m/z* 354.2 (100) $[M+H]^+$, 356.2 (40).

Step 3. To 6-chloro-2-(cyclopropylethynyl)-*N*-(4(difluoromethoxy)phenyl)-5-fluoropyrimidin-4-amine was added DMSO (2 mL) and NH_4OH (27%, 0.1 mL). The reaction mixture was sealed and stirred at 100°C for 2 days. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water (2 x 20 mL) and brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:4 ethyl acetate-hexane) to afford 2-(2-cyclopropylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine (149.0 mg, 64%). MS *m/z* 335.5 (80) $[M+H]^+$, 336.2 (100).

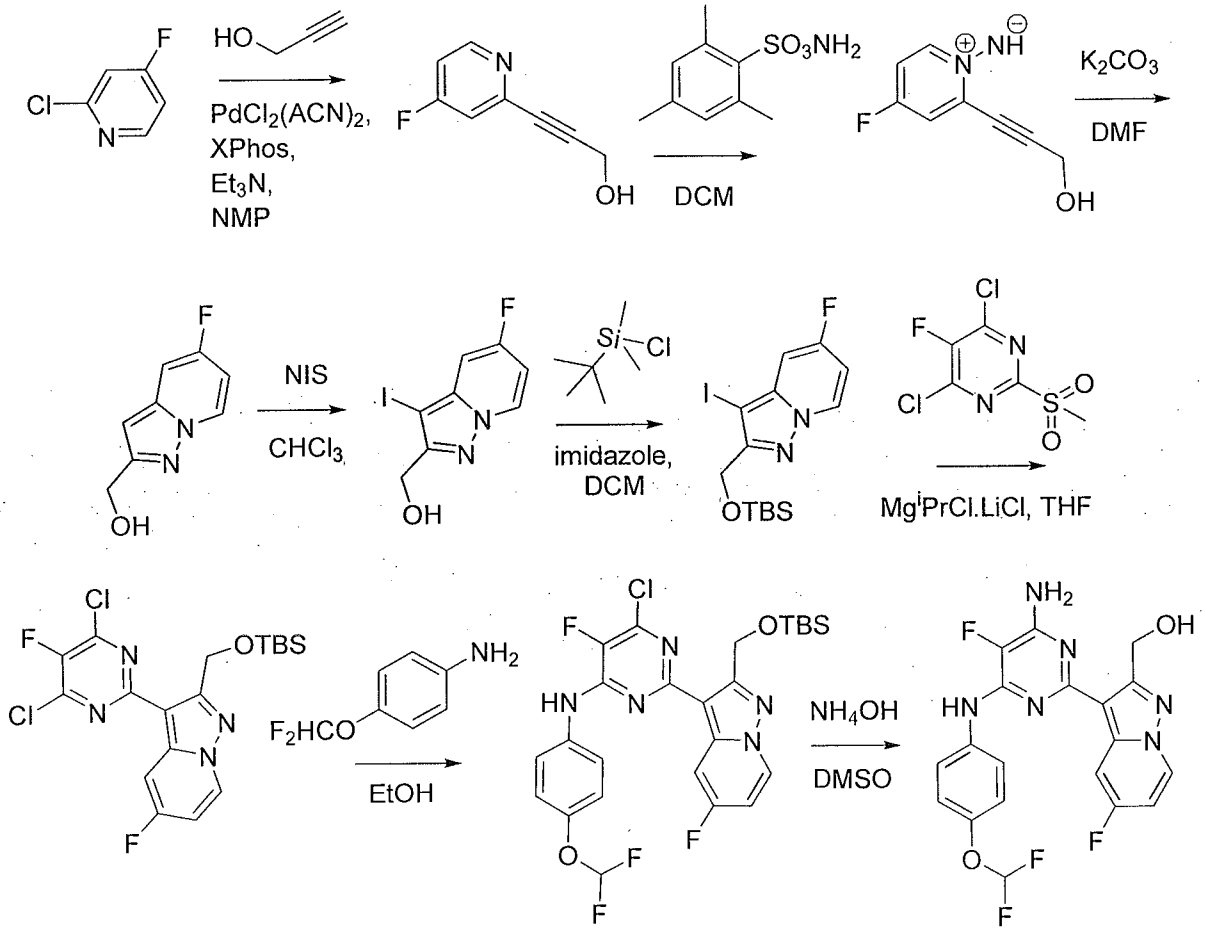
Step 4. A mixture of 2-(2-cyclopropylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine (100.0 mg, 0.30 mmol), pyridinium-1-ylazanide (74.0 mg, 0.30 mmol), K_2CO_3 (43.0 mg, 0.31 mmol) and DMF (2 mL) was stirred at room temperature for 1 day, and then at 80°C for 1 day. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed

with water and brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:1 dichloromethane:hexane, then 1:3 ethyl acetate:dichloromethane) to afford the title compound (32.0 mg, 28% yield): m.p. 53 - 55°C.

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.55 (d, J = 8.83 Hz, 1H), 8.41 (d, J = 6.94 Hz, 1H). 8.20 (br. s., 1H), 7.63 - 7.91 (m, 2H), 7.21 (ddd, J = 0.95, 6.78, 8.98 Hz, 1H), 7.17 (d, J = 8.83 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.86 (dt, J = 1.26, 6.78 Hz, 1H), 6.10 (br. s., 2H), 3.44 (m, 1H), 0.53 - 1.13 (m, 4H); MS m/z 427.3 (100) $[M+H]^+$, 428.3 (50).

Example 13

[3-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-5-fluoropyrazolo[1,5-a]pyridin-2-yl]methanol (Cpd 181)



Step 1. A mixture of 2-chloro-4-fluoropyridine (2.19 g, 16.65 mmol), prop-2-yn-1-ol (1.86 g, 33.29 mmol), bis(acetonitrile)dichloropalladium(II) (215.6 mg, 0.83 mmol) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (794.3 mg, 0.17 mmol) in NMP (15 mL) was degassed by three cycles of vacuum pumping and N_2 purging, and then

triethylamine (4.7 mL, 33.3 mmol) was added. The mixture was degassed and purged with N_2, then heated at 60°C overnight. The solution was cooled and poured into water (100 mL), and the product was extracted with ethyl acetate (150 mL). The extract was dried over $MgSO_4$, then filtered and concentrated under the reduced pressure. The residual material was separated by column chromatography (eluting with 0 to 10% dichloromethane-hexane) to yield 3-(4-fluoropyridin-2-yl)prop-2-yn-1-ol as an oil (2.40 g, 96%).

Step 2-4. To a solution of 3-(4-fluoropyridin-2-yl)prop-2-yn-1-ol (820.0 mg, 5.43 mmol) in dichloromethane (10 mL) was added 2-[(aminooxy)sulfonyl]-1,3,5-trimethylbenzene (1.5 g, 6.98 mmol) portion wise at 0°C. The resulting mixture was stirred at ambient temperature for 2 days. The solvent removed under a blowing N_2 stream to give a crude mixture. To the crude mixture in DMF (3 mL) was added K_2CO_3 (825.0 mg, 5.97 mmol) at 0°C. The resulting mixture was stirred at room temperature for 24 hours, and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was used in the next step without further purification.

A mixture of crude material, *N*-iodosuccinimide (1.2 g, 5.33 mmol) in chloroform (10 mL) was stirred at ambient temperature for 2 hours, and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:1 dichloromethane:hexane, then 1% methanol in 1:4 ethyl acetate:dichloromethane to afford (5-fluoro-3-iodopyrazolo[1,5-a]pyridin-2-yl)methanol as an oil (1.4 g, 50%).

Step 5. To a solution of (5-fluoro-3-iodopyrazolo[1,5-a]pyridin-2-yl)methanol (500.0 mg, 1.71 mmol) in dichloromethane (3 mL) was added imidazole (139.5 mg, 2.05 mmol), followed by tert-butyldimethylsilyl chloride (384.0 mg, 2.55 mmol) in dichloromethane (5 mL) added dropwise at 0°C. The resulting mixture was stirred at ambient temperature for 30 minutes, then filtered through a pad of silica gel/selite, washing with dichloromethane to provide 2-[(*tert*-butyldimethylsilyloxy)methyl]-5-fluoro-3-iodopyrazolo[1,5-*a*]pyridine (470.0 mg, 72%).

Step 6. To a solution of 2-[(*tert*-butyldimethylsilyloxy)methyl]-5-fluoro-3-iodopyrazolo[1,5-*a*]pyridine (470.0 mg, 1.15 mmol) in THF (5 mL) was added an isopropylmagnesium chloride lithium chloride complex solution (1.07 mL, 1.3 M in THF) at

-78°C dropwise. The mixture was warmed to 0°C and stirred for 30 minutes, and then 4,6-dichloro-5-fluoro-2-(methylsulfonyl)pyrimidine (4.80 g, 19.6 mmol) was added in one portion at -78°C. The mixture was stirrrd at 0°C for 1 hour and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1:9 ethyl acetate:hexane) to afford 2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-5-fluoropyrazolo[1,5-*a*]pyridine (205.0 mg, 40%).

Steps 7-8. A mixture of 2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-5-fluoropyrazolo[1,5-*a*]pyridine (102.0 mg, 0.23 mmol), 4-difluoromethoxy aniline (145.0 mg, 0.92 mmol) and ethanol (1 mL) was heated at 90°C overnight. After cooling, the mixture was poured into ice-water to afford a solid. The solid was collected by filtration, followed by washing with water and hexane. The solid was dried under the vacuum to provide 2-[2-[(*tert*-butyldimethylsilyloxy)methyl]-5-fluoropyrazolo[1,5-*a*]pyridin-3-yl]-6-chloro-*N*-(4-difluoromethoxy)phenyl]-5-fluoropyrimidin-4-amine (a mixture of TBS protected and unprotected product).

To the dried solid was added DMSO (3 mL) and NH_4OH (0.3 mL). The reaction mixture was sealed and stirred at 100°C for 2 days. The mixture was partitioned between ethyl acetate and water and the organic phase was washed with water (2 x 10 mL) and brine, dried over $MgSO_4$, then filtered and evaporated. The residual material was separated by silica gel column chromatography (eluting with 1-5 % methanol in dichloromethane) to provide the title compound as a white solid (25.0 mg, 25 % for two steps); m.p. 198 - 200°C.

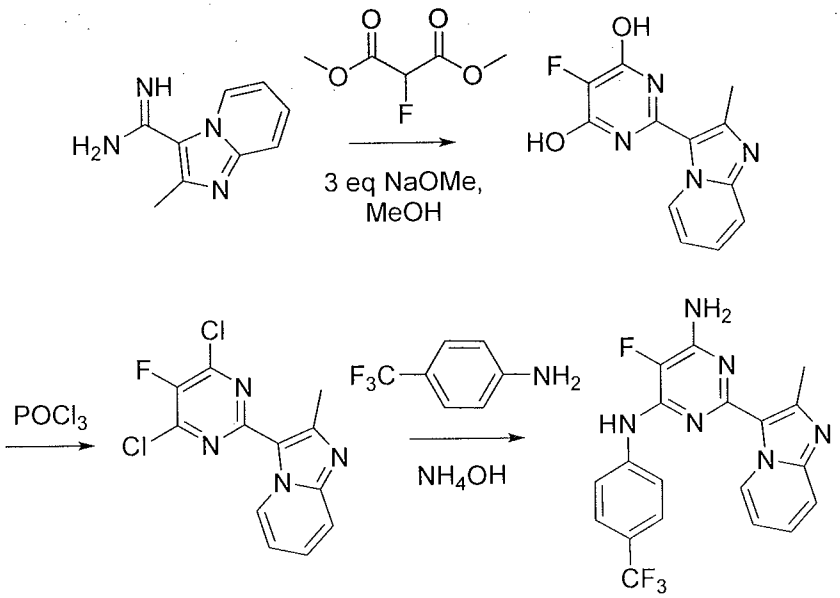
^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.50 - 8.64 (m, 1H), 8.35 (s, 1H), 8.06 - 8.21 (m, 1H), 7.64 (d, J = 8.83 Hz, 2H), 7.24 (d, J = 8.83 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.86 - 6.93 (m, 1H), 6.23 - 6.41 (m, 2H), 5.46 - 5.66 (m, 1H), 4.68 - 4.83 (m, 2H); MS *m/z* 435.2 (100) $[M+H]^+$, 436.2 (20).

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 13 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
186	N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.54 (dd, J = 5.20, 7.41 Hz, 1H), 8.25 (dd, J = 2.68, 10.88 Hz, 1H), 8.18 (br. s., 1H), 7.71 (d, J = 9.14 Hz, 2H), 7.21 (d, J = 9.14 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.76 - 6.88 (m, 1H), 6.14 (br. s., 2H), 3.24 (q, J = 7.57 Hz, 2H), 1.20 - 1.35 (m, 3H); m.p. 103-105 °C; MS *m/z* 433.6 $[M+H]^+$
187	2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.53 - 8.59 (m, 1H), 8.50 (br. s., 1H), 8.28 (dd, J = 2.68, 10.25 Hz, 1H), 7.93 (d, J = 8.51 Hz, 2H), 7.69 (d, J = 8.51 Hz, 2H), 6.83 (dt, J = 2.99, 7.33 Hz, 1H), 6.28 (br. s., 2H), 3.28 (q, J = 7.46 Hz, 2H), 1.28 (t, J = 7.57 Hz, 3H); m.p. 164-166 °C; MS *m/z* 435.2 $[M+H]^+$
188	N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.49 - 8.64 (m, 1H), 8.33 - 8.40 (m, 1H), 8.24 - 8.32 (m, 1H), 7.77 - 7.85 (m, 1H), 7.44 - 7.50 (m, 1H), 7.29 - 7.38 (m, 1H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.81 - 6.87 (m, 1H), 6.17 - 6.34 (m, 2H), 3.27 (d, J = 7.57 Hz, 2H), 1.28 (t, J = 7.57 Hz, 3H); m.p. 150-152 °C; MS *m/z* 452. $[M+H]^+$

Example 14

5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 169)



Step 1. To a solution of 2-methylimidazo[1,2-a]pyridine-3-carboximidamide pivaloate (250 mg, 0.905 mmol) and dimethyl 2-fluoromalonate (272 mg, 1.81 mmol) in MeOH (5 mL) was added 30% NaOMe in MeOH (0.2 mL). The mixture was heated at 85°C in a sealed tube for 72 hours until UPLC showed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure, then diluted with water (5 mL), and acidified with 1N HCl to about pH 7. A tan precipitate was collected by filtration giving 5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diol. 5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diol (180 mg, 76%). The product (180 mg, 0.69 mmol) was mixed with phosphorus oxychloride (3 mL) in a microwave vial, then the vial was sealed and microwaved for 15 minutes at 150°C. The reaction mixture was transferred into a 25 mL round-bottom flask and concentrated under reduced pressure. The remainder was redissolved in EtOAc (10 mL) and washed with an aqueous $NaHCO_3$ solution three times. The organic phase was dried over Na_2SO_4, then filtered and evaporated to afford 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-2-methylimidazo[1,2-a]pyridine (164 mg, 80%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.59 (dt, J = 6.9, 0.9 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 6.9 Hz, 1H), 2.77 (s, 3H); MS *m/z* 298.1 $[M+H]^+$.

Step 2. 3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-2-methylimidazo[1,2-a]pyridine (50 mg, 0.168 mmol) and 4-trifluoromethyl aniline (54 mg, 0.336 mmol) were mixed in EtOH (2 mL) and heated in a sealed tube at 100°C until UPLC showed complete consumption of the starting material (48 hours). The reaction mixture was cooled to room temperature and diluted with water (5 mL) to form a precipitate. The product was collected by filtration, then washed with hexanes. The crude product, without drying, was dissolved in CH_3CN (2 mL), then saturated ammonia (4 mL) in water was added. The reaction mixture was heated at 100°C in a sealed tube for 16 hours until UPLC showed complete consumption of starting material. A crude product was precipitated by addition of water (10 mL). The precipitate was filtered, then washed with hexanes and dried to yield the title compound (32 mg, 47 % over two steps) as a light tan solid.

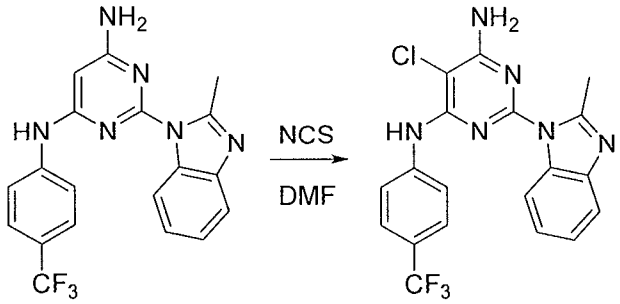
^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.76 (dt, J = 7.1, 1.0 Hz, 1H), 8.50 (br. s., 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.19 (ddd, J = 8.5, 6.5, 1.8 Hz, 1H), 6.74 (td, J = 6.9, 1.3 Hz, 1H), 6.27 (br. s., 2H), 2.64 (s, 3H); MS *m/z* 403.3 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 14 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
170	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine MS *m/z* 401.3 $[M+H]^+$
171	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.83 (d, J = 6.9 Hz, 1H), 9.25 (br. s, 1H), 7.80 (dd, J = 13.4, 2.0 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.31 - 7.39 (m, 2H), 7.18 (t, J = 73.1 Hz, 1H), 6.88 - 6.97 (m, 3H), 3.31 (s, 3H); MS *m/z* 419.3 $[M+H]^+$
174	5-fluoro-N-[4-(trifluoromethyl)phenyl]-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 9.39 (s, 1H), 7.83 (d, J = 8.51 Hz, 2H), 7.68 (d, J = 8.83 Hz, 2H), 7.11 (s, 2H), 2.75 (s, 3H), 2.72 (s, 3H), 2.55 (s, 3H); m.p. 166-168 °C; MS *m/z* 432.3 $[M+H]^+$
175	N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine m.p. 141-143 °C; MS *m/z* 430.4 $[M+H]^+$
176	N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.40 (s, 1H), 9.32 (s, 1H), 7.71 - 7.83 (m, 1H), 7.40 - 7.45 (m, 1H), 7.31 - 7.37 (m, 1H), 7.04- 7.32 (t, J = 70.00 Hz, 1H), 7.07 (s, 2H), 2.74 (s, 3H), 2.72 (s, 3H), 2.38 (s, 3H); m.p. 140-141 °C; MS *m/z* 448.4 $[M+H]^+$
251	N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ □ ppm 9.88 - 10.04 (m, 1H), 8.33 - 8.46 (m, 1H), 7.72 (d, J = 8.83 Hz, 2H), 7.48 - 7.59 (m, 1H), 7.39 (d, J = 8.83 Hz, 2H), 7.27 - 7.34 (m, 1H), 6.34 - 6.45 (br., s, 2H), 2.73 (s, 3H); m.p. 226-229 °C; MS *m/z* 388.2 $[M+H]^+$
252	5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.91 (dd, J = 2.52, 5.99 Hz, 1H), 8.10 (br. s., 1H), 7.45 - 7.58 (d, J = 8.83 Hz, 2H), 7.26 (d, J = 1.89 Hz, 1H), 6.96 (d, J = 8.83 Hz, 2H), 6.23 (br. s., 2H), 3.81 (s, 3H), 2.70 (s, 3H); m.p. 204-206 °C; MS *m/z* 384.2 $[M+H]^+$
253	5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine m.p. 210-212 °C; MS *m/z* 368.2 $[M+H]^+$

Example 15

5-chloro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine (Cpd 166)



To a solution of 2-(2-methyl-1H-benzo[d]imidazol-1-yl)-N4-(4-(trifluoromethyl)-phenyl)pyrimidine-4,6-diamine (76 mg, 0.20 mmol) in DMF (1.5 mL) was added N-chlorosuccinimide (29 mg, 0.22 mmol). The mixture was stirred for 2 hours at room temperature. Ice water (5 mL) and a saturated $NaHCO_3$ solution (2 mL) was added to the mixture. The resulting precipitate was filtered, washed by water, and dried under nitrogen to yield the title compound (77 mg, 92%) as an off-white solid.

^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.40 (1H, s) 7.95 - 8.00 (1H, m) 7.76 - 7.83 (2H, m) 7.57 (2H, d, *J*=8.51 Hz) 7.40 - 7.45 (1H, m) 7.06 - 7.11 (1H, m) 6.98 - 7.04 (1H, m) 6.52 - 6.75 (2H, m) 2.68 (3H, s); MS *m/z* 419.1 $[M+H]^+$.

Additional compounds of Formula (I) or a form thereof described herein may be prepared according to the procedure of Example 15 by substituting the appropriate starting materials, reagents and reaction conditions.

Cpd	Name & Data
167	5-chloro-2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.55 (1H, s) 8.07 - 8.12 (1H, m) 7.91 - 7.96 (2H, m) 7.71 (2H, d, *J*=8.51 Hz) 7.58 - 7.63 (1H, m) 7.13 - 7.26 (2H, m) 6.80 (2H, br. s.) 3.23 - 3.30 (2H, m) 1.31 (3H, t, *J*=7.41 Hz); MS *m/z* 433.2 $[M+H]^+$
168	5-chloro-N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 8.31 (1H, s) 8.09 - 8.13 (1H, m) 7.65 - 7.71 (2H, m) 7.55 - 7.60 (1H, m) 7.13 - 7.25 (4H, m) 6.99 (1H, t, *J*=74.40 Hz) 6.68 (2H, br. s.) 3.19 - 3.25 (2H, m) 1.28 (3H, t, *J*=7.41 Hz); MS *m/z* 431.2 $[M+H]^+$

Biological Examples

The following biological examples demonstrate the usefulness of the compounds described herein to inhibit Bmi-1 function and reduce the level of Bmi-1 protein.

Example 1

Sandwich ELISA Assay

Cell Seeding and Compound Treatment (Day 1):

HT-1080 cells were seeded at 8000 cells/well (50 μL) in 96-well tissue culture plates. After the cells became adherent (3-4 hours), 2x diluted stocks of test compounds in 50 μL DMEM containing 1% DMSO (final DMSO concentration was 0.5%) were added and the plates were incubated at 37°C under 5% CO_2 for 40-48 hours.

ELISA Plate First Antibody Preparation (Day 2):

The First Antibody (Millipore Mouse, monoclonal to mouse *Bmi-1*, clone F6, catalog #05-637) diluted to 2 μg/mL in PBS was added (100 μL) to each well of a Nunc MaxiSorp 96-well ELISA plate. The plate was covered with a plate seal and allowed to stand overnight.

Cell Lysate Preparation (Day 3):

Fresh 1x Lysis buffer was prepared on the day of the assay as follows: 1 mM EDTA, 150 mM NaCl, 0.5% Triton-X 100, 10 mM NaF, 20 mM B-Glycerophosphate, 1 mM DTT (in PBS, pH 7.2-7.4) and 1x HALT protease inhibitor cocktail (Pierce #78410).

The 1x Lysis Buffer (40 μL) was added to each well and the plate was shaken for 5-10 minutes on an orbital shaker to allow cell lysis, then diluent (1% BSA in PBS in 0.5% NP40) (100 μL) was added to each well.

A standard curve was prepared at the following Bmi-1 concentrations: 8000, 4000, 2000, 1000, 500, 250, 125, 0 pg/mL The Bmi-1 Recombinant Protein Standard (Novus Biologicals PCGF4 Recombinant Protein (P01), catalog # H00000648-P01) used to prepare the standard curve was stored at –80°C. On first thaw, the Bmi-1 Recombinant Protein Standard was diluted to 10 μg/μL in Blocking Buffer (1% BSA in PBS; BSA: Fisher Scientific Catalog #1600-100). Aliquots were taken and refrozen at –80°C. The aliquots may be kept at 4°C and reused after first thaw, but only within 1-2 weeks. The Bmi-1 Recombinant Protein Standard contains a GST-fusion tag that appears around 70 Kda on Western Blot.

ELISA Assay (Day 3):

The prepared ELISA plate was washed 3x with Wash Buffer (0.05% Tween-20 in PBS). The final wash was removed from the plate and the plate was blotted dry. Blocking Buffer (300 μL) (1% BSA in PBS) was added to each well. The plate was covered with a plate seal and incubated at room temperature for 1 hour. The blocked plate was washed 3x with Wash Buffer, then the final wash was removed and the plate was blotted dry. The previously prepared samples and standards were added (100 μL/well) and the plate was covered with a plate seal and incubated at 4°C overnight.

ELISA Assay (Day 4):

The prepared ELISA plate was removed from 4°C, incubated at room temperature for 30 minutes, then washed and blotted dry as previously described for Day 3. The Second Antibody (Cell Signaling Rabbit anti-Bmi-1, Cat# 2830) diluted to 1:600 in Blocking Buffer was added (100 μL) to each well, except as needed for background control wells. The plate was covered with a plate seal and incubated for 1.5 hrs at room temperature.

The ELISA plate was washed and blotted dry as previously described. The Third Antibody (Cell Signaling HRP conjugated anti-rabbit IgG (CellSignaling, Cat#:7074) diluted to 1:300 in Blocking Buffer was added (100 μL) to each well, except as needed for background control wells. The plate was incubated for 1 hr at room temperature.

The plate was washed and blotted dry as previously described, then prepared TMB substrate (TMB substrate kit, Pierce catalog #34021) (prepared by mixing kit reagents 1:1) (100 μL) was added per well. The plate was incubated for 20-30 minutes at room temperature in the dark, then Stop Solution (2 M sulfuric acid in water) (50 μL) was added per well. The plates were read at OD450 (experimental) and OD570 (reference).

As shown in Table 1, test compounds described herein had Bmi-1 ELISA EC_{50} values between > 0.1 μM to ≤ 3 μM (one star), an EC_{50} value between > 0.01 μM to ≤ 0.1 μM (two stars), an EC_{50} value between > 0.001 μM to ≤ 0.01 μM (three stars) or an EC_{50} value of ≤ 0.001 μM (four stars).

Table 1

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
1	**	72	**	143	***	214	**
2	*	73	**	144	**	215	*
3	**	74	*	145	***	216	**

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
4	**	75	*	146	**	217	**
5	*	76	**	147	*	218	***
6	**	77	**	148	*	219	*
7	*	78	**	149	**	220	**
8	*	79	*	150	**	221	*
9	***	80	**	151	**	222	*
10	**	81	**	152	**	223	*
11	*	82	**	153	**	224	**
12	**	83	**	154	*	225	**
13	*	84	*	155	**	226	*
14	*	85	*	156	***	227	**
15	**	86	**	157	**	228	**
16	**	87	*	158	*	229	*
17	*	88	**	159	*	230	*
18	*	89	*	160	**	231	*
19	*	90	*	161	**	232	**
20	*	91	*	162	**	233	**
21	***	92	**	163	**	234	**
22	**	93	**	164	**	235	**
23	*	94	**	165	***	236	*
24	*	95	**	166	*	237	**
25	*	96	*	167	**	238	*
26	*	97	**	168	*	239	**
27	*	98	*	169	*	240	***
28	*	99	*	170	*	241	**
29	**	100	*	171	*	242	***
30	*	101	**	172	*	243	**
31	**	102	**	173	*	244	**
32	*	103	**	174	*	245	**
33	**	104	**	175	*	246	**
34	***	105	**	176	*	247	**
35	*	106	**	177	*	248	**
36	**	107	**	178	*	249	**
37	**	108	*	179	***	250	**
38	*	109	**	180	*	251	*
39	*	110	**	181	**	252	**

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
40	*	111	**	182	*	253	***
41	*	112	**	183	**	254	**
42	**	113	**	184	***	255	*
43	**	114	**	185	**	256	**
44	*	115	**	186	*	257	**
45	*	116	**	187	*	258	***
46	*	117	**	188	*	259	*
47	*	118	*	189	*	260	*
48	*	119	**	190	*	261	**
49	*	120	**	191	**	262	**
50	**	121	***	192	*	263	**
51	*	122	**	193	**	264	***
52	*	123	***	194	*	265	***
53	*	124	**	195	*	266	**
54	*	125	*	196	***	267	*
55	*	126	**	197	***	268	*
56	*	127	**	198	***	269	*
57	*	128	**	199	***	270	***
58	*	129	**	200	***	271	***
59	*	130	**	201	**	272	**
60	**	131	**	202	*	273	***
61	*	132	**	203	***	274	**
62	**	133	**	204	**	275	**
63	**	134	**	205	***	276	***
64	**	135	**	206	**	277	****
65	**	136	**	207	***	278	*
66	**	137	**	208	***	279	**
67	*	138	**	209	**	280	**
68	**	139	*	210	*	281	***
69	**	140	**	211	*	282	***
70	*	141	**	212	**	283	*
71	**	142	**	213	***	284	**

Example 2

In Vitro Cancer Stem Cell Assay

The effect on inhibition of Bmi-1 function and reduction in the level of Bmi-1 protein by a compound of Formula (I) or a form thereof was tested in the *in vitro* pediatric Baylor Xenograft Derived (BXD) brain tumor model and in cells from primary patient cultures (PPC).

Cells were grown under conditions to measure either general cell growth (such as in fetal bovine serum (FBS) containing media in conventional tissue culture plates) or in conditions specifically for cancer stem cell (CSC) growth (low serum, nonadherent plates) to assess the effect of Bmi-1 inhibition and reduction in the level of Bmi-1 protein by a compound of Formula (I) on these populations. The cells were treated with a predetermined dose range of Compound 109 at fixed time points over a time period of from 24 hours to 13 days. The effect of inhibition on cell growth viability was quantitated using conventional 2D growth and neurosphere growth using a cell-counting kit (CCK) (supplied by Dojindo Molecular Technologies, Inc.).

Figure 1 demonstrates the effect of Compound 109 in a BXD GBM model where the CSC population (as measured by number of neurospheres) was dose dependently reduced over a period of 13 days in the presence of the stated concentrations of Compound 109.

Figure 2 demonstrates the effect of Compound 109 in a BXD GBM model where the CSC population (as measured by number of neurospheres) was universally reduced over a period of 13 days in the presence of the stated concentrations of Compound 109.

Figure 3 demonstrates the effect of Compound 109 in a tumorosphere assay where 2000 PPC CSCs per well were cultured either under standard 2D tissue culture conditions (with FBS) or conditions selective for CSC growth (attachment-free, serum-free) for 13 days in the presence of the stated concentrations of Compound 109. Both the monolayer and neurosphere CSC populations were reduced as the result of contacting the PPC CSCs with Compound 109, representative of a compound of Formula (I) or a form thereof, at concentrations of 62.5 nm and 15.6 nm, respectively.

Taken together, the data from Figures 1-3 demonstrate the preferential reduction of cancer stem cell populations compared to general cell populations as a result of inhibition of

Bmi-1 function and reduction in the level of Bmi-1 protein by a compound of Formula (I) or a form thereof.

Example 3

In Vivo Survival Assay

A glioblastoma animal model was developed in which U87-MG tumor cells were injected intracranially into nu/nu mice and a tumor was allowed to become established over a 10 day period. The mice were dosed daily with vehicle, Compound 109 or temozolomide (a standard-of-care agent), as indicated. The comparative results for survival for each treatment group (n = 10) from administration of vehicle, Compound 109 and temozolomide are shown in Figure 4.

Figure 4 demonstrates the effect of daily dosing of Compound 109 compared to temozolomide, at the indicated dose levels, on survival over a 40 day time period in an orthotopic model of glioblastoma. Cells were implanted intracranially into nude mice and dosing was begun 10 days later with either vehicle, Compound 109 or temozolomide. Compound 109 demonstrated extended survival of these tumor bearing mice over both vehicle and temozolomide ($p<0.0001$).

The following publications are incorporated by reference into the present application for any and all purposes to the same extent as if each individual publication was fully set forth herein:

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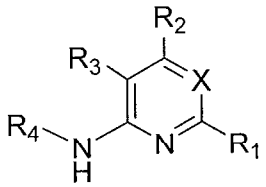
Without regard to whether a document cited herein was specifically and individually indicated as being incorporated by reference, all documents referred to herein are incorporated by reference into the present application for any and all purposes to the same extent as if each individual reference was fully set forth herein.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the scope of the claims presented herein.

What is claimed is:

1. A compound of Formula (I):



(I)

or a form thereof, wherein

R_1 is heteroaryl or heterocyclyl optionally substituted on a carbon atom ring member with one, two, three or four R_5 substituents, or on a nitrogen atom ring member with an oxygen atom substituent to form an N-oxide;

X is N or N substituted with an oxygen atom substituent to form an N-oxide;

R_2 is hydrogen, cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, hydroxyl-amino, hydroxyl-C_{1-8}alkyl-amino, C_{1-8}alkoxy-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, amino-carbonyl-amino, C_{1-8}alkyl-amino-carbonyl-amino, $(C_{1-8}alkyl)_2$-amino-carbonyl-amino, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-amino, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl, amino-sulfonyl-amino, C_{1-8}alkyl-amino-sulfonyl-amino, $(C_{1-8}alkyl)_2$-amino-sulfonyl-amino, $P(O)(R_7)_2$-amino or heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C_{1-8}alkyl substituents;

R_3 is hydrogen, cyano, halo, C_{1-8}alkyl, amino, C_{1-8}alkyl-amino or $(C_{1-8}alkyl)_2$-amino;

R_4 is C_{3-14}cycloalkyl, aryl, heteroaryl or heterocyclyl, each optionally substituted with one, two, three or four R_6 substituents;

R_5 is independently selected from cyano, halo, hydroxyl, nitro, oxo, C_{1-8}alkyl, cyano-C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl,

hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-thio, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino, C_{1-8}alkyl-sulfonyl, C_{3-14}cycloalkyl, aryl, aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino, heteroaryl, heteroaryl-C_{1-8}alkyl or heterocyclyl, wherein C_{3-14}cycloalkyl, aryl, heteroaryl or heterocyclyl and the aryl and heteroaryl portions of aryl-C_{1-8}alkyl, aryl-amino, aryl-C_{1-8}alky-amino and heteroaryl-C_{1-8}alkyl are each optionally substituted with one, two, three or four halo, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, hydroxyl-C_{1-8}alkoxy or carboxyl substituents;

R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{2-8}alkenyl, C_{1-8}alkoxy-C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy-C_{2-8}alkynyl, carboxyl, formyl, formyl-oxy, C_{1-8}alkyl-carbonyl, halo-C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-thio, halo-C_{1-8}alkyl-thio, amino, C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino, C_{1-8}alkyl-carbonyl, C_{1-8}alkyl-carbonyl-oxy, C_{1-8}alkyl-carbonyl-oxy-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl, halo-C_{1-8}alkoxy-carbonyl, C_{1-8}alkoxy-carbonyl-C_{1-8}alkyl, C_{1-8}alkoxy-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino-C_{1-8}alkyl, amino-carbonyl, C_{1-8}alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$-amino-carbonyl, C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkyl-carbonyl-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl, C_{1-8}alkyl-amino-C_{1-8}alkyl, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl, amino-C_{1-8}alkyl-amino, C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, $(C_{1-8}alkyl)_2$-amino-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl, hydroxyl-C_{1-8}alkyl-amino-C_{1-8}alkyl-amino, imino-C_{1-8}alkyl, hydroxyl-imino-C_{1-8}alkyl, C_{1-8}alkoxy-imino-C_{1-8}alkyl, C_{1-8}alkyl-sulfonyl, halo-C_{1-8}alkyl-sulfonyl, amino-sulfonyl, C_{1-8}alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$-amino-sulfonyl, $B(OR_8)_2$, C_{3-14}cycloalkyl, , heterocyclyl aryl or heteroaryl, wherein C_{3-14}cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with one, two, three or four halo or C_{1-8}alkyl substituents;

R_7 is independently hydroxyl or $(C_{1-8}alkoxy)_n$, wherein n represents an integer from 1 to 5; and,

R_8 is independently hydrogen or C_{1-8}alkyl;

wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

2. The compound of claim 1, wherein R_1 is optionally substituted heteroaryl or heterocyclyl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

3. The compound of claim 2, wherein R_1 is optionally substituted heteroaryl selected from 1H-pyrazolyl, 1H-indolyl, 1H-benzimidazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrazinyl or imidazo[1,2-a]pyrimidinyl.

4. A compound or a form thereof selected from the group consisting of:

N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine
N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine
N-(4-methoxyphenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
N-(4-chlorophenyl)-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine
2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-phenylpyrimidin-4-amine
2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine
N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
N-(4-bromophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine
2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine
2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine

N-(4-bromophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine

N-(4-chlorophenyl)-2-[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

N-(4-bromophenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(4-methylphenyl)-2-[2-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methylphenyl)pyrimidin-4-amine

2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]-N-[4-(difluoromethoxy)phenyl]pyrimidin-4-amine

N-(4-bromophenyl)-2-[5-chloro-1-methyl-2-(trifluoromethyl)-1H-indol-3-yl]pyrimidin-4-amine

N-(4-bromophenyl)-2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-amine

2-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidin-4-amine

N-(1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(6-methoxypyridin-3-yl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N^2,N^2-dimethyl-N^5-{2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-yl}pyridine-2,5-diamine

2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

2-[6-bromo-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-(4-methoxyphenyl)pyrimidin-4-amine

N-(3-fluoro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amin

N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(3-chloro-4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(4-ethoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-[4-(propan-2-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-[4-(1H-pyrazol-1-yl)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amin

N-(3-chloro-4-methoxyphenyl)-2-(2-methyl-1*H*-benzimidazol-1-yl)pyrimidin-4-amine

2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

N-(3-chloro-4-methoxyphenyl)-2-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]pyrimidin-4-amine

5-fluoro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

5-chloro-N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

N-(4-chlorophenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethoxy)phenyl]pyrimidin-4-amine

N-(4-methoxyphenyl)-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-[4-(difluoromethoxy)phenyl]-2-[6-methoxy-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

2-{[6-{[4-(difluoromethoxy)phenyl]amino}-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}ethanol

N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

N-[4-(difluoromethoxy)phenyl]-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-4-amine

N-[4-(trifluoromethyl)phenyl]-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine

2-{[2-(2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol

N^4-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)-N^6-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N^4-[4-(difluoromethoxy)phenyl]-N^6-(2-methoxyethyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-methoxyphenyl)-2-[2-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-4-amine

N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-amine

N-(4-methylphenyl)-2-[2-(trifluoromethyl)imidazo[1,2-a]pyrazin-3-yl]pyrimidin-4-amine

2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine

2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(trifluoromethoxy)phenyl]-2-[2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-4,6-diamine

2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

N-[4-(trifluoromethyl)phenyl]-2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrimidine-4,6-diamine

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]pyrimidine-4,6-diamine

N-[4-(trifluoromethyl)phenyl]-2-(2,5,6-trimethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[3-fluoro-4-(trifluoromethyl)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

[3-(4-amino-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridin-2-yl]methanol

2-(6-bromo-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2,6-dimethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-ethyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine 4,6-diamine

2-{[2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl]amino}ethanol

2-(6-ethenyl-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-fluoro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6 diamine

5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

2-(6-fluoro-2-methylimidazo[1,2-a]pyrimidin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-ethyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(imidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidin-4-amine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-4,6-difluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methyl-1H-imidazo[4,5-b]pyridin-1-yl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(2-cyclopropyl-4-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoropyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-[2-(difluoromethyl)-6-fluoro-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(methylsulfanyl)phenyl]pyrimidine-4,6-diamine

2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-[2-(1-methylcyclopropyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-[2-(propan-2-yl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-cyclopropyl-6-fluoro-1H-imidazo[4,5-b]pyridin-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(5-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(6-chloro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-6-fluoro-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

5-chloro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-chloro-2-(2-ethyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-chloro-N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

5-methyl-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine

5-fluoro-N-[4-(trifluoromethyl)phenyl]-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-5-fluoro-2-(2,6,8-trimethylimidazo[1,2-a]pyrazin-3-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-[6-fluoro-2-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

2-(2-cyclopropylpyrazolo[1,5-a]pyridin-3-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

[3-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-5-fluoropyrazolo[1,5-a]pyridin-2-yl]methanol

2-[2-(methylsulfanyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[6-(trifluoromethyl)pyridin-3-yl]pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine

2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-ethyl-5-fluoropyrazolo[1,5-a]pyridin-3-yl)-5-fluoropyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methoxyphenyl)pyrimidine-4,6-diamine

N-(3-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

methyl 4-{[6-amino-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzoate

5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-N-(3-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(dimethylamino)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

4-{[6-amino-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

N-(1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(3-fluoro-4-methoxyphenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(6-methoxypyridin-3-yl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

4-{[6-amino-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidin-4-yl]amino}benzonitrile

2-(2-methyl-1H-benzimidazol-1-yl)-N-(4-nitrophenyl)pyrimidine-4,6-diamine

N-(4-bromophenyl)-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(5,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]pyrimidine-4,6-diamine

5-fluoro-2-[2-(methoxymethyl)-1H-benzimidazol-1-yl]-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

2-(2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile

1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-6-carbonitrile

1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile

1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-6-carbonitrile

1-(4-amino-6-{[4-(difluoromethoxy)phenyl]amino}-5-fluoropyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile

1-{4-amino-5-fluoro-6-[(4-methylphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

1-{4-amino-5-fluoro-6-[(4-methoxyphenyl)amino]pyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

1-(4-amino-5-fluoro-6-{[4-(trifluoromethyl)phenyl]amino}pyrimidin-2-yl)-2-methyl-1H-benzimidazole-5-carbonitrile

1-{4-amino-6-[(4-chlorophenyl)amino]-5-fluoropyrimidin-2-yl}-2-methyl-1H-benzimidazole-5-carbonitrile

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)-3-fluorophenyl]-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-6-nitro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

5-fluoro-N-(4-methoxyphenyl)-2-(2-methylpyrazolo[1,5-a]pyridin-3-yl)pyrimidine-4,6-diamine

N-(1,3-benzodioxol-5-yl)-2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

2-(4,6-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

2-(5,7-difluoro-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

N-[4-(difluoromethoxy)phenyl]-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

N-(1,3-benzodioxol-5-yl)-5-fluoro-2-(6-methoxy-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

5-fluoro-2-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-N-(4-methoxyphenyl)-2-(2-methyl-5-nitro-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-N-[4-(difluoromethoxy)phenyl]-5-fluoropyrimidine-4,6-diamine

2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-5-fluoro-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

N-[4-(dimethylamino)phenyl]-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(3-methylphenyl)pyrimidine-4,6-diamine

N-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-(6-fluoro-2-methyl-1H-benzimidazol-1-yl)pyrimidine-4,6-diamine

2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

N-(1,3-benzodioxol-5-yl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-2-(2-ethyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methylphenyl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine

N-(4-chlorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

N-(4-chloro-3-fluorophenyl)-2-(2-cyclopropyl-1H-benzimidazol-1-yl)-5-fluoropyrimidine-4,6-diamine

5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)pyrimidine-4,6-diamine

5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-(4-methoxyphenyl)pyrimidine-4,6-diamine

5-fluoro-2-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-N-[4-(trifluoromethoxy)phenyl]pyrimidine-4,6-diamine, and,

2-(6-amino-2-methyl-1H-benzimidazol-1-yl)-5-fluoro-N-[4-(trifluoromethyl)phenyl]pyrimidine-4,6-diamine;

wherein the form of the compound is selected from a salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

5. A method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering to the subject an effective amount of the compound of claim 1.

6. The method of claim 5, further comprising contacting a cell having elevated Bmi-1 levels from the subject with an amount of the compound, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell, determining an effective amount of the compound that inhibits Bmi-1 function in the cell and subsequently administering the effective amount of the compound to the subject.

7. The method of claim 6, wherein the effective amount of the compound determined to inhibit Bmi-1 function in the contacted cell reduces Bmi-1 levels in the contacted cell.

8. The method of claim 7, wherein the effective amount of the compound is in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day.

9. The method of claim 7, wherein the effective amount of the compound or a form thereof is in a range of from about 0.1 ng to about 3500 mg.

10. The method of claim 5, comprising administering the compound in combination with one or more additional agents selected from anti-cancer agents, anti-proliferative agents, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, anti-inflammatory agents, alkylating agents, steroidal and non-steriodal anti-inflammatory agents, pain relievers, leukotriene antagonists, β2-agonists, anticholinergic agents, hormonal agents, biological agents, tubulin binding agents, glucocorticoids, corticosteroid agents, antibacterial agents, antihistamines, anti-malarial agents, anti-viral agents, antibiotics and the like; and, optionally with radiation therapy.

11. A use of the compound of claim 1 in the manufacture of a medicament for inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering an effective amount of the medicament to the subject.

12. A method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering to the subject an effective amount of the compound of claim 4.

13. The method of claim 12, further comprising contacting a cell having elevated Bmi-1 levels from the subject with an amount of the compound, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell, determining an

effective amount of the compound that inhibits Bmi-1 function in the cell and subsequently administering the effective amount of the compound to the subject.

14. The method of claim 13, wherein the effective amount of the compound determined to inhibit Bmi-1 function in the contacted cell reduces Bmi-1 levels in the contacted cell.

15. The method of claim 14, wherein the effective amount of the compound is in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day.

16. The method of claim 14, wherein the effective amount of the compound is in a range of from about 0.1 ng to about 3500 mg.

17. The method of claim 12, comprising administering the compound in combination with one or more additional agents selected from anti-cancer agents, anti-proliferative agents, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, anti-inflammatory agents, alkylating agents, steroidal and non-steriodal anti-inflammatory agents, pain relievers, leukotriene antagonists, β2-agonists, anticholinergic agents, hormonal agents, biological agents, tubulin binding agents, glucocorticoids, corticosteroid agents, antibacterial agents, antihistamines, anti-malarial agents, anti-viral agents, antibiotics and the like; and, optionally with radiation therapy.

18. A use of the compound of claim 4 in the manufacture of a medicament for inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering an effective amount of the medicament to the subject.

19. A pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound of claim 1 in admixture with a pharmaceutically acceptable excipient.

20. A pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound of claim 4 in admixture with a pharmaceutically acceptable excipient.

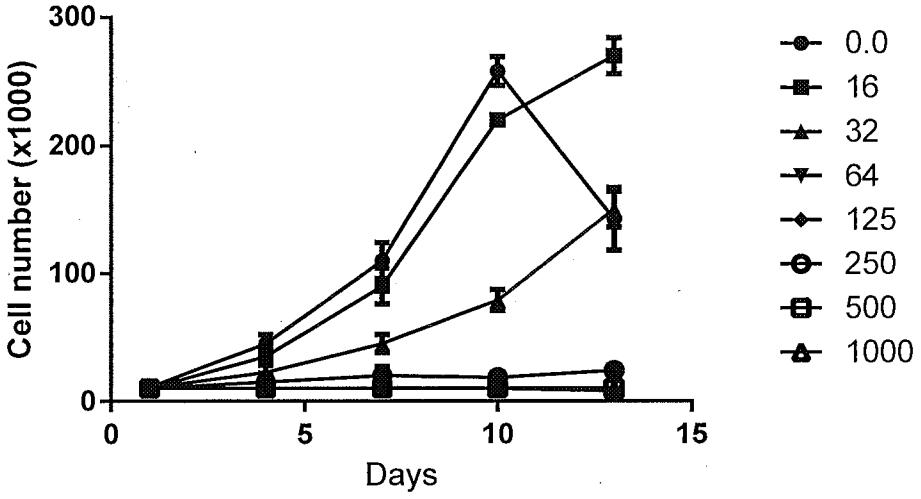


Figure 1

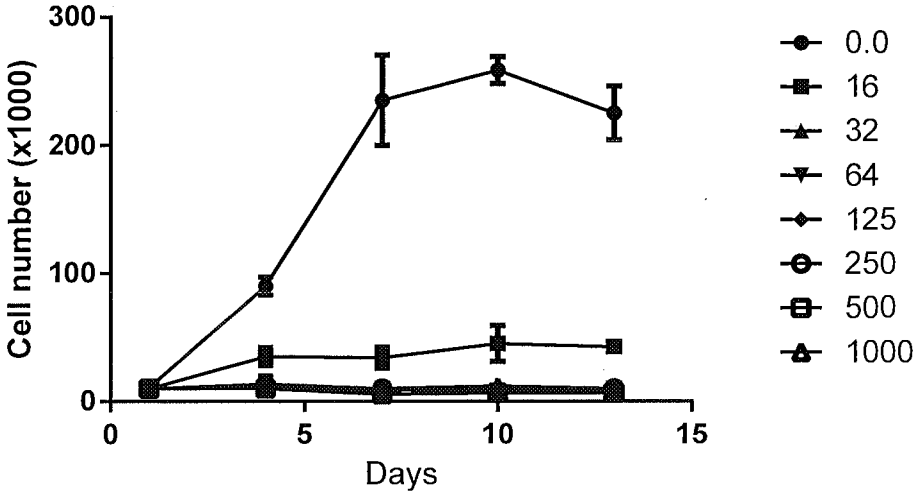


Figure 2

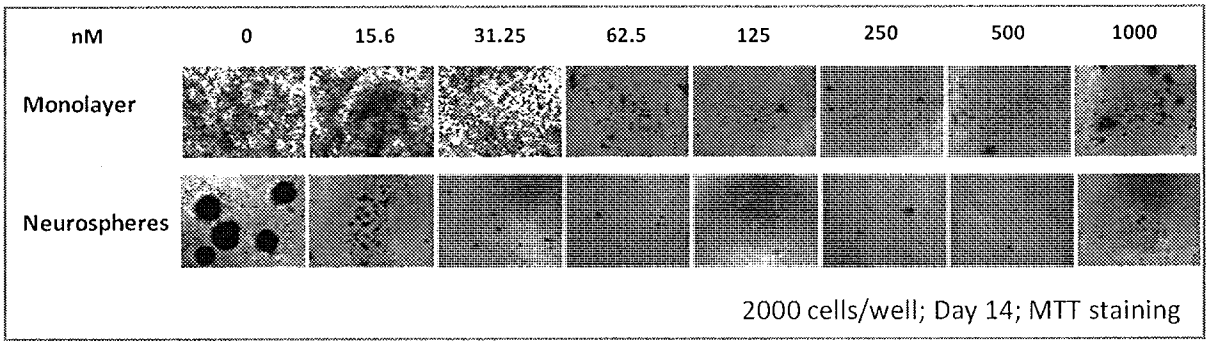


Figure 3

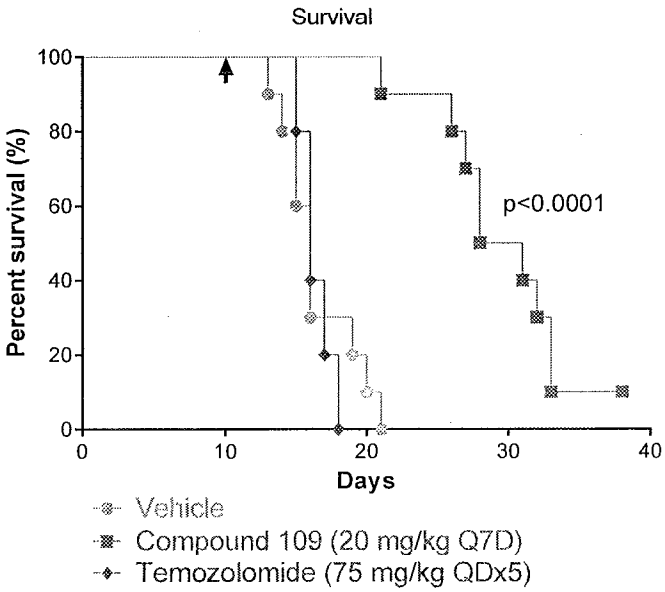


Figure 4

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[Continued on next page]

(54) Title: SUBSTITUTED REVERSE PYRIMIDINE BMI-1 INHIBITORS

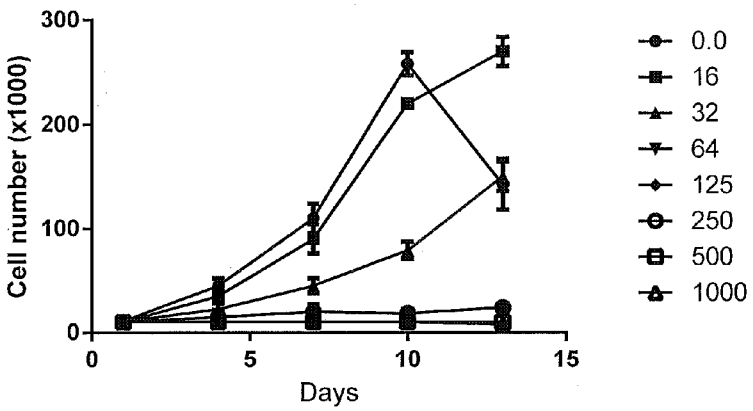

Figure 1

(57) Abstract: Amine substituted reverse pyrimidine compounds and forms thereof that inhibit the function and reduce the level of B-cell specific Moloney murine leukemia virus integration site 1 (Bmi-1) protein and methods for their use to inhibit Bmi-1 function and reduce the level of Bmi-1 to treat a cancer mediated by Bmi-1 are described herein.

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, STN, Google Scholar, PubChem

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0171245 A1 (CHARIFSON et al) 05 July 2012 (05.07.2012) entire document	1-20
A	WO 2011/121418 A1 (CAMACHO GOMEZ et al) 06 October 2011 (06.10.2011) entire document	1-20
A	US 7,226,927 B2 (CAI et al) 05 June 2007 (05.06.2007) entire document	1-20
A	US 2011/0190239 A1 (MOON et al) 04 August 2011 (04.08.2011) entire document	1-20
A, P	WO 2013/004332 A1 (HEINRICH et al) 10 January 2013 (10.01.2013) entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 May 2014	2 0 MAY 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-3, 5-11, and 19 have been analyzed subject to the restriction that the claims read on the formula (I) or form thereof as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound of Formula (I) or a form thereof, wherein R1 is heteroaryl optionally substituted on a carbon atom ring member with one R5 substituent; X is N; R2 is hydrogen; R3 is hydrogen; R4 is C3-14cycloalkyl; and R5 is cyano; wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof; methods of treatment thereof; and pharmaceutical compositions thereof.

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-20 as they read on the elected species (See Extra Sheet).

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Claims 1-20 have been analyzed subject to the restriction that the claims read on the formula (I) or form thereof as described in the Reply to Invitation to Pay Additional Fees in the International Application dated 01 April 2014. The claims are restricted to a compound of Formula (I) or a form thereof, wherein X is N; R1 is heteroaryl optionally substituted on a carbon atom ring member with two R5 substituent; R2 is amino; R3 is halo; R4 is aryl optionally substituted with one R6 substituent; and R5 is is independently selected from halo and C1-8alkyl; and R6 is halo-C1-8alkyl, wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof; methods of treatment thereof; and pharmaceutical compositions thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-20 are drawn to compounds of Formula (I) or a form thereof; methods of treatment thereof; and pharmaceutical compositions thereof.

The first invention of Group I+ is restricted to a compound of Formula (I) or a form thereof, wherein R1 is heteroaryl optionally substituted on a carbon atom ring member with one R5 substituent; X is N; R2 is hydrogen; R3 is hydrogen; R4 is C3-14cycloalkyl; and R5 is cyano; wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof; methods of treatment thereof; and pharmaceutical compositions thereof. It is believed that claims 1-3, 5-11, and 19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of Formula (I) or a form thereof, wherein R1 is heterocyclyl optionally substituted on a carbon atom ring member with one R5 substituent; X is N; R2 is hydrogen; R3 is hydrogen; R4 is C3-14cycloalkyl; and R5 is cyano; wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof; methods of treatment thereof; and pharmaceutical compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables R1, X, R2, R3, and R4.

The Groups I+ share the technical features of a compound of Formula (I) or a form thereof or species thereof, wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof; a method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering to the subject an effective amount of the compound thereof; a use of the compound thereof in the manufacture of a medicament; and a pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound thereof in admixture with a pharmaceutically acceptable excipient. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 7,226,927 to Cai et al. teach a compound of Formula (I) or a form thereof, wherein R1 is heterocyclyl; X is N; R2 is C1alkyl; R3 is hydrogen; R4 is aryl optionally substituted two R6 substituents; and R6 is independently selected from halo and C1alkoxy; wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof (Col. 14 Lns. 62-65 and Col. 18 Lns 13-14, ...novel compounds within the scope of Formulae I-III. Exemplary preferred compounds that may be...4-(2-Chloro-5-methoxyanilino)-2-morpholino-6-(methyl)pyrimidine...; Col. 84 Lns. 13-19, ...The caspase activity (Ratio) and potency (EC50) are summarized in Table I...; Cols. 85-86, Table I-continued, Compd # 131); a method of inhibiting to treat cancer in a subject in need thereof comprising administering to the subject an effective amount of the compound thereof (Col. 24 Lns 51-56, ...a therapeutic method useful to modulate in vivo apoptosis or in vivo neoplastic disease, comprising administering to a subject in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-III...; a use of the compound thereof in the manufacture of a medicament; and a pharmaceutical composition for use in treating a cancer comprising an effective amount of the compound thereof in admixture with a pharmaceutically acceptable excipient (Col. 26 Lns. 14-24, ...the present invention is directed to a composition effective to inhibit neoplasia comprising a bioconjugates of said compound of Formulae I-III, which functions as a caspase cascade activator and inducer of apoptosis, in bioconjugation...The antibodies and other molecules will deliver the compound of Formulae I-III to its targets and make it an effective anticancer agent...; Col. 29 Lns. 46-54, The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients...).

Additionally, US 2011/0190239 to Moon et al. teach a similar compound to the instant compound of Formula (I) (Para. [0008], one embodiment is a compound of Formula (I) selected from a compound of...Formula (Ic)...) a method of inhibiting Bmi-1 function and reducing the level of Bmi-1 to treat a cancer mediated by Bmi-1 in a subject in need thereof comprising administering to the subject an effective amount of the compound thereof (Para. [0001], Compounds, pharmaceutical compositions, and methods of using such compounds or compositions thereof for treating a disease modulated by B-cell specific Moloney murine leukemia virus integration site 1 (Bmi-1) protein expression are described. The compounds or compositions and methods of using such compounds or compositions are useful for treating cancer by down-regulating Bmi-1 protein expression); a use of the compound thereof in the manufacture of a medicament; and a pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound thereof in admixture with a pharmaceutically acceptable excipient (Para. [0270], pharmaceutical compositions described herein may be formulated as suspensions comprising a compound of Formula (I) or a form thereof in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

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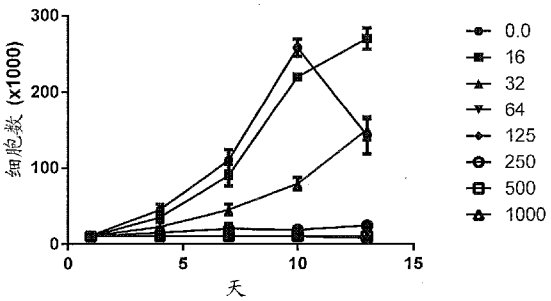
(54)发明名称

取代的反向嘧啶Bmi-1抑制剂

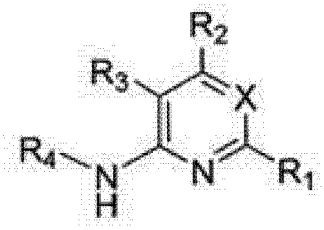
(57)摘要

本文中描述了抑制B-细胞特异性莫罗尼鼠白血病病毒整合位点1(Bmi-1)蛋白功能并降低其含量的胺取代的反向嘧啶化合物和其形式和其用于抑制Bmi-1功能并降低Bmi-1含量以治疗由Bmi-1介导的癌症的方法。



CN 104918919 A

1. 式 (I) 化合物：



(I)

或其形式，其中

R_1为任选在碳原子环成员上被一个、两个、三个或四个 R_5取代基取代或在氮原子环成员上被氧原子取代基取代以形成 N- 氧化物的杂芳基或杂环基；

X 为 N 或被氧原子取代基取代以形成 N- 氧化物的 N;

R_2为氢，氰基，卤素，羟基，硝基，C_{1-8}烷基，羟基 -C_{1-8}烷基，C_{1-8}烷氧基，氨基，C_{1-8}烷基 - 氨基，(C_{1-8}烷基)$_2$- 氨基，羟基 - 氨基，羟基 -C_{1-8}烷基 - 氨基，C_{1-8}烷氧基 -C_{1-8}烷基 - 氨基，C_{1-8}烷硫基，C_{1-8}烷基 - 羰基，C_{1-8}烷基 - 羰基 - 氨基，氨基 - 羰基，C_{1-8}烷基 - 氨基 - 羰基，(C_{1-8}烷基)$_2$- 氨基 - 羰基，氨基 - 羰基 - 氨基，C_{1-8}烷基 - 氨基 - 羰基 - 氨基，(C_{1-8}烷基)$_2$- 氨基 - 羰基 - 氨基，C_{1-8}烷氧基 - 羰基，C_{1-8}烷氧基 - 羰基 - 氨基，氨基 - 磺酰基，C_{1-8}烷基 - 氨基 - 磺酰基，(C_{1-8}烷基)$_2$- 氨基 - 磺酰基，氨基 - 磺酰基 - 氨基，C_{1-8}烷基 - 氨基 - 磺酰基 - 氨基，(C_{1-8}烷基)$_2$- 氨基 - 磺酰基 - 氨基，P(O)(R_7)$_2$- 氨基或杂芳基，其中杂芳基任选被一个、两个、三个或四个C_{1-8}烷基取代基取代；

R_3为氢，氰基，卤素，C_{1-8}烷基，氨基，C_{1-8}烷基 - 氨基或 (C_{1-8}烷基)$_2$- 氨基；

R_4为C_{3-14}环烷基，芳基，杂芳基或杂环基，各自任选被一个、两个、三个或四个 R_6取代基取代；

R_5独立地选自氰基，卤素，羟基，硝基，氧代，C_{1-8}烷基，氰基 -C_{1-8}烷基，卤素 -C_{1-8}烷基，羟基 -C_{1-8}烷基，C_{1-8}烷氧基，C_{1-8}烷氧基 -C_{1-8}烷基，卤素 -C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基 -C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷氧基 -C_{2-8}炔基，羧基，氨基，C_{1-8}烷基 - 氨基，(C_{1-8}烷基)$_2$- 氨基，氨基 -C_{1-8}烷基，C_{1-8}烷基 - 氨基 -C_{1-8}烷基，(C_{1-8}烷基)$_2$- 氨基 -C_{1-8}烷基，羟基 -C_{1-8}烷基 - 氨基，羟基 -C_{1-8}烷基 - 氨基 -C_{1-8}烷基，羟基 -C_{1-8}烷基 - 氨基 -C_{1-8}烷基 - 氨基，C_{1-8}烷硫基，C_{1-8}烷基 - 羰基，C_{1-8}烷基 - 羰基 - 氨基，C_{1-8}烷基 - 羰基 - 氧基，C_{1-8}烷基 - 羰基 - 氧基 -C_{1-8}烷基，C_{1-8}烷氧基 - 羰基，C_{1-8}烷氧基 - 羰基 -C_{1-8}烷基，C_{1-8}烷氧基 - 羰基 - 氨基，C_{1-8}烷基 - 磺酰基，C_{3-14}环烷基，芳基，芳基 -C_{1-8}烷基，芳基 - 氨基，芳基 -C_{1-8}烷基 - 氨基，杂芳基，杂芳基 -C_{1-8}烷基或杂环基，其中C_{3-14}环烷基，芳基，杂芳基或杂环基和芳基 -C_{1-8}烷基，芳基 - 氨基，芳基 -C_{1-8}烷基 - 氨基和杂芳基 -C_{1-8}烷基的芳基和杂芳基部分各自任选被一个、两个、三个、或四个卤素，C_{1-8}烷基，卤素 -C_{1-8}烷基，羟基 -C_{1-8}烷基，C_{1-8}烷氧基，卤素 -C_{1-8}烷氧基，羟基 -C_{1-8}烷氧基或羧基取代基取代；

R_6独立地选自氰基，卤素，羟基，硝基，C_{1-8}烷基，卤素 -C_{1-8}烷基，羟基 -C_{1-8}烷基，C_{1-8}烷氧基，卤素 -C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基 -C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷

氧基 -C_{2-8}炔基，羧基，甲酰基，甲酰基 - 氧基，C_{1-8}烷基 - 羰基，卤素 -C_{1-8}烷基 - 羰基，C_{1-8}烷硫基，卤素 -C_{1-8}烷硫基，氨基，C_{1-8}烷基 - 氨基，(C_{1-8}烷基)$_2$- 氨基，C_{1-8}烷基 - 羰基，C_{1-8}烷基 - 羰基 - 氧基，C_{1-8}烷基 - 羰基 - 氧基 -C_{1-8}烷基，C_{1-8}烷氧基 - 羰基，卤素 -C_{1-8}烷氧基 - 羰基，C_{1-8}烷氧基 - 羰基 -C_{1-8}烷基，C_{1-8}烷氧基 - 羰基 - 氨基，C_{1-8}烷氧基 - 羰基 - 氨基 -C_{1-8}烷基，氨基 - 羰基，C_{1-8}烷基 - 氨基 - 羰基，(C_{1-8}烷基)$_2$- 氨基 - 羰基，C_{1-8}烷基 - 羰基 - 氨基，C_{1-8}烷基 - 羰基 - 氨基 -C_{1-8}烷基，氨基 -C_{1-8}烷基，C_{1-8}烷基 - 氨基 -C_{1-8}烷基，(C_{1-8}烷基)$_2$- 氨基 -C_{1-8}烷基，氨基 -C_{1-8}烷基 - 氨基，C_{1-8}烷基 - 氨基 -C_{1-8}烷基 - 氨基，(C_{1-8}烷基)$_2$- 氨基 -C_{1-8}烷基 - 氨基，羟基 -C_{1-8}烷基 - 氨基，羟基 -C_{1-8}烷基 - 氨基 -C_{1-8}烷基，羟基 -C_{1-8}烷基 - 氨基 -C_{1-8}烷基 - 氨基，亚氨基 -C_{1-8}烷基，羟基 - 亚氨基 -C_{1-8}烷基，C_{1-8}烷氧基 - 亚氨基 -C_{1-8}烷基，C_{1-8}烷基 - 磺酰基，卤素 -C_{1-8}烷基 - 磺酰基，氨基 - 磺酰基，C_{1-8}烷基 - 氨基 - 磺酰基，(C_{1-8}烷基)$_2$- 氨基 - 磺酰基，$B(OR_8)_2$，C_{3-14}环烷基，杂环基 芳基或杂芳基，其中C_{3-14}环烷基，杂环基，芳基，和杂芳基各自任选被一个、两个、三个或四个卤素或C_{1-8}烷基取代基取代；

R_7独立地为羟基或(C_{1-8}烷氧基)$_n$，其中 n 代表 1 至 5 的整数；和，

R_8独立地为氢或C_{1-8}烷基；

其中所述化合物的形式选自其游离酸、游离碱、盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对映异构体或互变异构体。

2. 权利要求 1 所述的化合物，其中R_1为选自如下的任选取代的杂芳基或杂环基：1H- 吡唑基，1H- 咪唑基，1,2- 噁唑基，吡啶基，1H- 吲哚基，2H- 吲唑基，4,5,6,7- 四氢 -2H- 吲唑基，1H- 苯并咪唑基，咪唑并 [2,1-b][1,3] 噻唑基，吡唑并 [1,5-a] 吡啶基，吡唑并 [1,5-c] 嘧啶基，咪唑并 [1,2-a] 吡啶基，5,6,7,8- 四氢咪唑并 [1,2-a] 吡啶基，1H- 咪唑并 [4,5-b] 吡啶基，1H- 咪唑并 [4,5-c] 吡啶基，4,5,6,7- 四氢 -3H- 咪唑并 [4,5-c] 吡啶基，咪唑并 [1,2-a] 吡嗪基，咪唑并 [1,2-a] 嘧啶基，7H- 嘌呤基或喹啉基。

3. 权利要求 2 所述的化合物，其中 R_1为选自如下的任选取代的杂芳基：1H- 吡唑基，1H- 吲哚基，1H- 苯并咪唑基，吡唑并 [1,5-a] 吡啶基，咪唑并 [1,2-a] 吡啶基，1H- 咪唑并 [4,5-b] 吡啶基，咪唑并 [1,2-a] 吡嗪基或咪唑并 [1,2-a] 嘧啶基。

4. 选自如下的化合物或其形式：

N-(4- 甲氧基苯基)-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4- 胺

N-(2,3- 二氢 -1,4- 苯并二氧杂环己二烯 -6- 基)-2-(2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基) 嘧啶 -4- 胺

2-(2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

N-(4- 甲氧基苯基)-2-(2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基) 嘧啶 -4- 胺

N-(4- 氯苯基)-2-(2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基) 嘧啶 -4- 胺

2-(2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-N- 苯基嘧啶 -4- 胺

2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

N-(4- 氯苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-(4- 甲基苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-(4- 溴苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲氧基)苯基]嘧啶-4-胺

N-(4-溴苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺

N-(4-氯苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

N-(4-溴苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(4-甲基苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲基苯基)嘧啶-4-胺

2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺

N-(4-溴苯基)-2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]嘧啶-4-胺

N-(4-溴苯基)-2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺

2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲基苯基)嘧啶-4-胺

N-(1,3-苯并二氧杂环戊烯-5-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(2,3-二氢-1,4-苯并二氧杂环己二烯-6-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(6-甲氧基吡啶-3-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N^2,N^2-二甲基-N^5-{2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-基}吡啶-2,5-二胺

2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

N-(3-氟-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(3-氯-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(3-氯-4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-(4-乙氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-[4-(丙-2-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

N-[4-(1H-吡唑-1-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧

啶 -4- 胺

N-(3- 氯 -4- 甲氧基苯基)-2-(2- 甲基 -1*H*- 苯并咪唑 -1- 基) 嘧啶 -4- 胺

2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

N-(3- 氯 -4- 甲氧基苯基)-2-[2-(三氟甲基)-1H- 苯并咪唑 -1- 基] 嘧啶 -4- 胺

5- 氟 -N-(4- 甲基苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

5- 氯 -N-(4- 甲基苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-(4- 甲氧基苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡嗪 -3- 基] 嘧啶 -4- 胺

2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡嗪 -3- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

N-(4- 氯苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡嗪 -3- 基] 嘧啶 -4- 胺

2-[6- 甲氧基 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

2-[6- 甲氧基 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基]-N-[4-(三氟甲氧基) 苯基] 嘧啶 -4- 胺

N-(4- 甲氧基苯基)-2-[6- 甲氧基 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-[4-(二氟甲氧基) 苯基]-2-[6- 甲氧基 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

2-{[6-{[4-(二氟甲氧基) 苯基] 氨基 }-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4- 基] 氨基 } 乙醇

N-[4-(二氟甲氧基) 苯基]-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡嗪 -3- 基] 嘧啶 -4- 胺

2-[6- 氟 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4- 胺

N-[4-(二氟甲氧基) 苯基]-2-[6- 氟 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-[4-(三氟甲基) 苯基]-2-[2-(三氟甲基) 吡唑并 [1,5-a] 吡啶 -3- 基] 嘧啶 -4- 胺

2-{[2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-6-{[4-(三氟甲基) 苯基] 氨基 } 嘧啶 -4- 基] 氨基 } 乙醇

N^4-(2- 甲氧基乙基)-2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N^6-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

N^4-[4-(二氟甲氧基) 苯基]-N^6-(2- 甲氧基乙基)-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 甲氧基苯基)-2-[2-(三氟甲基) 吡唑并 [1,5-a] 吡啶 -3- 基] 嘧啶 -4- 胺

N-[4-(二氟甲氧基) 苯基]-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4- 胺

N-(4- 甲基苯基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡嗪 -3- 基] 嘧啶 -4- 胺

2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

2-(5,6- 二氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基) 苯基]-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧

啶 -4,6- 二胺

2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(三氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4,6-二胺

2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

N-[4-(三氟甲基)苯基]-2-(1,3,5-三甲基-1H-吡唑-4-基)嘧啶-4,6-二胺

2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-6-氟咪唑并[1,2-a]吡啶-3-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺

N-[4-(三氟甲基)苯基]-2-(2,5,6-三甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[3-氟-4-(三氟甲基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-5-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

[3-(4-氨基-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-6-氟咪唑并[1,2-a]吡啶-2-基]甲醇

2-(6-溴-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2,6-二甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(6-乙基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二

胺

2-(4,6- 二氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[3- 氟 -4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-{[2-(4,6- 二氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-6-{[4-(三氟甲基)苯基]氨基}嘧啶 -4- 基]氨基}乙醇

2-(6- 乙烯基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-(2- 环丙基 -6- 氟 -1H- 咪唑并 [4,5-b] 吡啶 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-(6- 氯 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-(6- 氟 -2- 甲基 -1H- 咪唑并 [4,5-b] 吡啶 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

5- 氟 -2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(6- 氯 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(二氟甲氧基)苯基]嘧啶 -4,6- 二胺

2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(5- 氯 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(二氟甲氧基)苯基]嘧啶 -4,6- 二胺

2-(6-氟-2-甲基咪唑并[1,2-a]嘧啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3- 氟苯基]-2-(5,6- 二氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基)苯基]-2-(5,6- 二氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)嘧啶 -4,6- 二胺

2-(2- 环丙基 -6- 氟 -1H- 咪唑并 [4,5-b] 吡啶 -1- 基)-N-[4-(二氟甲氧基)苯基]嘧啶 -4,6- 二胺

2-(6- 氯 -2- 甲基 -1H- 咪唑并 [4,5-b] 吡啶 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

2-(6- 氯 -2- 乙基 -1H- 咪唑并 [4,5-b] 吡啶 -1- 基)-N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基)苯基]-5- 氟 -2-(2- 甲基 -1H- 苯并咪唑 -1- 基)嘧啶 -4,6- 二胺

2-(2- 乙基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-[4-(三氟甲基)苯基]嘧啶 -4,6- 二胺

5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二

胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺

2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-[2-(二氟甲基)-6-氟-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(甲基硫烷基)苯基]嘧啶-4,6-二胺

2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二

胺

2-[2-(丙-2-基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-甲基吡唑并[1,5-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

5-氯-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

5-氯-2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

5-氯-N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

5-甲基-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)嘧啶-4,6-二胺

5- 氟 -N-[4-(三氟甲基) 苯基]-2-(2,6,8- 三甲基咪唑并 [1,2-a] 吡嗪 -3- 基) 嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基) 苯基]-5- 氟 -2-(2,6,8- 三甲基咪唑并 [1,2-a] 吡嗪 -3- 基) 嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基)-3- 氟苯基]-5- 氟 -2-(2,6,8- 三甲基咪唑并 [1,2-a] 吡嗪 -3- 基) 嘧啶 -4,6- 二胺

5- 氟 -2-(2- 甲基吡唑并 [1,5-a] 吡啶 -3- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

5- 氟 -2-[6- 氟 -2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

2-(2- 环丙基吡唑并 [1,5-a] 吡啶 -3- 基)-N-[4-(二氟甲氧基) 苯基]-5- 氟嘧啶 -4,6- 二胺

[3-(4- 氨基 -6-{[4-(二氟甲氧基) 苯基] 氨基 }-5- 氟嘧啶 -2- 基)-5- 氟吡唑并 [1,5-a] 吡啶 -2- 基] 甲醇

2-[2-(甲基硫烷基)-1H- 苯并咪唑 -1- 基]-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[6-(三氟甲基) 吡啶 -3- 基] 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

N-(4- 氯苯基)-5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基) 苯基]-2-(2- 乙基 -5- 氟吡唑并 [1,5-a] 吡啶 -3- 基)-5- 氟嘧啶 -4,6- 二胺

2-(2- 乙基 -5- 氟吡唑并 [1,5-a] 吡啶 -3- 基)-5- 氟 -N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-5-氟吡唑并 [1,5-a] 吡啶-3-基)-5-氟嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(3- 甲氧基苯基) 嘧啶 -4,6- 二胺

N-(3- 氯苯基)-5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲氧基) 苯基] 嘧啶 -4,6- 二胺

4-{[6- 氨基 -5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4- 基] 氨基 } 苯甲腈

4-{[6- 氨基 -5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4- 基] 氨基 } 苯甲酸甲酯

5- 氟 -2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(3- 甲基苯基) 嘧啶 -4,6- 二胺

5- 氟 -N-(3- 甲氧基苯基)-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

N-(4- 甲氧基苯基)-2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-[4-(二甲基氨基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

5-氟-N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-(4-氯苯基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

4-{[6-氨基-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈

N-(1,3-苯并二氧杂环戊烯-5-基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-(3-氟-4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-(6-甲氧基吡啶-3-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-(4-氯苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

4-{[6-氨基-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈

2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-硝基苯基)嘧啶-4,6-二胺

N-(4-溴苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺

2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺

N-(4-氯苯基)-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲基苯基)嘧啶-4,6-二胺

5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲氧基苯基)嘧啶-4,6-二胺

N-(4-氯苯基)-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈

1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈

1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈

1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈

1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈

1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈

1-{4-氨基-6-[(4-氯苯基)氨基]-5-氟嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

5-氟-N-(4-甲氧基苯基)-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-(4-氯苯基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

5-氟-N-(4-甲氧基苯基)-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)嘧啶-4,6-二胺

N-(1,3-苯并二氧杂环戊烯-5-基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺

2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺

2-(5,7-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

N-(4-氯苯基)-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧

啶 -4,6- 二胺

5- 氟 -2-(6- 甲氧基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 甲氧基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

N-(1,3- 苯并二氧杂环戊烯 -5- 基)-5- 氟 -2-(6- 甲氧基 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯苯基)-5- 氟 -2-(6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基) 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

5- 氟 -2-(6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

5- 氟 -2-(2- 甲基 -5- 硝基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

5- 氟 -N-(4- 甲氧基苯基)-2-(2- 甲基 -5- 硝基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

2-(6- 氨基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

2-(6- 氨基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(二氟甲氧基) 苯基]-5- 氟嘧啶 -4,6- 二胺

2-(6- 氨基 -2- 甲基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

N-(4- 氯苯基)-5- 氟 -2-(5- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯 -3- 氟苯基)-5- 氟 -2-(5- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯 -3- 氟苯基)-5- 氟 -2-(2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯 -3- 氟苯基)-5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯苯基)-2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

N-[4-(二甲基氨基) 苯基]-2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

N-(4- 氯 -3- 氟苯基)-2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(3- 甲基苯基) 嘧啶 -4,6- 二胺

N-(2,2- 二氟 -1,3- 苯并二氧杂环戊烯 -5- 基)-2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基) 嘧啶 -4,6- 二胺

2-(2- 乙基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-(4- 甲基苯基) 嘧啶 -4,6- 二胺

2-(2- 乙基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺

2-(2- 乙基 -1H- 苯并咪唑 -1- 基)-5- 氟 -N-[4-(三氟甲氧基) 苯基] 嘧啶 -4,6- 二

胺

N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-(4-氯苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-(4-氯-3-氟苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺

2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

N-(4-氯苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

N-(4-氯-3-氟苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺

5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺，和，

2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺；

其中所述化合物的形式选自其盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对映体或互变异构体。

5.抑制Bmi-1功能并降低Bmi-1含量以对有此需要的对象治疗由Bmi-1介导的癌症的方法，其包括对该对象给予有效量的权利要求1的化合物。

6.权利要求5所述的方法，其进一步包括使来自所述对象的具有升高的Bmi-1含量的细胞与一定量的所述化合物接触，其中所述细胞选自癌细胞、肿瘤细胞、癌症干细胞、或肿瘤干细胞，确定所述化合物抑制细胞中Bmi-1功能的有效量，和随后对所述对象给予该有效量的所述化合物。

7.权利要求6所述的方法，其中被确定为抑制接触的细胞中Bmi-1功能的有效量的所述化合物降低了所述接触的细胞中Bmi-1含量。

8.权利要求7所述的方法，其中所述化合物的有效量为约0.001 mg/Kg/天至约500 mg/Kg/天。

9.权利要求7所述的方法，其中所述化合物或其形式的有效量为约0.1 ng至约3500 mg。

10.权利要求5所述的方法，包括给予所述化合物和一种或多种选自如下的附加试剂的组合：抗癌剂，抗增殖剂，化疗剂，免疫调节剂，抗血管生成剂，抗炎剂，烷基化剂，甾族和非甾族抗炎剂，镇痛剂，白三烯拮抗剂，β2-激动剂，抗胆碱剂，激素试剂，生物制剂，微管蛋白结合剂，糖皮质激素，皮质甾类试剂，抗菌剂，抗组胺药，抗疟疾试剂，抗病毒剂，抗生素等；并任选与放射疗法组合。

11.权利要求1所述的化合物在制备药物中的用途，所述药物用于抑制Bmi-1功能并降低Bmi-1含量以对有此需要的对象治疗由Bmi-1介导的癌症，包括对该对象给予有效量的所述药物。

12. 抑制 Bmi-1 功能并降低 Bmi-1 含量以对有此需要的对象治疗由 Bmi-1 介导的癌症的方法，包括对该对象给予有效量的权利要求 4 所述的化合物。

13. 权利要求 12 所述的方法，还包括使来自所述对象的具有升高的 Bmi-1 含量的细胞与一定量的所述化合物接触，其中所述细胞选自癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞，确定所述化合物抑制细胞中 Bmi-1 功能的有效量，和随后给予该对象该有效量的所述化合物。

14. 权利要求 13 所述的方法，其中被确定为抑制接触的细胞中 Bmi-1 功能的有效量的化合物降低了该接触的细胞中 Bmi-1 含量。

15. 权利要求 14 所述的方法，其中所述化合物的有效量为约 0.001 mg/Kg/ 天至约 500 mg/Kg/ 天。

16. 权利要求 14 所述的方法，其中所述化合物的有效量为约 0.1 ng 至约 3500 mg。

17. 权利要求 12 所述的方法，包括给予所述化合物与一种或多种选自如下的附加试剂的组合：抗癌剂，抗增殖剂，化疗剂，免疫调节剂，抗血管生成剂，抗炎剂，烷基化剂，甾族和非甾族抗炎剂，镇痛剂，白三烯拮抗剂，β2- 激动剂，抗胆碱剂，激素试剂，生物制剂，微管蛋白结合剂，糖皮质激素，皮质甾类试剂，抗菌剂，抗组胺药，抗疟疾试剂，抗病毒剂，抗生素等；并任选与放射疗法组合。

18. 权利要求 4 的化合物在制备药物中的用途，所述药物用于抑制 Bmi-1 功能并降低 Bmi-1 含量以对有此需要的对象治疗由 Bmi-1 介导的癌症，包括对该对象给予有效量的该药物。

19. 用于治疗由 Bmi-1 介导的癌症的药物组合物，其包含有效量的权利要求 1 的化合物和药学上可接受的赋形剂的混合。

20. 用于治疗由 Bmi-1 介导的癌症的药物组合物，其包含有效量的权利要求 4 的化合物和药学上可接受的赋形剂的混合。

取代的反向嘧啶 Bmi-1 抑制剂

[0001] 简介

描述了抑制 B- 细胞特异性莫罗尼鼠白血病病毒整合位点 1(Bmi-1) 蛋白的功能和降低其含量的取代的反向 (reverse) 嘧啶化合物和使用此类化合物治疗由 Bmi-1 介导的癌症的方法。更具体地，抑制 Bmi-1 功能并降低 Bmi-1 含量的胺取代的反向嘧啶化合物用于治疗由 Bmi-1 介导的癌症。

[0002] 背景

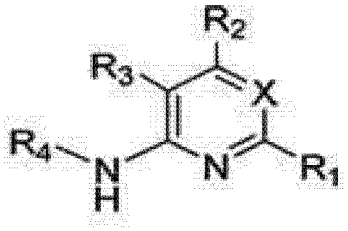
Bmi-1 最初由其在各种白血病和淋巴瘤中的过度表达识别。随后，Bmi-1 已经示出在正常细胞中过度表达时具有致癌活性并在维护癌症干细胞群体中起作用。Bmi-1 在很多肿瘤类型中增加并且在血液系统癌症和很多实体瘤包括脑癌中是重要的。由 siRNA 导致的在肿瘤细胞中 Bmi-1 含量的减少导致细胞凋亡和 / 或细胞衰老并提高对细胞毒素剂的敏感性。Bmi-1 充当 PRC1 复合体 (多梳抑制复合体 -1) 的关键调节组分，但没有酶活性。因此，由传统药物发现方法靶向 Bmi-1 是有问题的。

[0003] 由于细胞内 Bmi-1 含量通过转录和转录后机制紧密调节，能够利用该调节靶向该重要蛋白。因此，仍然需要提供抑制 Bmi-1 功能并降低 Bmi-1 含量以治疗由 Bmi-1 介导的癌症的化合物。

[0004] 概述

本文中描述了抑制 Bmi-1 功能并降低 Bmi-1 含量的某些胺取代的反向嘧啶化合物和它们用于治疗由 Bmi-1 介导的癌症的方法。

[0005] 描述了式 (I) 化合物：



(I)

其中 X, R_1, R_2, R_3 和 R_4 如上文定义，包括其形式和药物组合物，和使用此类化合物、其形式或组合物对有此需要的人类对象治疗由 Bmi-1 介导的癌症的方法。

[0006] 附图简述

图 1 示范了由于采用式 (I) 化合物或其形式治疗导致 BXD GBM 模型中 CSC 群体的剂量依赖性降低。

[0007] 图 2 示范了由于采用式 (I) 化合物或其形式治疗导致 BXD GBM 模型中 CSC 群体的降低。

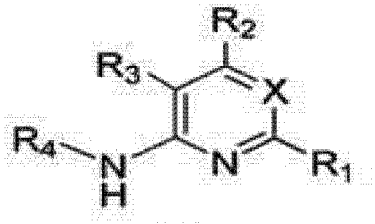
[0008] 图 3 示范了由于使细胞接触式 (I) 化合物或其形式导致肿瘤球分析中单层和神经球 CSC 群体的降低。

[0009] 图 4 示范了在恶性胶质瘤原位模型中采用媒介物、替莫唑胺或式 (I) 化合物、或其形式治疗的小鼠存活的对比效果。

[0010] 详述

描述了用于抑制Bmi-1功能并降低Bmi-1含量的胺取代的反向嘧啶化合物和用于治疗由Bmi-1介导的癌症的方法。

[0011] 在一种实施方案中为式(I)化合物：



(I)

或其形式，其中

R_1为任选在碳原子环成员上被一个、两个、三个或四个R_5取代基取代或在氮原子环成员上被氧原子取代基取代以形成N-氧化物的杂芳基或杂环基；

X为N或被氧原子取代基取代以形成N-氧化物的N;

R_2为氢，氰基，卤素，羟基，硝基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，氨基，C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基，羟基-氨基，羟基-C_{1-8}烷基-氨基，C_{1-8}烷氧基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氨基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，氨基-羰基-氨基，C_{1-8}烷基-氨基-羰基-氨基，(C_{1-8}烷基)$_2$-氨基-羰基-氨基，C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-氨基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基，氨基-磺酰基-氨基，C_{1-8}烷基-氨基-磺酰基-氨基，(C_{1-8}烷基)$_2$-氨基-磺酰基-氨基，P(O)(R_7)$_2$-氨基或杂芳基，其中杂芳基任选被一个、两个、三个或四个C_{1-8}烷基取代基取代；

R_3为氢，氰基，卤素，C_{1-8}烷基，氨基，C_{1-8}烷基-氨基或(C_{1-8}烷基)$_2$-氨基；

R_4为C_{3-14}环烷基，芳基，杂芳基或杂环基，各自任选被一个、两个、三个或四个R_6取代基取代；

R_5独立地选自氰基，卤素，羟基，硝基，氧代，C_{1-8}烷基，氰基-C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，C_{1-8}烷氧基-C_{1-8}烷基，卤素-C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基-C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷氧基-C_{2-8}炔基，羧基，氨基，C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基，氨基-C_{1-8}烷基，C_{1-8}烷基-氨基-C_{1-8}烷基，(C_{1-8}烷基)$_2$-氨基-C_{1-8}烷基，羟基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氨基，C_{1-8}烷基-羰基-氧基，C_{1-8}烷基-羰基-氧基-C_{1-8}烷基，C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-C_{1-8}烷基，C_{1-8}烷氧基-羰基-氨基，C_{1-8}烷基-磺酰基，C_{3-14}环烷基，芳基，芳基-C_{1-8}烷基，芳基-氨基，芳基-C_{1-8}烷基-氨基，杂芳基，杂芳基-C_{1-8}烷基或杂环基，其中C_{3-14}环烷基，芳基，杂芳基或杂环基和芳基-C_{1-8}烷基，芳基-氨基，芳基-C_{1-8}烷基-氨基和杂芳基-C_{1-8}烷基的芳基和杂芳基部分各自任选被一个、两个、三个或四个卤素，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，羟基-C_{1-8}烷氧基或羧基取代基取代；

R_6独立地选自氰基，卤素，羟基，硝基，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基-C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷氧基-C_{2-8}炔基，羧基，甲酰基，甲酰基-氧基，C_{1-8}烷基-羰基，卤素-C_{1-8}烷基-羰基，C_{1-8}烷硫基，卤素-C_{1-8}烷硫基，氨基，C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氧基，C_{1-8}烷基-羰基-氧基-C_{1-8}烷基，C_{1-8}烷氧基-羰基，卤素-C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-C_{1-8}烷基，C_{1-8}烷氧基-羰基-氨基，C_{1-8}烷氧基-羰基-氨基-C_{1-8}烷基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，C_{1-8}烷基-羰基-氨基，C_{1-8}烷基-羰基-氨基-C_{1-8}烷基，氨基-C_{1-8}烷基，C_{1-8}烷基-氨基-C_{1-8}烷基，(C_{1-8}烷基)$_2$-氨基-C_{1-8}烷基，氨基-C_{1-8}烷基-氨基，C_{1-8}烷基-氨基-C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基-氨基，亚氨基-C_{1-8}烷基，羟基-亚氨基-C_{1-8}烷基，C_{1-8}烷氧基-亚氨基-C_{1-8}烷基，C_{1-8}烷基-磺酰基，卤素-C_{1-8}烷基-磺酰基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基，$B(OR_8)_2$，C_{3-14}环烷基，杂环基，芳基或杂芳基，其中C_{3-14}环烷基，杂环基，芳基，和杂芳基各自任选被一个、两个、三个或四个卤素或C_{1-8}烷基取代基取代；

R_7独立地为羟基或(C_{1-8}烷氧基)$_n$，其中n代表1至5的整数；和，

R_8独立地为氢或C_{1-8}烷基。

[0012] 另一实施方案包括式(I)化合物，其中R_1是任选取代的杂芳基或杂环基，其选自1H-吡唑基，1H-咪唑基，1,2-噁唑基，吡啶基，1H-吲哚基，2H-吲唑基，4,5,6,7-四氢-2H-吲唑基，1H-苯并咪唑基，咪唑并[2,1-b][1,3]噻唑基，吡唑并[1,5-a]吡啶基，吡唑并[1,5-c]嘧啶基，咪唑并[1,2-a]吡啶基，5,6,7,8-四氢咪唑并[1,2-a]吡啶基，1H-咪唑并[4,5-b]吡啶基，1H-咪唑并[4,5-c]吡啶基，4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶基，咪唑并[1,2-a]吡嗪基，咪唑并[1,2-a]嘧啶基，7H-嘌呤基或喹啉基。

[0013] 另一实施方案包括式(I)化合物，其中R_1是任选取代的杂芳基或杂环基，其选自1H-吡唑基，1H-咪唑基，1,2-噁唑基，吡啶基，1H-吲哚基，2H-吲唑基，4,5,6,7-四氢-2H-吲唑基，1H-苯并咪唑基，咪唑并[2,1-b][1,3]噻唑基，吡唑并[1,5-a]吡啶基，咪唑并[1,2-a]吡啶基，5,6,7,8-四氢咪唑并[1,2-a]吡啶基，1H-咪唑并[4,5-b]吡啶基，1H-咪唑并[4,5-c]吡啶基，4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶基，咪唑并[1,2-a]吡嗪基，咪唑并[1,2-a]嘧啶基，7H-嘌呤基或喹啉基。

[0014] 另一实施方案包括式(I)化合物，其中R_1是任选取代的杂芳基或杂环基，其选自1H-吡唑-4-基，1H-咪唑-1-基，1H-咪唑-5-基，1,2-噁唑-4-基，1,2-噁唑-5-基，吡啶-4-基，1H-吲哚-1-基，1H-吲哚-3-基，1H-吲哚-4-基，2H-吲唑-3-基，4,5,6,7-四氢-2H-吲唑-3-基，1H-苯并咪唑-1-基，咪唑并[2,1-b][1,3]噻唑-5-基，吡唑并[1,5-a]吡啶-2-基，吡唑并[1,5-a]吡啶-3-基，吡唑并[1,5-a]吡啶-7-基，吡唑并[1,5-c]嘧啶-3-基，咪唑并[1,2-a]吡啶-2-基，咪唑并[1,2-a]吡啶-3-基，咪唑并[1,2-a]吡啶-5-基，5,6,7,8-四氢咪唑并[1,2-a]吡啶-3-基，1H-咪唑并[4,5-b]吡啶-1-基，1H-咪唑并[4,5-c]吡啶-1-基，4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶-3-基，咪唑并[1,2-a]吡嗪-3-基，咪唑并[1,2-a]嘧啶-3-基，

7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0015] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基或杂环基，其选自 1H- 吡唑 -4- 基， 1H- 咪唑 -1- 基， 1H- 咪唑 -5- 基， 1,2- 噁唑 -4- 基， 1,2- 噁唑 -5- 基，吡啶 -4- 基， 1H- 吲哚 -1- 基， 1H- 吲哚 -4- 基， 2H- 吲唑 -3- 基， 4,5,6,7- 四氢 -2H- 吲唑 -3- 基， 1H- 苯并咪唑 -1- 基， 咪唑并 [2,1-b][1,3] 噻唑 -5- 基， 吡唑并 [1,5-a] 吡啶 -3- 基， 吡唑并 [1,5-a] 吡啶 -7- 基， 咪唑并 [1,2-a] 吡啶 -3- 基， 咪唑并 [1,2-a] 吡啶 -5- 基， 5,6,7,8- 四氢咪唑并 [1,2-a] 吡啶 -3- 基， 1H- 咪唑并 [4,5-b] 吡啶 -1- 基，1H- 咪唑并 [4,5-c] 吡啶 -1- 基， 4,5,6,7- 四氢 -3H- 咪唑并 [4,5-c] 吡啶 -3- 基， 咪唑并 [1,2-a] 吡嗪 -3- 基， 咪唑并 [1,2-a] 嘧啶 -3- 基， 7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0016] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基或杂环基，其选自 1H- 吡唑 -4- 基， 1H- 咪唑 -1- 基， 1H- 咪唑 -5- 基， 1,2- 噁唑 -4- 基， 1,2- 噁唑 -5- 基，吡啶 -4- 基， 1H- 吲哚 -1- 基， 1H- 吲哚 -4- 基， 2H- 吲唑 -3- 基， 4,5,6,7- 四氢 -2H- 吲唑 -3- 基， 1H- 苯并咪唑 -1- 基， 咪唑并 [2,1-b][1,3] 噻唑 -5- 基， 吡唑并 [1,5-a] 吡啶 -3- 基， 吡唑并 [1,5-a] 吡啶 -7- 基， 咪唑并 [1,2-a] 吡啶 -3- 基， 咪唑并 [1,2-a] 吡啶 -5- 基， 5,6,7,8- 四氢咪唑并 [1,2-a] 吡啶 -3- 基， 1H- 咪唑并 [4,5-b] 吡啶 -1- 基，1H- 咪唑并 [4,5-c] 吡啶 -1- 基， 4,5,6,7- 四氢 -3H- 咪唑并 [4,5-c] 吡啶 -3- 基， 7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0017] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑基， 1H- 咪唑基， 1,2- 噁唑基， 吡啶基， 1H- 吲哚基， 2H- 吲唑基， 1H- 苯并咪唑基，咪唑并 [2,1-b][1,3] 噻唑基， 吡唑并 [1,5-a] 吡啶基， 吡唑并 [1,5-c] 嘧啶基， 咪唑并 [1,2-a] 吡啶基， 1H- 咪唑并 [4,5-b] 吡啶基， 1H- 咪唑并 [4,5-c] 吡啶基， 咪唑并 [1,2-a] 吡嗪基， 咪唑并 [1,2-a] 嘧啶基， 7H- 嘌呤基或喹啉基。

[0018] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑基， 1H- 咪唑基， 1,2- 噁唑基， 吡啶基， 1H- 吲哚基， 2H- 吲唑基， 1H- 苯并咪唑基，咪唑并 [2,1-b][1,3] 噻唑基， 吡唑并 [1,5-a] 吡啶基， 咪唑并 [1,2-a] 吡啶基， 1H- 咪唑并 [4,5-b] 吡啶基， 1H- 咪唑并 [4,5-c] 吡啶基， 咪唑并 [1,2-a] 吡嗪基， 咪唑并 [1,2-a] 嘧啶基， 7H- 嘌呤基或喹啉基。

[0019] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑基， 1H- 咪唑基， 1,2- 噁唑基， 吡啶基， 1H- 吲哚基， 2H- 吲唑基， 1H- 苯并咪唑基，咪唑并 [2,1-b][1,3] 噻唑基， 吡唑并 [1,5-a] 吡啶基， 咪唑并 [1,2-a] 吡啶基， 1H- 咪唑并 [4,5-b] 吡啶基， 1H- 咪唑并 [4,5-c] 吡啶基， 7H- 嘌呤基或喹啉基。

[0020] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑基， 1H- 吲哚基， 1H- 苯并咪唑基， 吡唑并 [1,5-a] 吡啶基， 咪唑并 [1,2-a] 吡啶基，1H- 咪唑并 [4,5-b] 吡啶基， 咪唑并 [1,2-a] 吡嗪基或咪唑并 [1,2-a] 嘧啶基。

[0021] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑基， 1H- 吲哚基， 1H- 苯并咪唑基， 吡唑并 [1,5-a] 吡啶基， 咪唑并 [1,2-a] 吡啶基或 1H- 咪唑并 [4,5-b] 吡啶基。

[0022] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自咪唑并 [1,2-a] 吡嗪基或咪唑并 [1,2-a] 嘧啶基。

[0023] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的咪唑并 [1,2-a] 吡嗪基。

[0024] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的咪唑并 [1,2-a] 嘧啶基。

[0025] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 咪唑 -1- 基，1H- 咪唑 -5- 基，1,2- 噁唑 -4- 基，1,2- 噁唑 -5- 基，吡啶 -4- 基，1H- 吲哚 -1- 基，1H- 吲哚 -3- 基，1H- 吲哚 -4- 基，2H- 吲唑 -3- 基，1H- 苯并咪唑 -1- 基，咪唑并 [2,1-b][1,3] 噻唑 -5- 基，吡唑并 [1,5-a] 吡啶 -2- 基，吡唑并 [1,5-a] 吡啶 -3- 基，吡唑并 [1,5-a] 吡啶 -7- 基，吡唑并 [1,5-c] 嘧啶 -3- 基，咪唑并 [1,2-a] 吡啶 -2- 基，咪唑并 [1,2-a] 吡啶 -3- 基，咪唑并 [1,2-a] 吡啶 -5- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，1H- 咪唑并 [4,5-c] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基，咪唑并 [1,2-a] 嘧啶 -3- 基，7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0026] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 咪唑 -1- 基，1H- 咪唑 -5- 基，1,2- 噁唑 -4- 基，1,2- 噁唑 -5- 基，吡啶 -4- 基，1H- 吲哚 -1- 基，1H- 吲哚 -4- 基，2H- 吲唑 -3- 基，1H- 苯并咪唑 -1- 基，咪唑并 [2,1-b][1,3] 噻唑 -5- 基，吡唑并 [1,5-a] 吡啶 -3- 基，吡唑并 [1,5-a] 吡啶 -7- 基，咪唑并 [1,2-a] 吡啶 -3- 基，咪唑并 [1,2-a] 吡啶 -5- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，1H- 咪唑并 [4,5-c] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基，咪唑并 [1,2-a] 嘧啶 -3- 基，7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0027] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 咪唑 -1- 基，1H- 咪唑 -5- 基，1,2- 噁唑 -4- 基，1,2- 噁唑 -5- 基，吡啶 -4- 基，1H- 吲哚 -1- 基，1H- 吲哚 -4- 基，2H- 吲唑 -3- 基，1H- 苯并咪唑 -1- 基，咪唑并 [2,1-b][1,3] 噻唑 -5- 基，吡唑并 [1,5-a] 吡啶 -7- 基，咪唑并 [1,2-a] 吡啶 -5- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，1H- 咪唑并 [4,5-c] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基，咪唑并 [1,2-a] 嘧啶 -3- 基，7H- 嘌呤 -7- 基或喹啉 -4- 基。

[0028] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 吲哚 -1- 基，1H- 吲哚 -3- 基，1H- 吲哚 -4- 基，1H- 苯并咪唑 -1- 基，吡唑并 [1,5-a] 吡啶 -2- 基，吡唑并 [1,5-a] 吡啶 -3- 基，吡唑并 [1,5-a] 吡啶 -7- 基，咪唑并 [1,2-a] 吡啶 -2- 基，咪唑并 [1,2-a] 吡啶 -3- 基，咪唑并 [1,2-a] 吡啶 -5- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基或咪唑并 [1,2-a] 嘧啶 -3- 基。

[0029] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 吲哚 -3- 基，1H- 苯并咪唑 -1- 基，吡唑并 [1,5-a] 吡啶 -2- 基，吡唑并 [1,5-a] 吡啶 -3- 基，咪唑并 [1,2-a] 吡啶 -2- 基，咪唑并 [1,2-a] 吡啶 -3- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基或咪唑并 [1,2-a] 嘧啶 -3- 基。

[0030] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的杂芳基，其选自 1H- 吡唑 -4- 基，1H- 吲哚 -3- 基，1H- 苯并咪唑 -1- 基，吡唑并 [1,5-a] 吡啶 -3- 基，咪唑并 [1,2-a] 吡啶 -3- 基，1H- 咪唑并 [4,5-b] 吡啶 -1- 基，咪唑并 [1,2-a] 吡嗪 -3- 基或咪唑并 [1,2-a] 嘧啶 -3- 基。

[0031] 另一实施方案包括式 (I) 化合物，其中 R_1是任选取代的咪唑并 [1,2-a] 吡嗪 -3- 基。

[0032] 另一实施方案包括式(I)化合物，其中R_1是任选取代的咪唑并[1,2-a]嘧啶-3-基。

[0033] 另一实施方案包括式(I)化合物，其中R_1是任选取代的杂环基，其选自4,5,6,7-四氢-2H-吲唑基，5,6,7,8-四氢咪唑并[1,2-a]吡啶基或4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶基。

[0034] 另一实施方案包括式(I)化合物，其中R_1是任选取代的杂环基，其选自4,5,6,7-四氢-2H-吲唑-3-基，5,6,7,8-四氢咪唑并[1,2-a]吡啶-3-基或4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶-3-基。

[0035] 另一实施方案包括式(I)化合物，其中X为N。

[0036] 另一实施方案包括式(I)化合物，其中X为被氧原子取代基取代以形成N-氧化物的N。

[0037] 另一实施方案包括式(I)化合物，其中R_2为氰基，卤素，羟基，硝基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，氨基，C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基，羟基-氨基，羟基-C_{1-8}烷基-氨基，C_{1-8}烷氧基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氨基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，氨基-羰基-氨基，C_{1-8}烷基-氨基-羰基-氨基，(C_{1-8}烷基)$_2$-氨基-羰基-氨基，C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-氨基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基，氨基-磺酰基-氨基，C_{1-8}烷基-氨基-磺酰基-氨基，(C_{1-8}烷基)$_2$-氨基-磺酰基-氨基，P(O)$(R_7)_2$-氨基或杂芳基，其中杂芳基任选被一个、两个、三个、或四个C_{1-8}烷基取代基取代。

[0038] 另一实施方案包括式(I)化合物，其中R_2为氰基，卤素，硝基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，氨基，羟基-氨基，羟基-C_{1-8}烷基-氨基，C_{1-8}烷氧基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，氨基-羰基，氨基-羰基-氨基，C_{1-8}烷氧基-羰基-氨基，氨基-磺酰基-氨基或杂芳基，其中杂芳基任选被一个、两个、三个或四个C_{1-8}烷基取代基取代。

[0039] 另一实施方案包括式(I)化合物，其中R_2为氰基，卤素，羟基，硝基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，氨基，C_{1-8}烷基-氨基，(C_{1-8}烷基)$_2$-氨基，羟基-氨基，羟基-C_{1-8}烷基-氨基，C_{1-8}烷氧基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氨基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，氨基-羰基-氨基，C_{1-8}烷基-氨基-羰基-氨基，(C_{1-8}烷基)$_2$-氨基-羰基-氨基，C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-氨基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基，氨基-磺酰基-氨基，C_{1-8}烷基-氨基-磺酰基-氨基，(C_{1-8}烷基)$_2$-氨基-磺酰基-氨基或P(O)$(R_7)_2$-氨基。

[0040] 另一实施方案包括式(I)化合物，其中R_2为氰基，卤素，硝基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，氨基，羟基-氨基，羟基-C_{1-8}烷基-氨基，C_{1-8}烷氧基-C_{1-8}烷基-氨基，C_{1-8}烷硫基，氨基-羰基，氨基-羰基-氨基，C_{1-8}烷氧基-羰基-氨基或氨基-磺酰基-氨基。

[0041] 另一实施方案包括式(I)化合物，其中R_2为杂芳基，其中杂芳基任选被一个、两个、三个或四个C_{1-8}烷基取代基取代。

[0042] 另一实施方案包括式(I)化合物,其中 R_2 杂芳基是任选取代的 1H-吡咯基。

[0043] 另一实施方案包括式(I)化合物,其中 R_2 杂芳基是任选取代的 1H-吡咯-1-基。

[0044] 另一实施方案包括式(I)化合物,其中 R_3为氢。

[0045] 另一实施方案包括式(I)化合物,其中 R_3为氰基,卤素,C_{1-8}烷基,氨基,C_{1-8}烷基-氨基或(C_{1-8}烷基)$_2$-氨基。

[0046] 另一实施方案包括式(I)化合物,其中 R_3为氰基,卤素,C_{1-8}烷基或氨基。

[0047] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的 C_{3-14}环烷基,其选自 2,3-二氢-1H-茚基;或,任选取代的芳基,其选自苯基或萘基;或,任选取代的杂芳基,其选自 1,3-噻唑基,1,2-噁唑基,吡啶基,嘧啶基,1H-吲哚基,苯并呋喃基,苯并噁唑基,1,3-苯并噻唑基,喹啉基或异喹啉基;或,任选取代的杂环基,其选自 1,3-苯并二氧杂环戊烯基或 2,3-二氢-1,4-苯并二氧杂环己二烯基。

[0048] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的 C_{3-14}环烷基,其选自 2,3-二氢-1H-茚基。

[0049] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的 C_{3-14}环烷基,其选自 2,3-二氢-1H-茚-2-基。

[0050] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的芳基,其选自苯基或萘基。

[0051] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂芳基,其选自 1,3-噻唑基,1,2-噁唑基,吡啶基,嘧啶基,1H-吲哚基,苯并呋喃基,苯并噁唑基,1,3-苯并噻唑基,喹啉基或异喹啉基;或,任选取代的杂环基,其选自 1,3-苯并二氧杂环戊烯基或 2,3-二氢-1,4-苯并二氧杂环己二烯基。

[0052] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂芳基,其选自 1,3-噻唑-2-基,1,2-噁唑-5-基,吡啶-2-基,吡啶-3-基,嘧啶-5-基,1H-吲哚-5-基,苯并呋喃-5-基,苯并噁唑-5-基,1,3-苯并噻唑-2-基,喹啉-3-基,喹啉-6-基或异喹啉-3-基;或,任选取代的杂环基,其选自 1,3-苯并二氧杂环戊烯-5-基或 2,3-二氢-1,4-苯并二氧杂环己二烯-6-基。

[0053] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂芳基,其选自 1,3-噻唑基,1,2-噁唑基,吡啶基,吡啶基,嘧啶基,1H-吲哚基,苯并呋喃基,苯并噁唑基,1,3-苯并噻唑基,喹啉基或异喹啉基。

[0054] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂芳基,其选自 1,3-噻唑-2-基,1,2-噁唑-5-基,吡啶-2-基,吡啶-3-基,嘧啶-5-基,1H-吲哚-5-基,苯并呋喃-5-基,苯并噁唑-5-基,1,3-苯并噻唑-2-基,喹啉-3-基,喹啉-6-基或异喹啉-3-基。

[0055] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂环基,其选自 1,3-苯并二氧杂环戊烯基或 2,3-二氢-1,4-苯并二氧杂环己二烯基。

[0056] 另一实施方案包括式(I)化合物,其中 R_4是任选取代的杂环基,其选自 1,3-苯并二氧杂环戊烯-5-基或 2,3-二氢-1,4-苯并二氧杂环己二烯-6-基。

[0057] 另一实施方案包括式(I)化合物,其中 R_5独立地选自氰基,卤素,羟基,硝基,C_{1-8}烷基,氰基-C_{1-8}烷基,卤素-C_{1-8}烷基,羟基-C_{1-8}烷基,C_{1-8}烷氧基,C_{1-8}烷氧基-C_{1-8}烷基,卤素-C_{1-8}烷氧基,C_{2-8}烯基,C_{1-8}烷氧基-C_{2-8}烯基,羧基,氨基,C_{1-8}烷基-氨

基，C_{1-8}烷基－氨基－C_{1-8}烷基，羟基－C_{1-8}烷基－氨基，C_{1-8}烷硫基，C_{1-8}烷基－羰基，C_{1-8}烷基－羰基－氧基－C_{1-8}烷基，C_{1-8}烷氧基－羰基，C_{1-8}烷基－磺酰基，C_{3-14}环烷基，芳基－C_{1-8}烷基，芳基－氨基，芳基－C_{1-8}烷基－氨基，杂芳基或杂芳基－C_{1-8}烷基，其中杂芳基和芳基－C_{1-8}烷基，芳基－氨基，芳基－C_{1-8}烷基－氨基和杂芳基－C_{1-8}烷基的芳基和杂芳基部分各自任选被一个、两个、三个或四个卤素或卤素－C_{1-8}烷氧基取代基取代。

[0058] 另一实施方案包括式（I）化合物，其中R_5独立地选自氰基，卤素，羟基，硝基，氧代，C_{1-8}烷基，氰基－C_{1-8}烷基，卤素－C_{1-8}烷基，羟基－C_{1-8}烷基，C_{1-8}烷氧基，C_{1-8}烷氧基－C_{1-8}烷基，卤素－C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基－C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷氧基－C_{2-8}炔基，羧基，氨基，C_{1-8}烷基－氨基，（C_{1-8}烷基）$_2$－氨基，氨基－C_{1-8}烷基，C_{1-8}烷基－氨基－C_{1-8}烷基，（C_{1-8}烷基）$_2$－氨基－C_{1-8}烷基，羟基－C_{1-8}烷基－氨基，羟基－C_{1-8}烷基－氨基－C_{1-8}烷基，羟基－C_{1-8}烷基－氨基－C_{1-8}烷基－氨基，C_{1-8}烷硫基，C_{1-8}烷基－羰基，C_{1-8}烷基－羰基－氨基，C_{1-8}烷基－羰基－氧基，C_{1-8}烷基－羰基－氧基－C_{1-8}烷基，C_{1-8}烷氧基－羰基，C_{1-8}烷氧基－羰基－C_{1-8}烷基，C_{1-8}烷氧基－羰基－氨基或C_{1-8}烷基－磺酰基。

[0059] 另一实施方案包括式（I）化合物，其中R_5独立地选自氰基，卤素，羟基，硝基，C_{1-8}烷基，氰基－C_{1-8}烷基，卤素－C_{1-8}烷基，羟基－C_{1-8}烷基，C_{1-8}烷氧基，C_{1-8}烷氧基－C_{1-8}烷基，卤素－C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基－C_{2-8}烯基，羧基，氨基，C_{1-8}烷基－氨基，C_{1-8}烷基－氨基－C_{1-8}烷基，羟基－C_{1-8}烷基－氨基，C_{1-8}烷硫基，C_{1-8}烷基－羰基，C_{1-8}烷基－羰基－氧基－C_{1-8}烷基，C_{1-8}烷氧基－羰基或C_{1-8}烷基－磺酰基。

[0060] 另一实施方案包括式（I）化合物，其中R_5独立地选自任选取代的C_{3-14}环烷基，其选自环丙基或环丁基；或在芳基和芳基部分上被任选取代的芳基，芳基－C_{1-8}烷基，芳基－氨基或芳基－C_{1-8}烷基－氨基，其中芳基选自苯基；和，其中在C_{3-14}环烷基，芳基和芳基部分上的任选取代基选自一个、两个、三个或四个卤素，C_{1-8}烷基，卤素－C_{1-8}烷基，羟基－C_{1-8}烷基，C_{1-8}烷氧基，卤素－C_{1-8}烷氧基，羟基－C_{1-8}烷基或羧基取代基；或，在杂芳基和杂芳基部分上被任选取代的杂芳基或杂芳基－C_{1-8}烷基，其中杂芳基选自四唑基或吡啶基；和，其中杂芳基和杂芳基部分上的任选取代基选自一个、两个、三个或四个卤素，C_{1-8}烷基，卤素－C_{1-8}烷基，羟基－C_{1-8}烷基，C_{1-8}烷氧基，卤素－C_{1-8}烷氧基，羟基－C_{1-8}烷基或羧基取代基。

[0061] 另一实施方案包括式（I）化合物，其中R_5独立地选自任选取代的C_{3-14}环烷基，其选自环丙基或环丁基；或，在芳基部分上被任选取代的芳基－C_{1-8}烷基，芳基－氨基或芳基－C_{1-8}烷基－氨基，其中芳基选自苯基；和，其中在C_{3-14}环烷基和芳基部分上的任选取代基选自一个、两个、三个或四个卤素或卤素－C_{1-8}烷氧基取代基；或，在杂芳基和杂芳基部分上被任选取代的杂芳基或杂芳基－C_{1-8}烷基，其中杂芳基选自四唑基或吡啶基；和，其中在杂芳基和杂芳基部分上的任选取代基选自一个、两个、三个或四个卤素或卤素－C_{1-8}烷氧基取代基。

[0062] 另一实施方案包括式（I）化合物，其中R_5独立地选自任选取代的C_{3-14}环烷基，其选自环丙基或环丁基。

[0063] 另一实施方案包括式（I）化合物，其中R_5独立地选自在芳基和芳基部分上被任选取代的芳基，芳基－C_{1-8}烷基，芳基－氨基或芳基－C_{1-8}烷基－氨基，其中芳基选自苯基；

和，其中所述任选的取代基选自一个、两个、三个或四个卤素，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，羟基-C_{1-8}烷基或羧基取代基。

[0064] 另一实施方案包括式(I)化合物，其中R_5独立地选自在芳基部分被任选取代的芳基-C_{1-8}烷基，芳基-氨基或芳基-C_{1-8}烷基-氨基，其中芳基选自苯基；和，其中所述任选的取代基选自一个、两个、三个或四个卤素或卤素-C_{1-8}烷氧基取代基。

[0065] 另一实施方案包括式(I)化合物，其中R_5独立地选自在杂芳基和杂芳基部分上被任选取代的杂芳基或杂芳基-C_{1-8}烷基，其中杂芳基选自四唑基或吡啶基；和，其中所述任选的取代基选自一个、两个、三个或四个卤素，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，羟基-C_{1-8}烷基或羧基取代基。

[0066] 另一实施方案包括式(I)化合物，其中R_5独立地选自在杂芳基和杂芳基部分上被任选取代的杂芳基或杂芳基-C_{1-8}烷基，其中杂芳基选自四唑基或吡啶基；和，其中所述任选的取代基选自一个、两个、三个或四个卤素或卤素-C_{1-8}烷氧基取代基。

[0067] 另一实施方案包括式(I)化合物，其中R_5独立地选自在杂芳基和杂芳基部分上被任选取代的杂芳基或杂芳基-C_{1-8}烷基，其中杂芳基选自2H-四唑-2-基，四唑-1-基，吡啶-2-基，吡啶-3-基或吡啶-4-基；和，其中所述任选的取代基选自一个、两个、三个或四个卤素或卤素-C_{1-8}烷氧基取代基。

[0068] 另一实施方案包括式(I)化合物，其中R_6独立地选自氰基，卤素，羟基，硝基，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，C_{2-8}烯基，C_{2-8}炔基，甲酰基，甲酰基-氧基，C_{1-8}烷基-羰基，卤素-C_{1-8}烷基-羰基，C_{1-8}烷硫基，卤素-C_{1-8}烷硫基，氨基，C_{1-8}烷基-羰基，C_{1-8}烷氧基-羰基，氨基-羰基，C_{1-8}烷基-氨基-羰基，氨基-C_{1-8}烷基，$(C_{1-8}烷基)_2$-氨基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基，羟基-亚氨基-C_{1-8}烷基，C_{1-8}烷基-磺酰基，$B(OR_8)_2$，C_{3-14}环烷基，杂环基，芳基或杂芳基，其中C_{3-14}环烷基，杂环基，芳基和杂芳基各自任选被一个、两个、三个或四个卤素或C_{1-8}烷基取代基取代。

[0069] 另一实施方案包括式(I)化合物，其中R_6独立地选自氰基，卤素，羟基，硝基，C_{1-8}烷基，卤素-C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基，卤素-C_{1-8}烷氧基，C_{2-8}烯基，C_{1-8}烷氧基-C_{2-8}烯基，C_{2-8}炔基，C_{1-8}烷氧基-C_{2-8}炔基，羧基，甲酰基，甲酰基-氧基，C_{1-8}烷基-羰基，卤素-C_{1-8}烷基-羰基，C_{1-8}烷硫基，卤素-C_{1-8}烷硫基，氨基，C_{1-8}烷基-氨基，$(C_{1-8}烷基)_2$-氨基，C_{1-8}烷基-羰基，C_{1-8}烷基-羰基-氧基，C_{1-8}烷基-羰基-氧基-C_{1-8}烷基，C_{1-8}烷氧基-羰基，卤素-C_{1-8}烷氧基-羰基，C_{1-8}烷氧基-羰基-C_{1-8}烷基，C_{1-8}烷氧基-羰基-氨基，C_{1-8}烷氧基-羰基-氨基-C_{1-8}烷基，氨基-羰基，C_{1-8}烷基-氨基-羰基，$(C_{1-8}烷基)_2$-氨基-羰基，C_{1-8}烷基-羰基-氨基，C_{1-8}烷基-羰基-氨基-C_{1-8}烷基，氨基-C_{1-8}烷基，C_{1-8}烷基-氨基-C_{1-8}烷基，$(C_{1-8}烷基)_2$-氨基-C_{1-8}烷基，氨基-C_{1-8}烷基-氨基，C_{1-8}烷基-氨基-C_{1-8}烷基-氨基，$(C_{1-8}烷基)_2$-氨基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基，羟基-C_{1-8}烷基-氨基-C_{1-8}烷基-氨基，亚氨基-C_{1-8}烷基，羟基-亚氨基-C_{1-8}烷基，C_{1-8}烷氧基-亚氨基-C_{1-8}烷基，C_{1-8}烷基-磺酰基，卤素-C_{1-8}烷基-磺酰基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，$(C_{1-8}烷基)_2$-氨基-磺酰基或$B(OR_8)_2$。

[0070] 另一实施方案包括式(I)化合物，其中R_6独立地选自氰基，卤素，羟基，硝基，

C_{1-8}烷基，卤素 -C_{1-8}烷基，羟基 -C_{1-8}烷基，C_{1-8}烷氧基，卤素 -C_{1-8}烷氧基，C_{2-8}烯基，C_{2-8}炔基，甲酰基，甲酰基 - 氧基，C_{1-8}烷基 - 羰基，卤素 -C_{1-8}烷基 - 羰基，C_{1-8}烷硫基，卤素 -C_{1-8}烷硫基，氨基，C_{1-8}烷基 - 羰基，C_{1-8}烷氧基 - 羰基，氨基 - 羰基，C_{1-8}烷基 - 氨基 - 羰基，氨基 -C_{1-8}烷基，(C_{1-8}烷基)$_2$- 氨基 -C_{1-8}烷基 - 氨基，羟基 -C_{1-8}烷基 - 氨基，羟基 - 亚氨基 -C_{1-8}烷基，C_{1-8}烷基 - 磺酰基，C_{1-8}烷基 - 氨基 - 磺酰基或 $B(OR_8)_2$。

[0071] 另一实施方案包括式 (I) 化合物，其中 R_6独立地选自 C_{3-14}环烷基，杂环基，芳基或杂芳基，其中 C_{3-14}环烷基，杂环基，芳基和杂芳基各自任选被一个、两个、三个或四个卤素或 C_{1-8}烷基取代基取代。

[0072] 另一实施方案包括式 (I) 化合物，其中 R_6独立地选自 C_{3-14}环烷基或杂环基，其中 C_{3-14}环烷基和杂环基各自任选被两个 C_{1-8}烷基取代基取代。

[0073] 另一实施方案包括式 (I) 化合物，其中 R_6 任选取代的 C_{3-14}环烷基选自环丙基；任选取代的杂环基选自吗啉基或 1,3,2- 二氧杂硼杂环戊烷基；任选取代的芳基选自苯基；或，任选取代的杂芳基选自 1H- 吡唑基。

[0074] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的 C_{3-14}环烷基选自环丙基。

[0075] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的杂环基选自吗啉基或 1,3,2- 二氧杂硼杂环戊烷基。

[0076] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的杂环基选自吗啉 -4- 基或 1,3,2- 二氧杂硼杂环戊烷 -2- 基。

[0077] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的芳基选自苯基。

[0078] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的杂芳基选自 1H- 吡唑基。

[0079] 另一实施方案包括式 (I) 化合物，其中 R_6任选取代的杂芳基选自 1H- 吡唑 -1- 基。

[0080] 另一实施方案包括式 (I) 化合物，其中 R_7为羟基。

[0081] 另一实施方案包括式 (I) 化合物，其中 R_7为 (C_{1-8}烷氧基)$_n$，其中 n 代表 1 至 5 的整数。

[0082] 另一实施方案包括式 (I) 化合物，其中 R_8为氢。

[0083] 另一实施方案包括式 (I) 化合物，其中 R_8为 C_{1-8}烷基。

[0084] 另一实施方案包括式 (I) 化合物或其形式，其中所述式 (I) 化合物的形式选自其游离酸、有机碱、盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对应异构体或互变异构体。

[0085] 另一实施方案包含式 (I) 化合物或其形式，其中所述式 (I) 化合物的形式选自其游离酸、游离碱、盐、酯、水合物、溶剂合物、或多晶型物。

[0086] 另一实施方案包括式 (I) 化合物或其形式，其中所述式 (I) 化合物的形式选自其盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对应异构体或互变异构体。

[0087] 另一实施方案包括式 (I) 化合物或其形式，其中所述式 (I) 化合物的形式选自其游离酸、游离碱、盐、水合物、或多晶型物。

[0088] 另一实施方案包括式 (I) 化合物或其形式，其中所述式 (I) 化合物的形式选自其游离酸、游离碱、水合物、溶剂合物或多晶型物。

[0089] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式选自其盐、水合物、溶剂合物或多晶型物。

[0090] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式选自其游离酸、游离碱或盐。

[0091] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式选自其游离酸或游离碱。

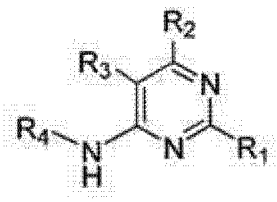
[0092] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式选自其盐。

[0093] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式选自其多晶型物。

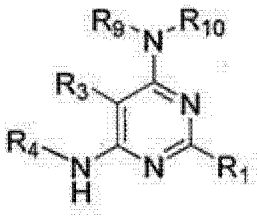
[0094] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式为药学上可接受的。

[0095] 另一实施方案包括式(I)化合物或其形式，其中所述式(I)化合物的形式是分离的。

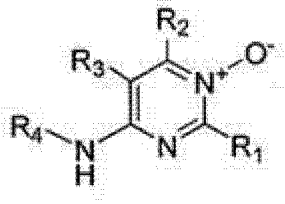
[0096] 另一实施方案包括式(I)化合物或其形式，其中所述化合物为式(II)、式(III)或式(IV)化合物：



式(II)，



式(III)或



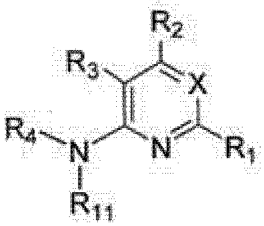
式(IV)

或其形式，其中：

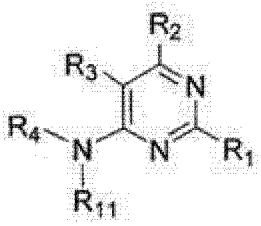
R_9 和 R_{10}独立地为氢，羟基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基-C_{1-8}烷基，C_{1-8}烷基-羰基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，C_{1-8}烷氧基-羰基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基或$P(O)(R_7)_2$。

[0097] 另一实施方案包括式(III)化合物，其中R_9 和 R_{10}之一为氢，另一个为羟基，C_{1-8}烷基，羟基-C_{1-8}烷基，C_{1-8}烷氧基-C_{1-8}烷基，C_{1-8}烷基-羰基，氨基-羰基，C_{1-8}烷基-氨基-羰基，(C_{1-8}烷基)$_2$-氨基-羰基，C_{1-8}烷氧基-羰基，氨基-磺酰基，C_{1-8}烷基-氨基-磺酰基，(C_{1-8}烷基)$_2$-氨基-磺酰基或$P(O)(R_7)_2$。

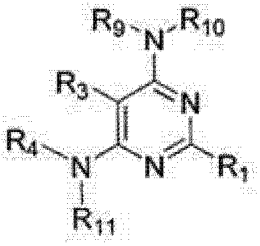
[0098] 另一实施方案包括式(I)化合物或其形式，其中该化合物为式(Ia)、式(IIa)、式(IIIa)或式(IVa)化合物：



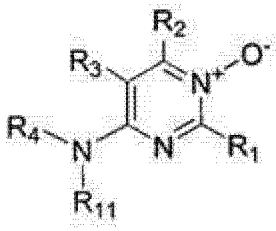
式 (Ia),



式 (IIa),



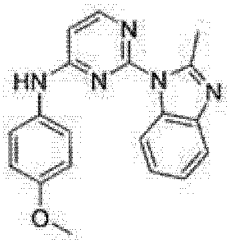
式 (IIIa) 或



式 (IVa)

或其形式，其中 R_2，R_3，R_9，R_{10}或 R_{11}独立地为氘。

[0099] 另一实施方案包括选自如下的式 (I) 化合物或其形式：



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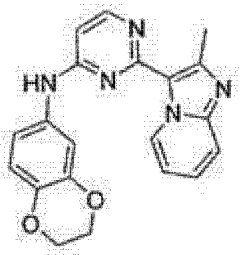

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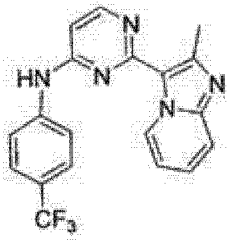

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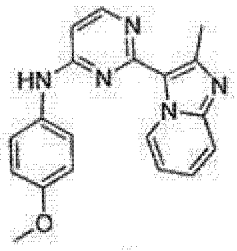

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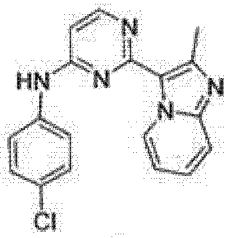

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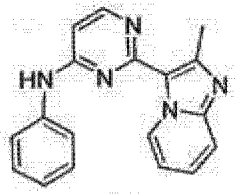

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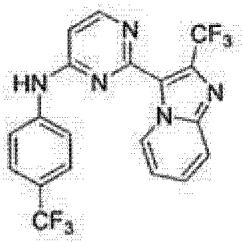

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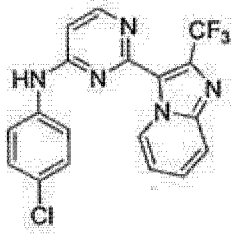

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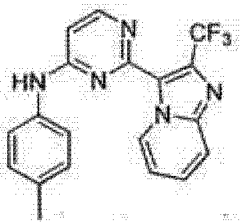

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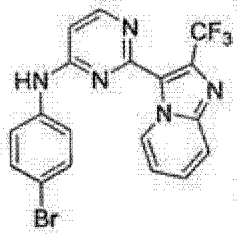

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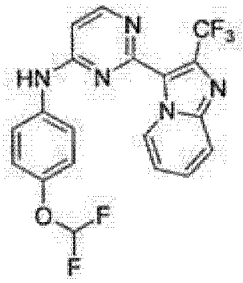

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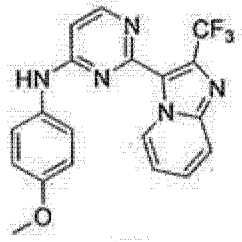

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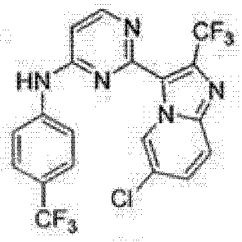

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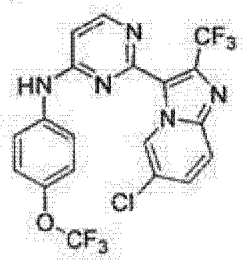

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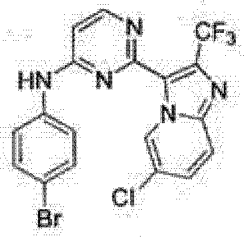

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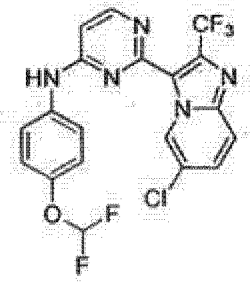

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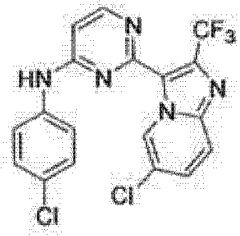

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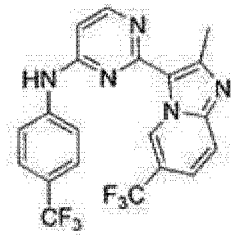

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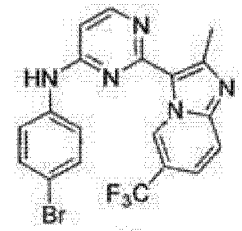

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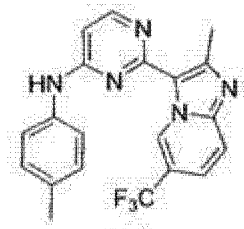

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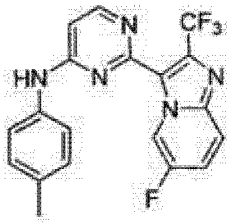

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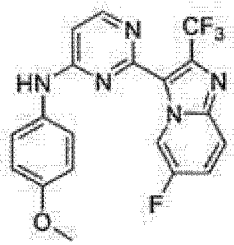

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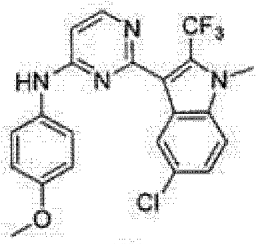

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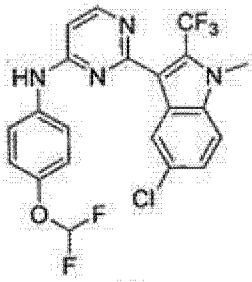

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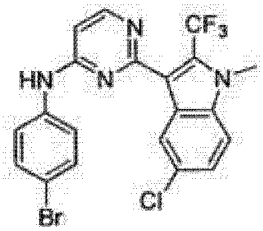

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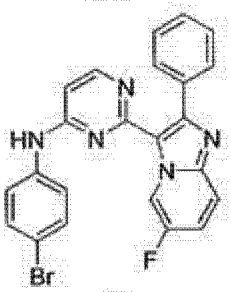

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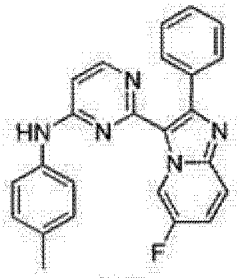

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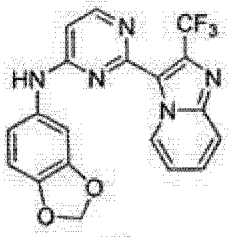

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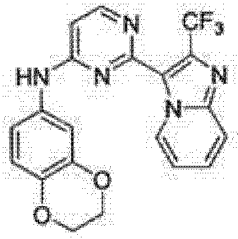

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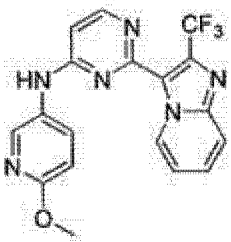

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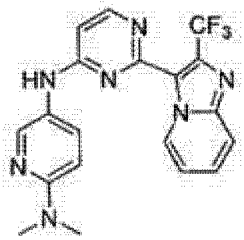

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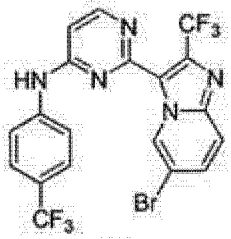

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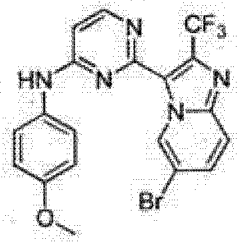

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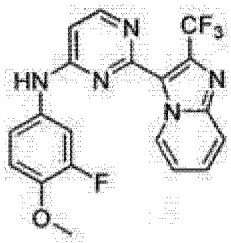

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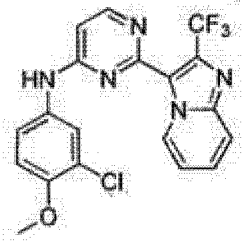

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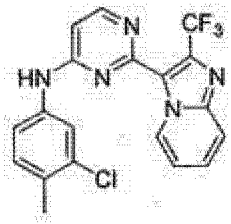

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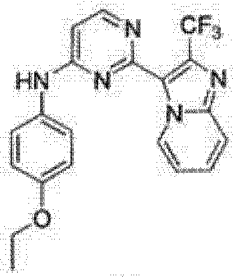

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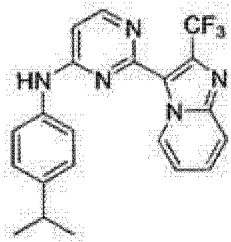

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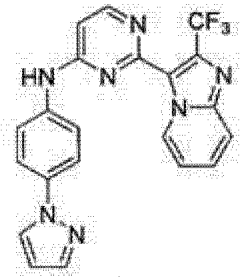

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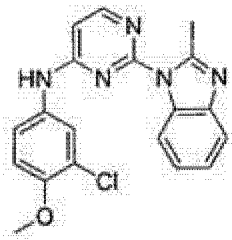

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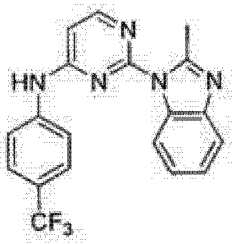

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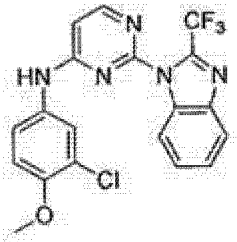

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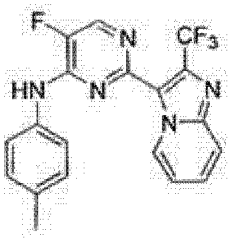

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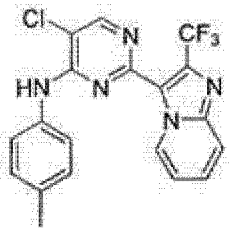

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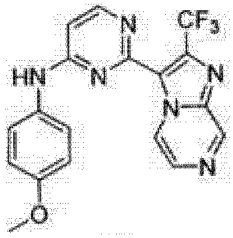

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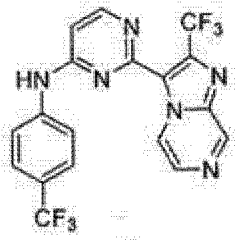

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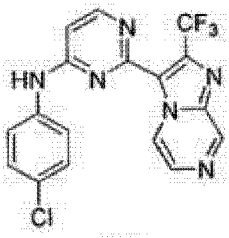

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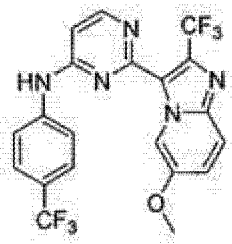

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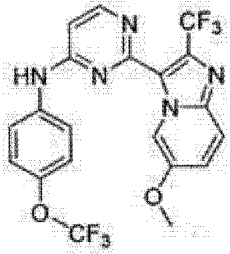

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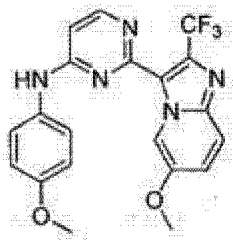

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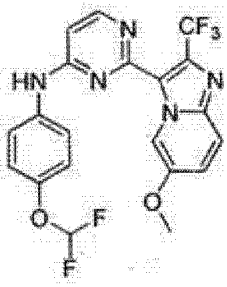

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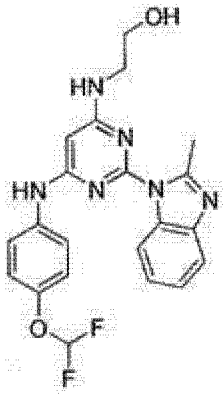

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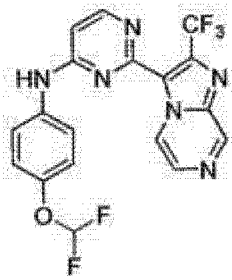

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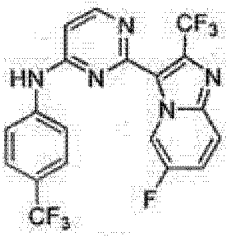

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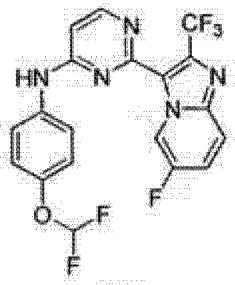

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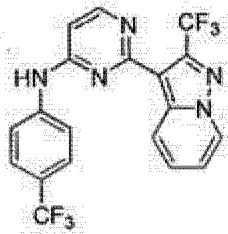

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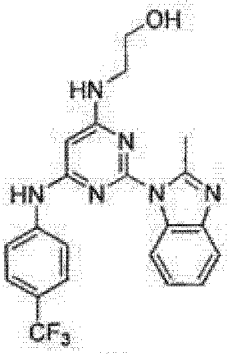

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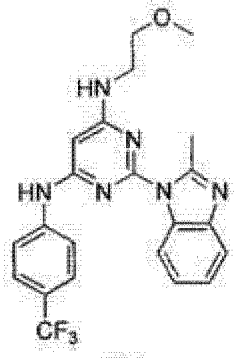

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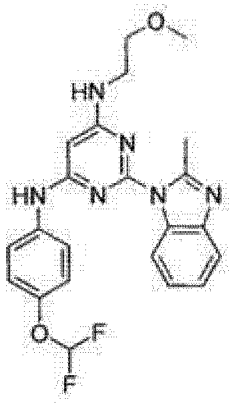

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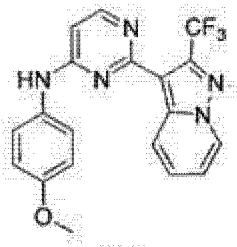

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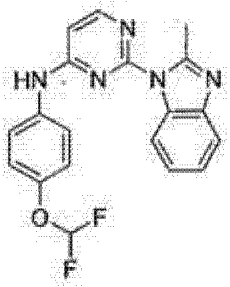

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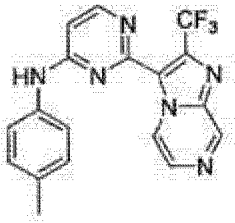

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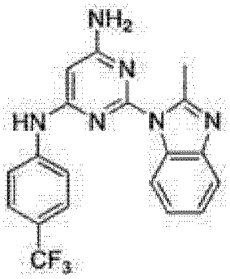

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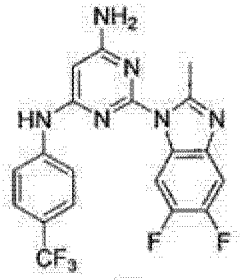

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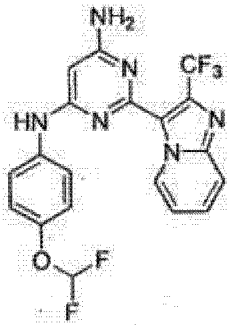

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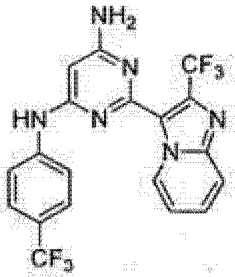

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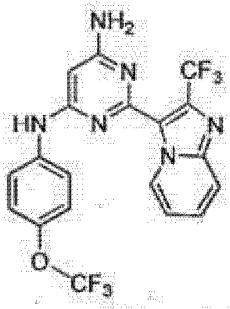

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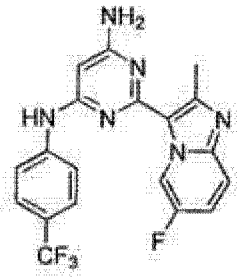

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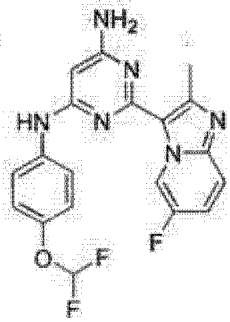

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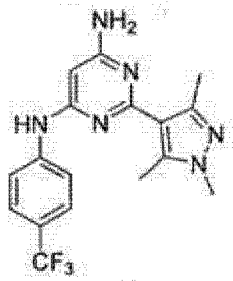

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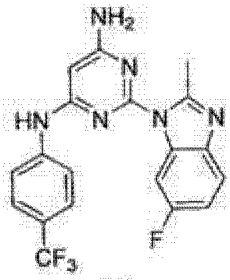

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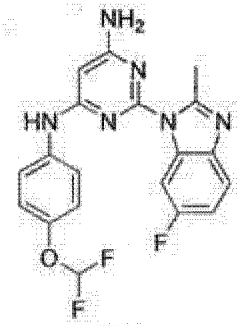

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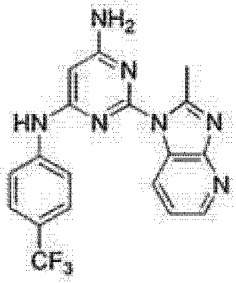

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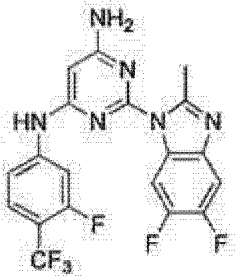

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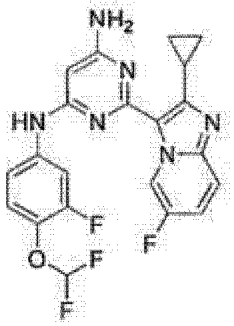

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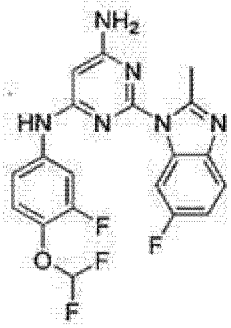

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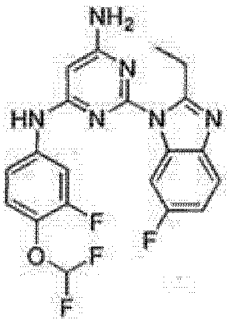

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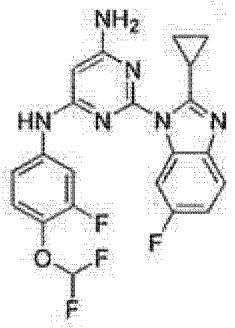

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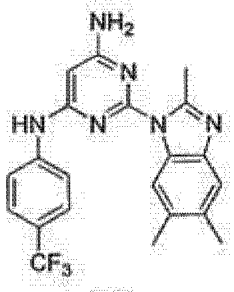

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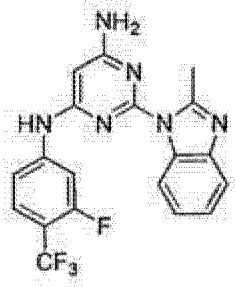

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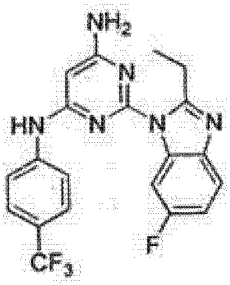

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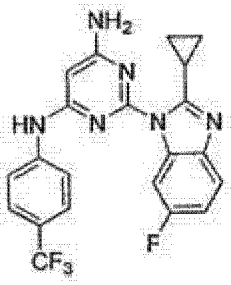

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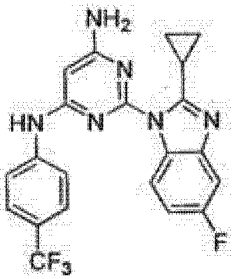

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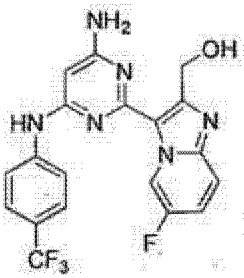

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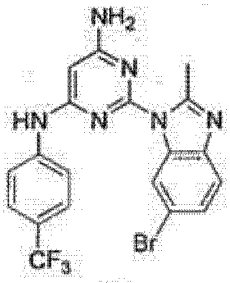

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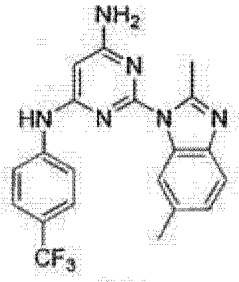

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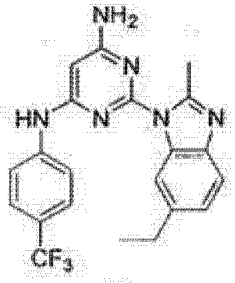

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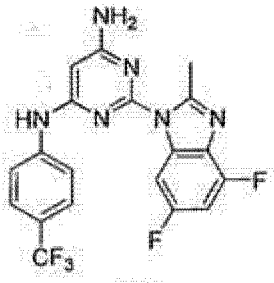

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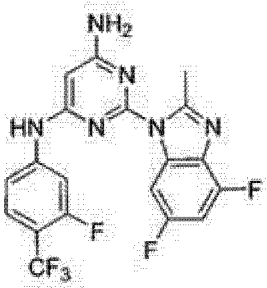

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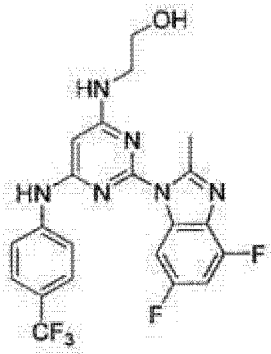

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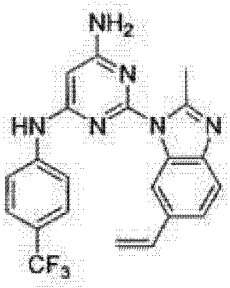

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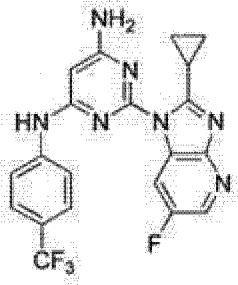

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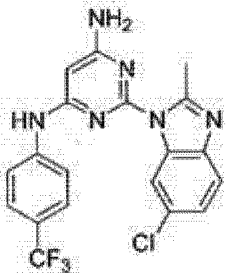

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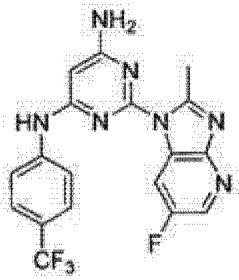

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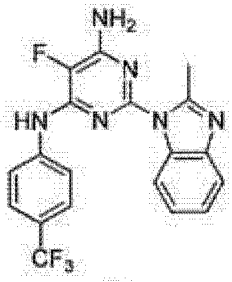

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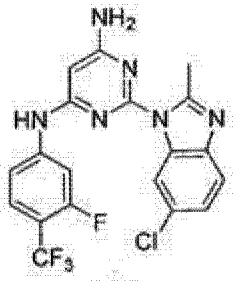

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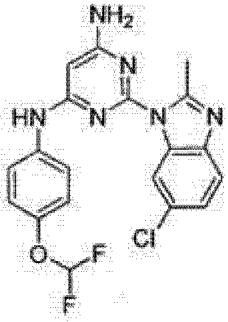

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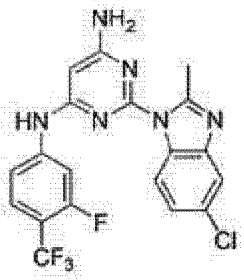

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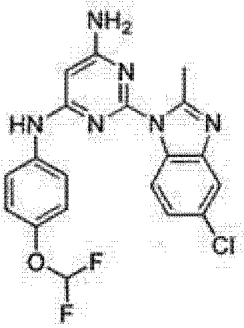

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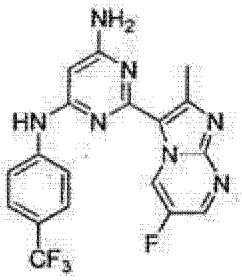

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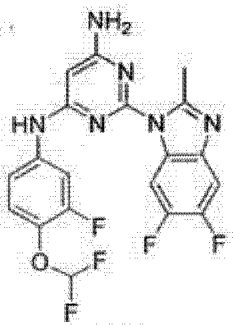

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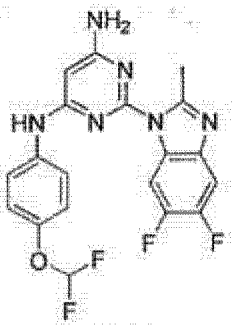

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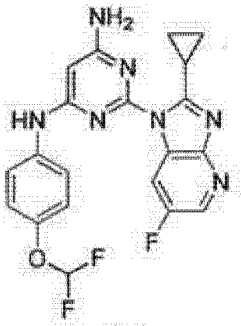

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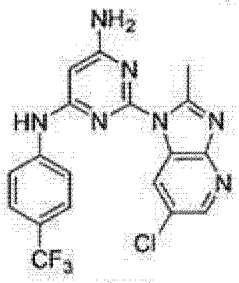

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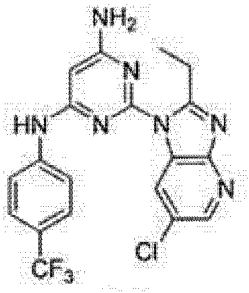

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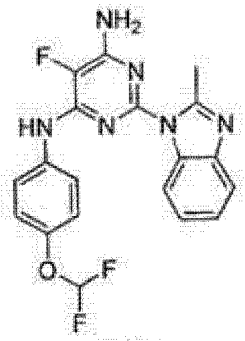

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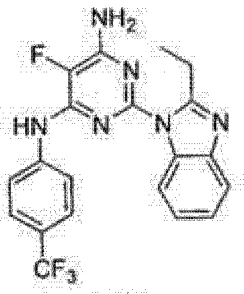

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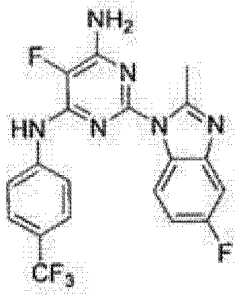

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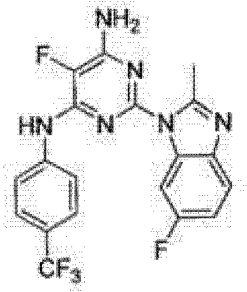

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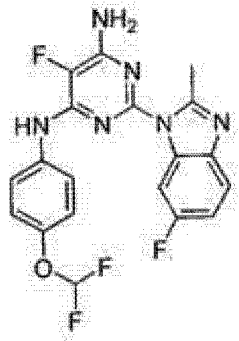

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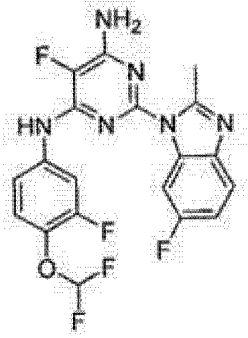

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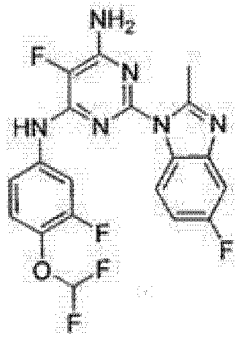

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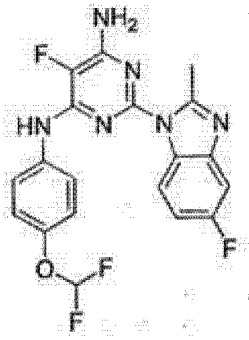

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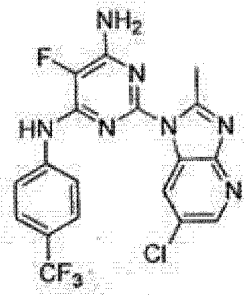

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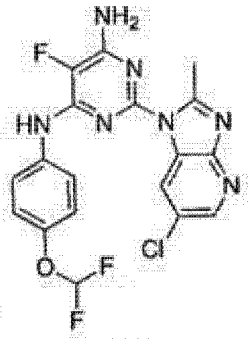

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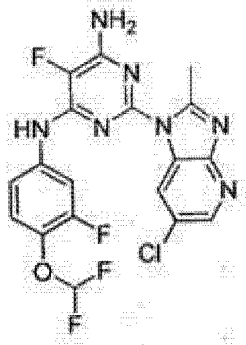

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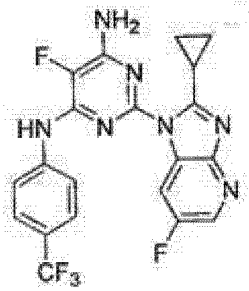

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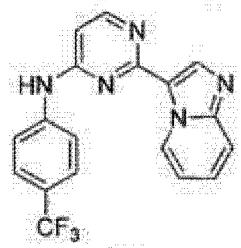

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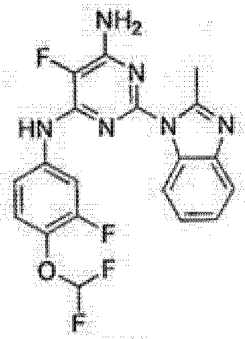

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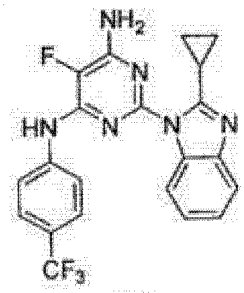

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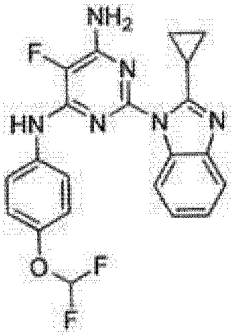

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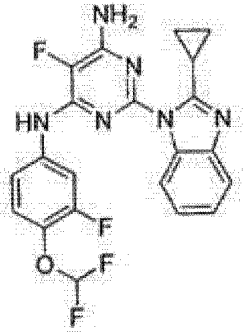

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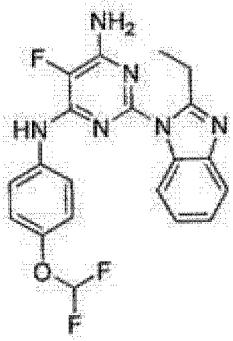

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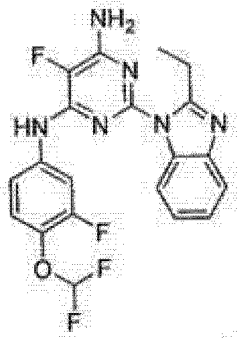

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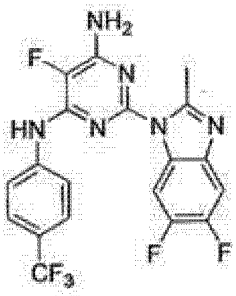

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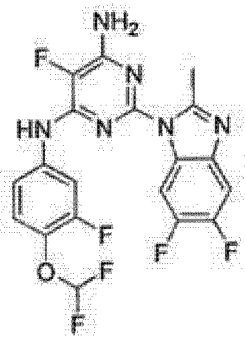

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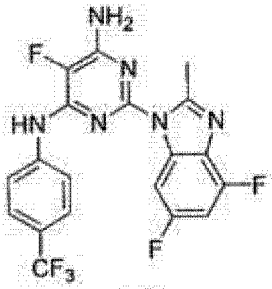

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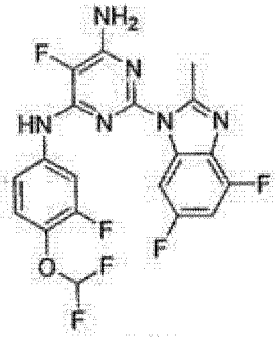

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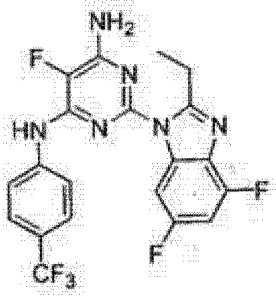

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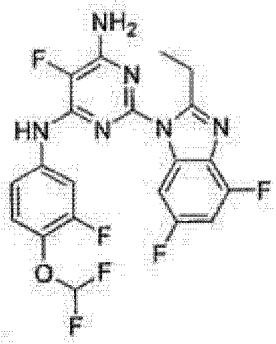

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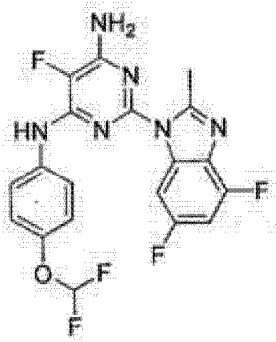

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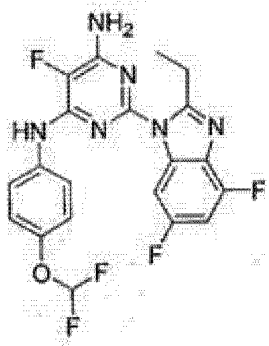

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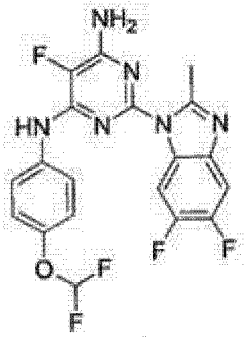

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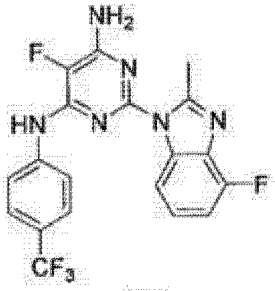

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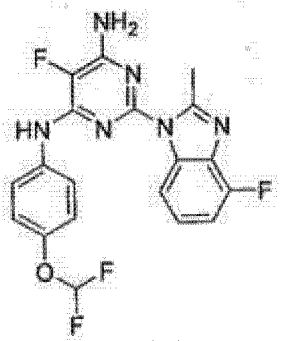

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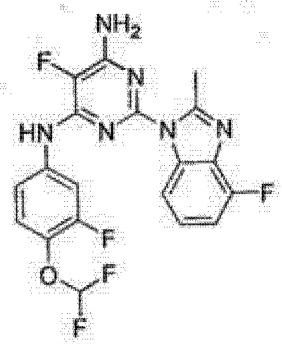

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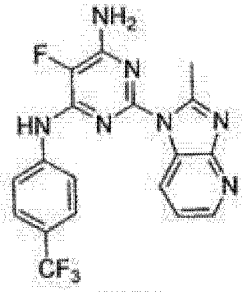

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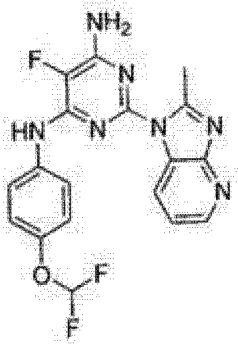

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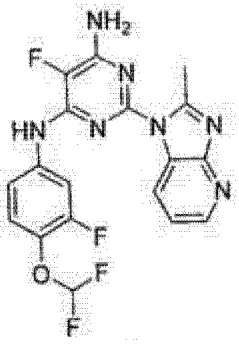

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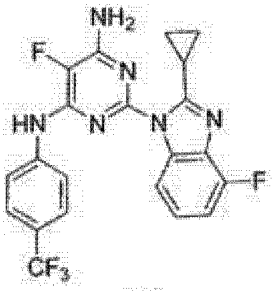

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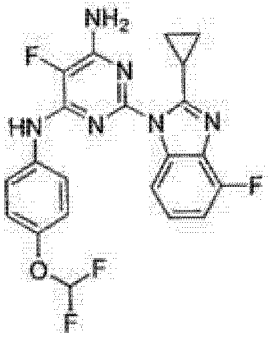

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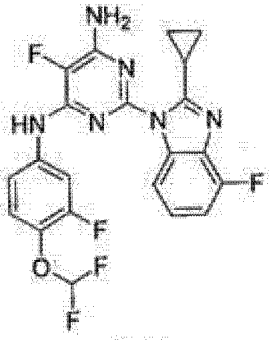

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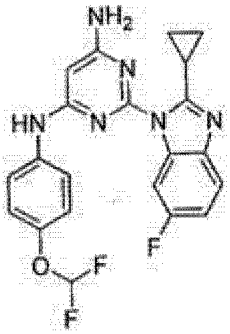

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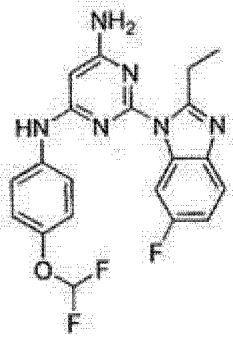

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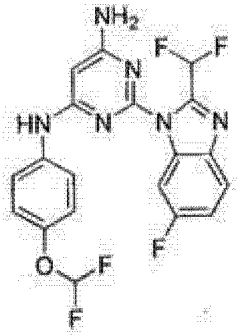

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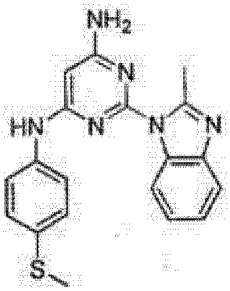

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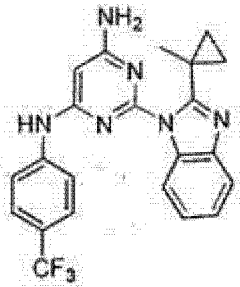

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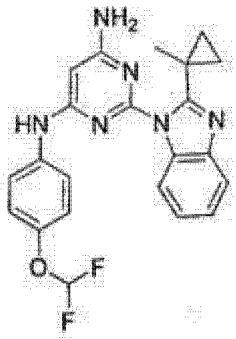

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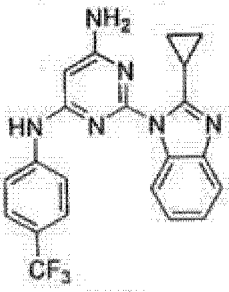

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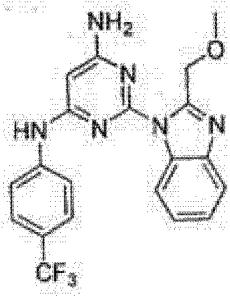

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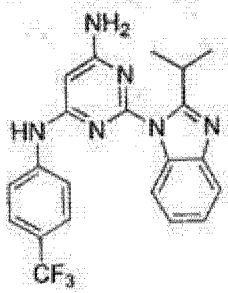

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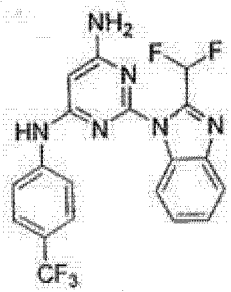

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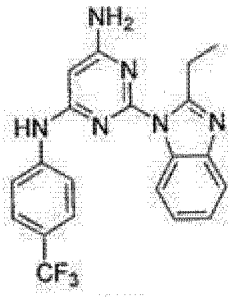

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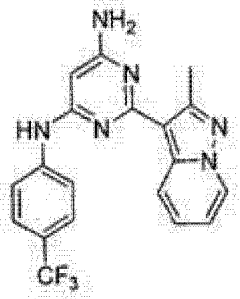

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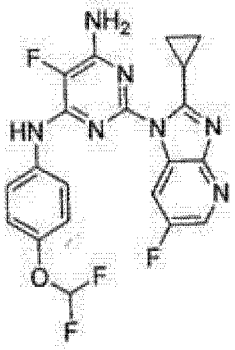

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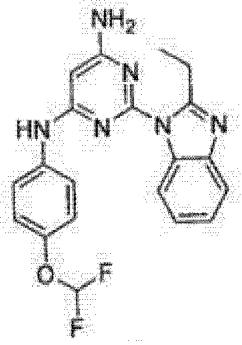

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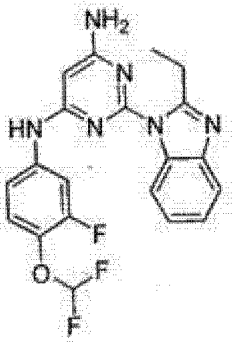

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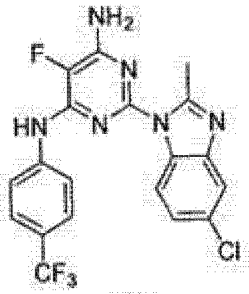

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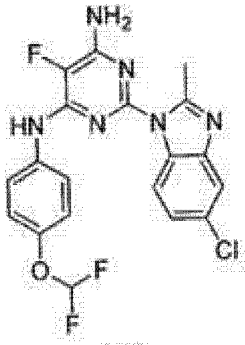

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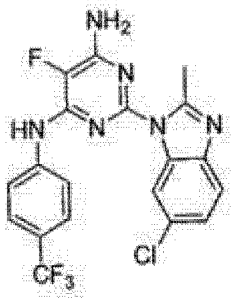

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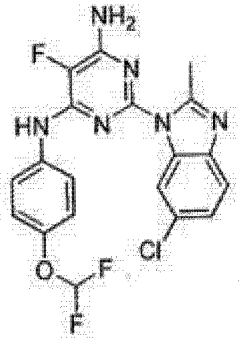

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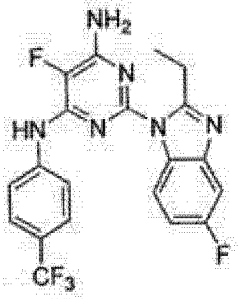

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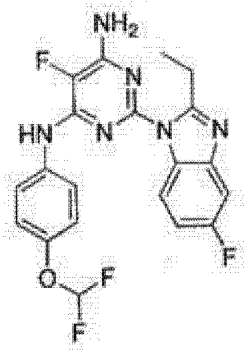

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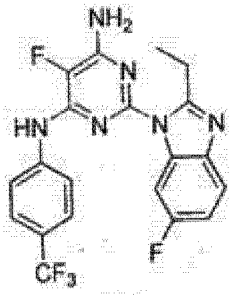

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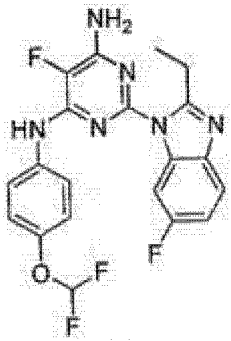

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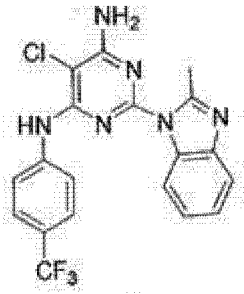

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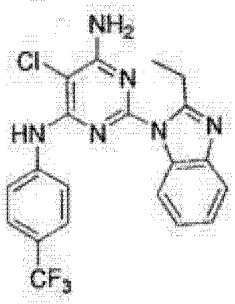

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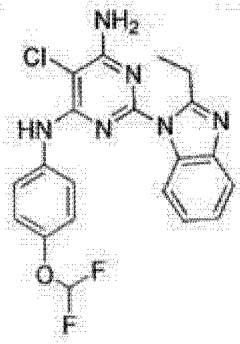

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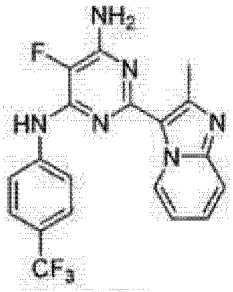

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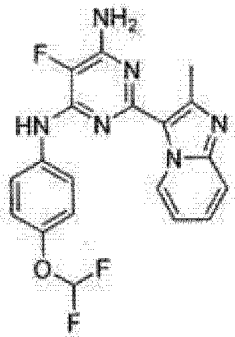

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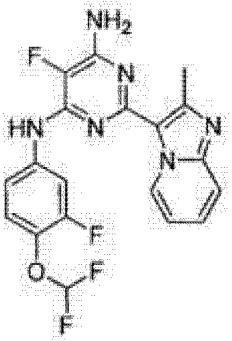

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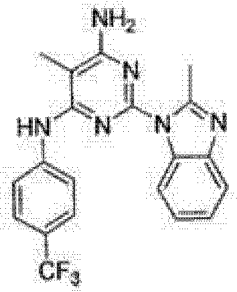

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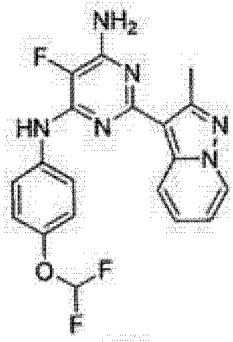

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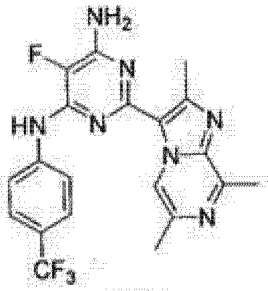

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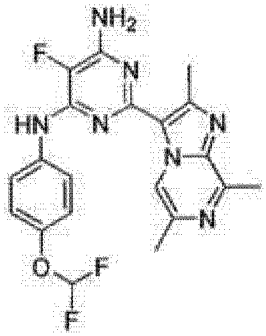

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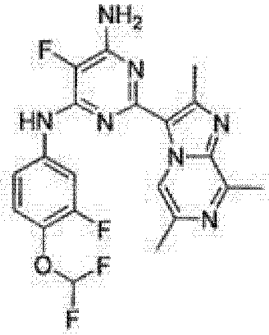

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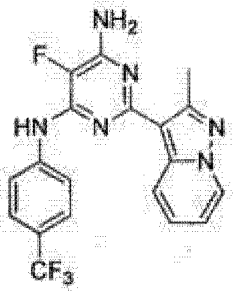

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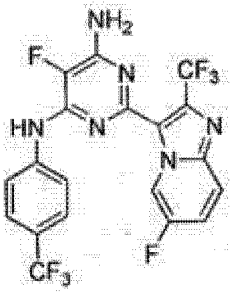

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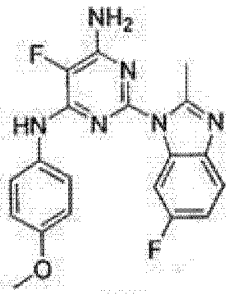

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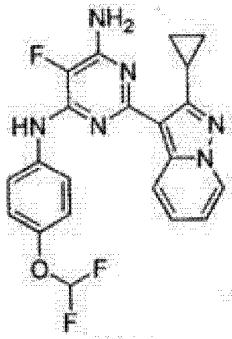

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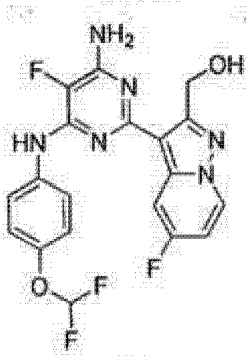

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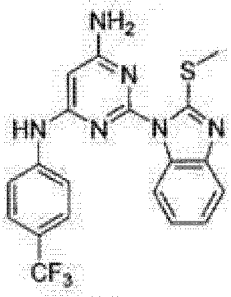

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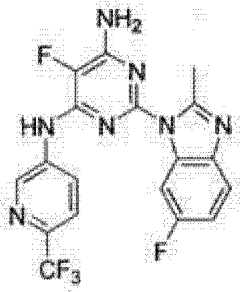

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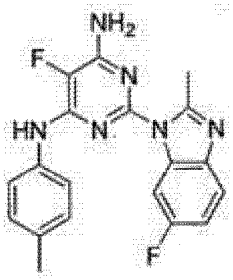

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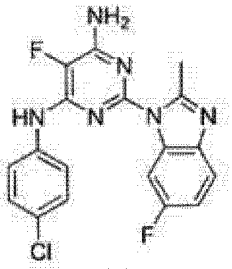
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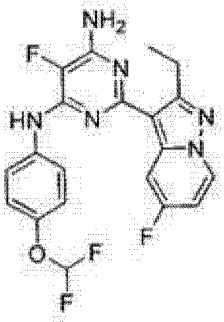
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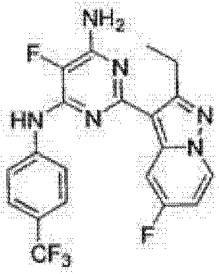
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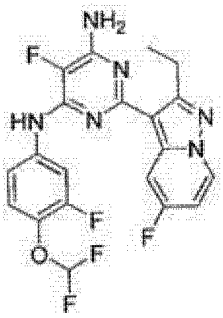
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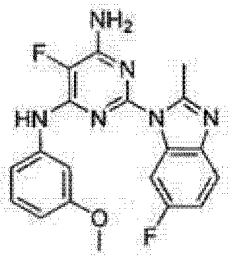
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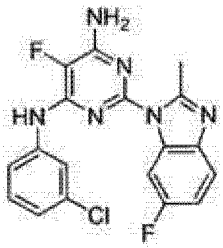
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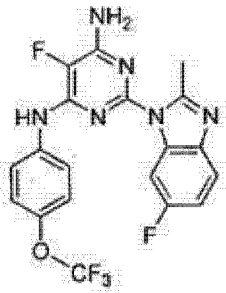
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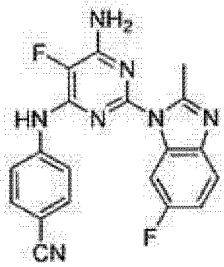
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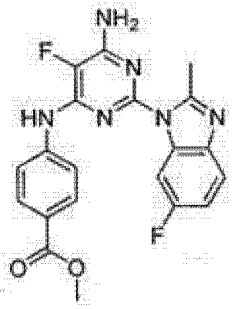
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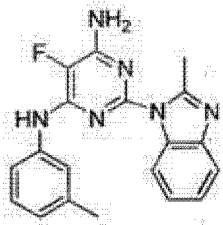
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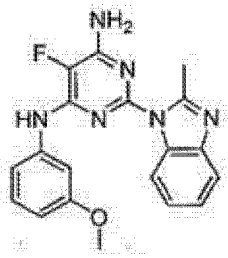
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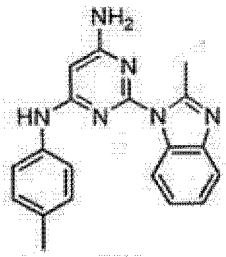
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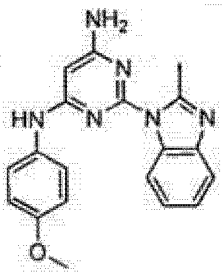
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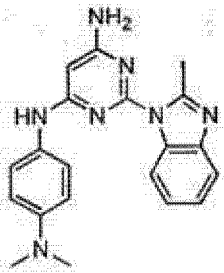
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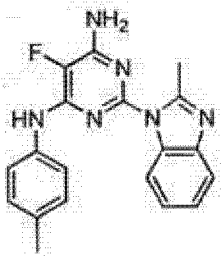
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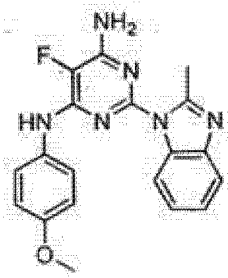
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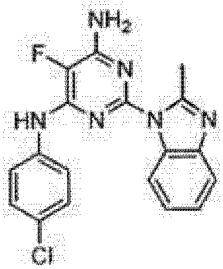
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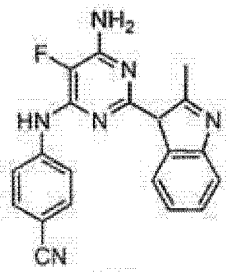
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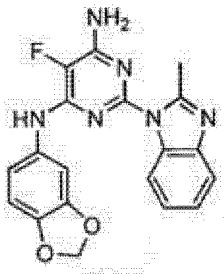
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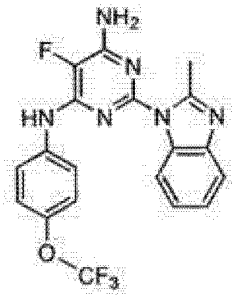
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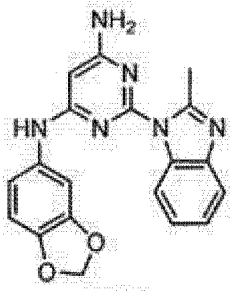

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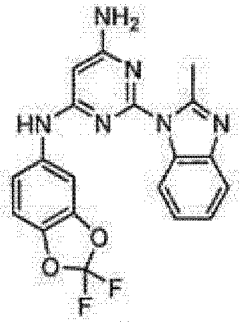

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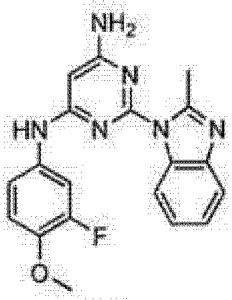

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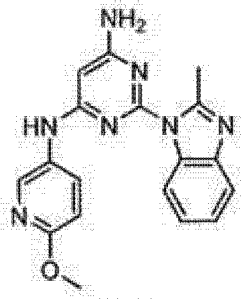

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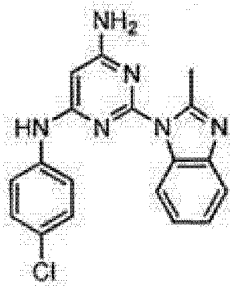

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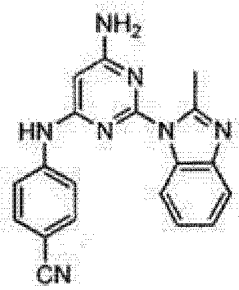

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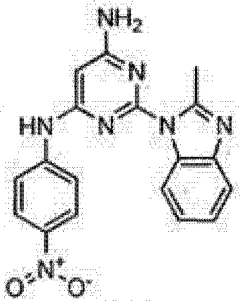

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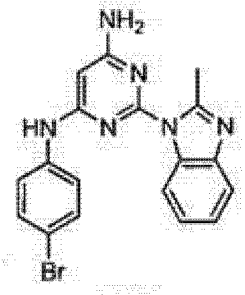

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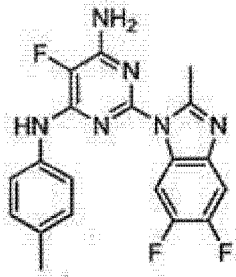

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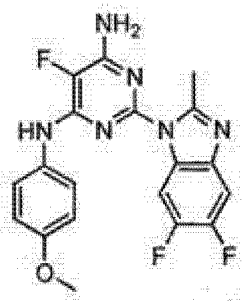

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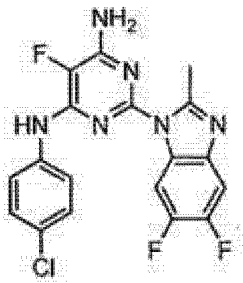

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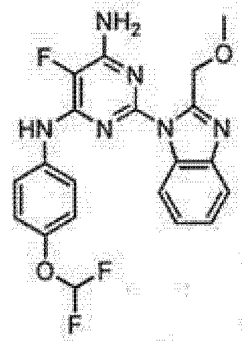

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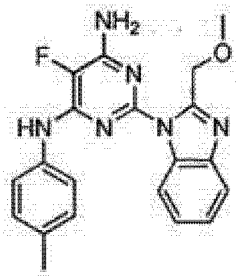

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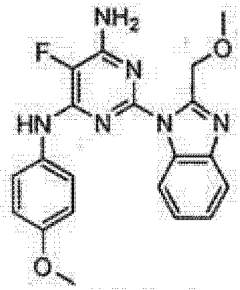

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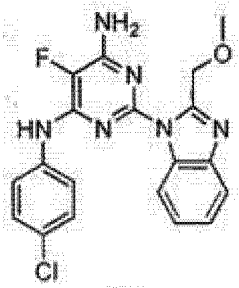

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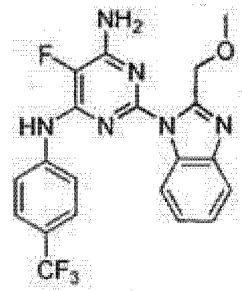

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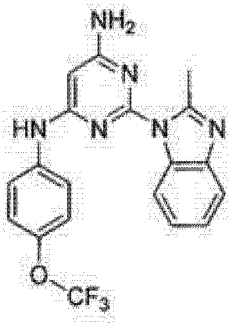

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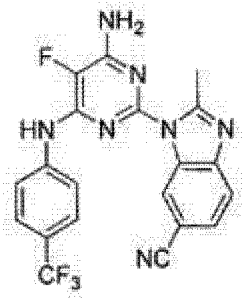

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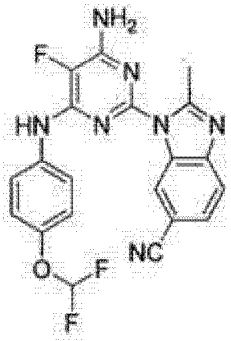

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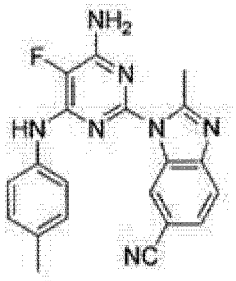

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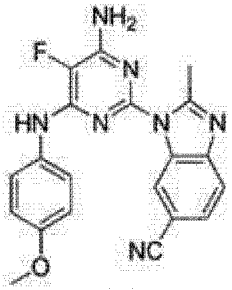

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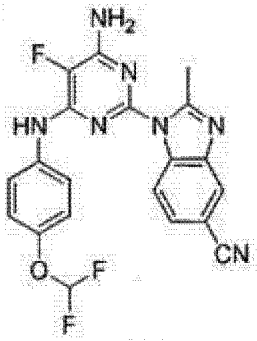

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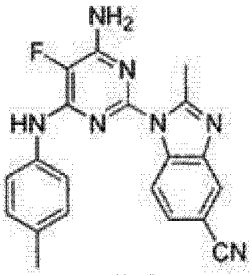

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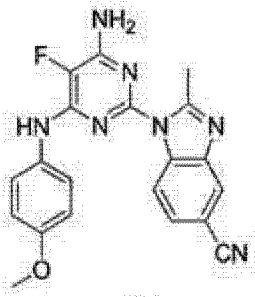

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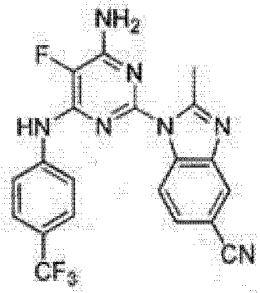

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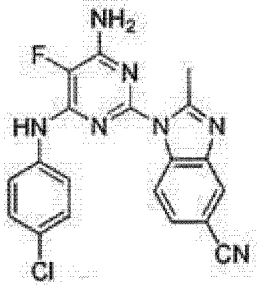

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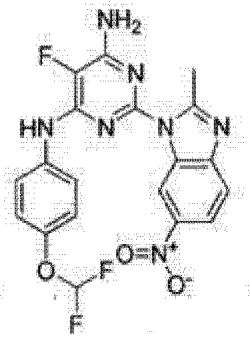

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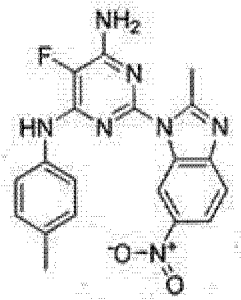

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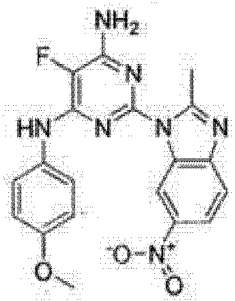

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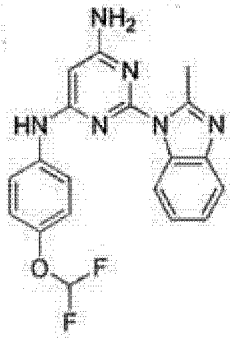

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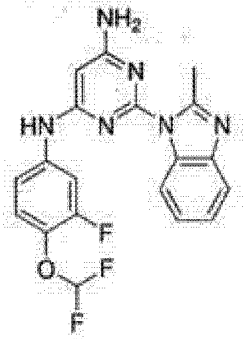

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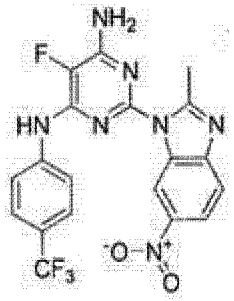

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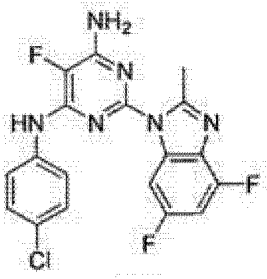

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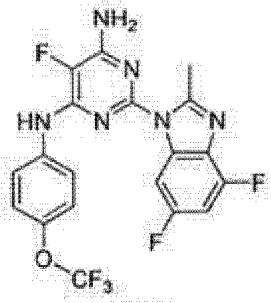

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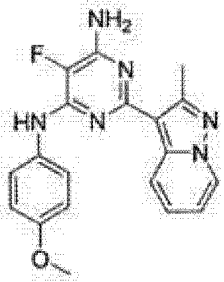

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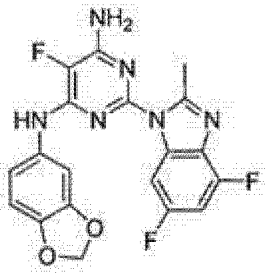

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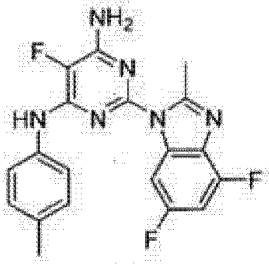

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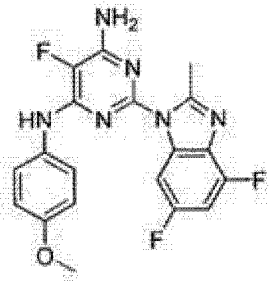

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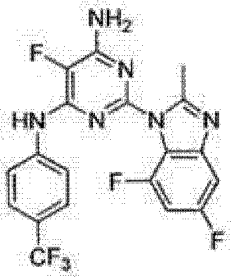

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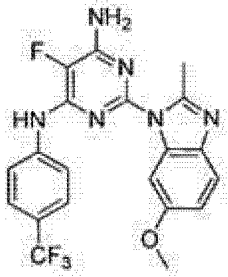

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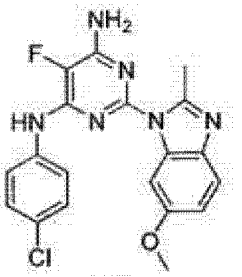

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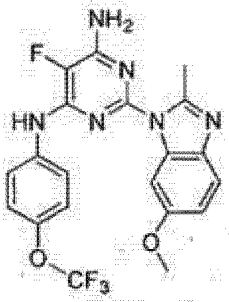

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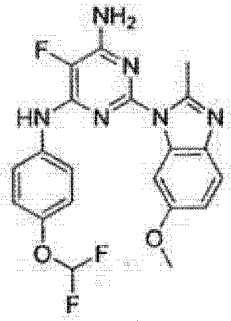

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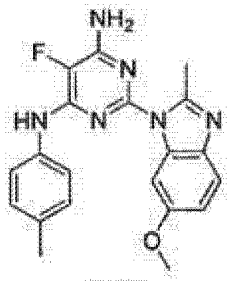

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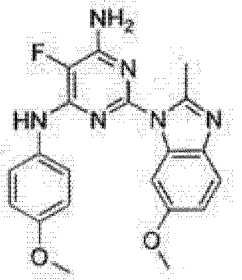

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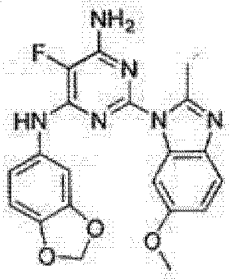

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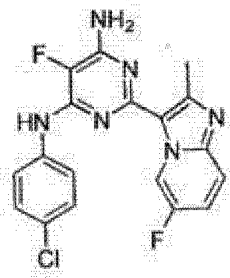

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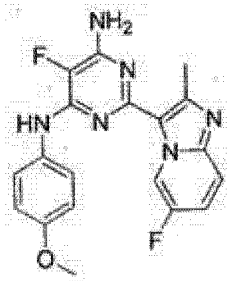

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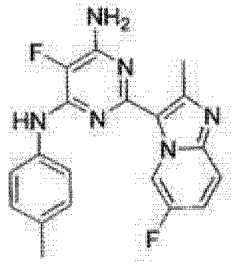

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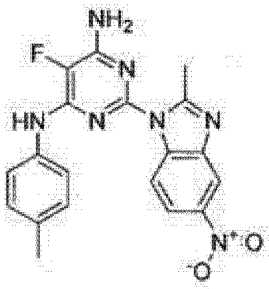

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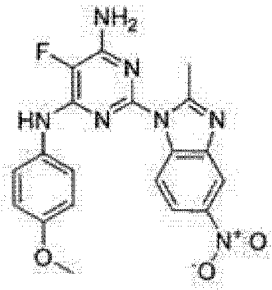

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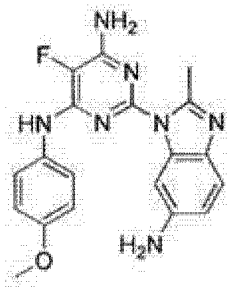

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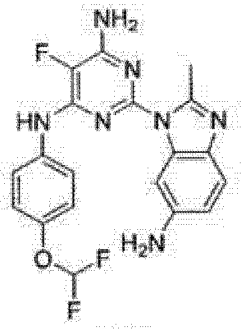

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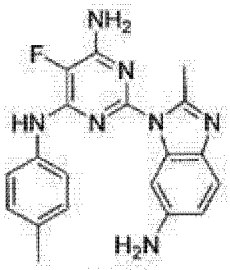

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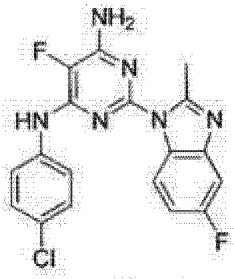

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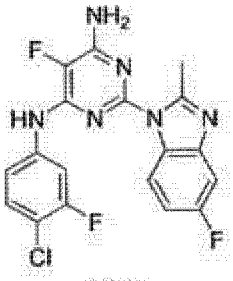

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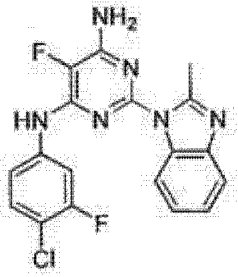

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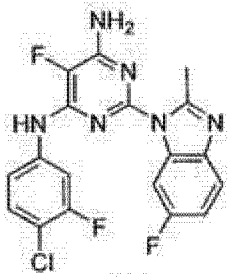

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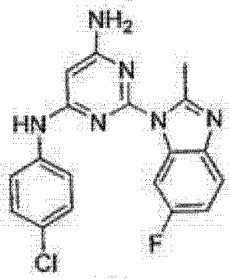

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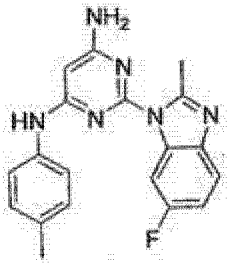

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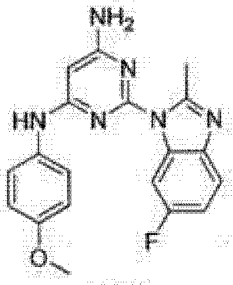

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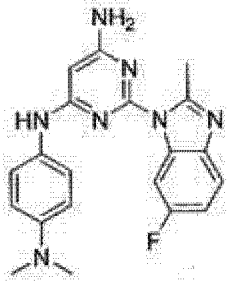

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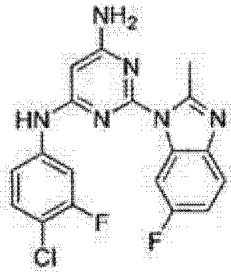

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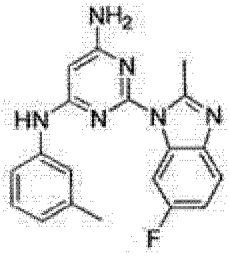

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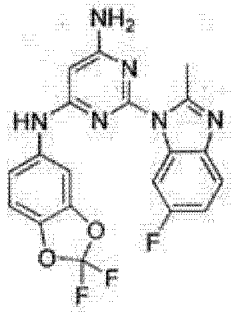

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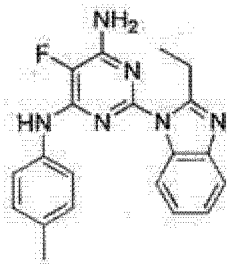

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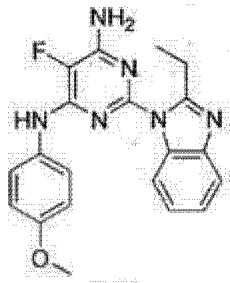

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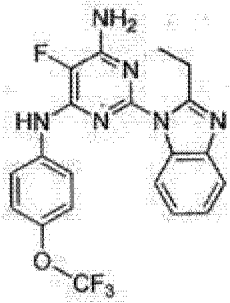

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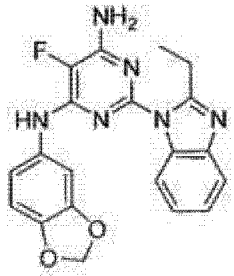

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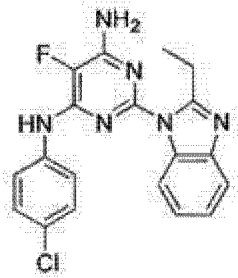

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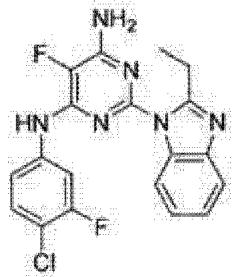

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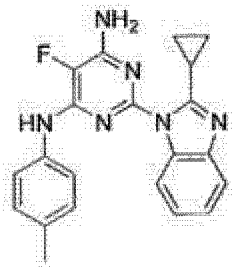

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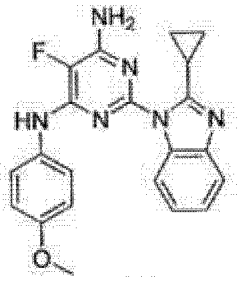

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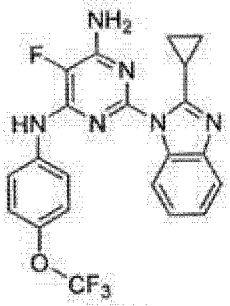

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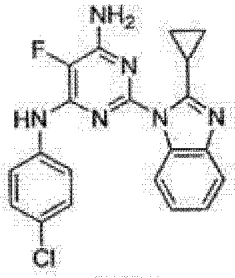

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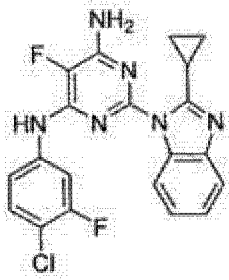

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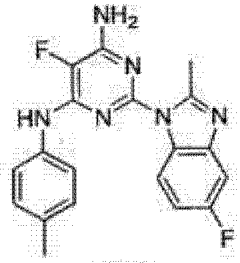

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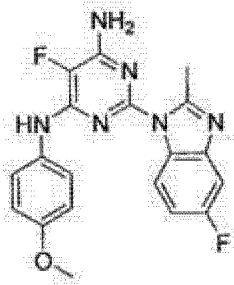

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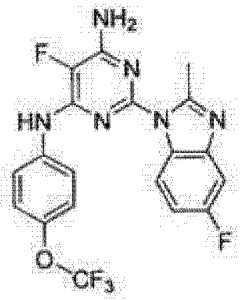

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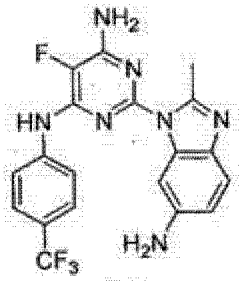


284;

其中式（I）化合物的形式选自其盐、酯、水合物、溶剂合物、螯合剂、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对应异构体或互变异构体。

[0100] 另一实施方案包括选自如下的式（I）化合物或其形式：

Cpd	名称
1	N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-胺
2	N-(2,3-二氢-1,4-苯并二氧杂环己二烯-6-基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺
3	2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺
4	N-(4-甲氧基苯基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺
5	N-(4-氯苯基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺
6	2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-苯基嘧啶-4-胺
7	2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺
8	N-(4-氯苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺
9	N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺
10	N-(4-溴苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺
11	N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

12 N-(4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

13 2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

14 2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲氧基)苯基]嘧啶-4-胺

15 N-(4-溴苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

16 2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺

17 N-(4-氯苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

18 2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

19 N-(4-溴苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

20 N-(4-甲基苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

21 2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲基苯基)嘧啶-4-胺

22 2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

23 2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

24 2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺

25 N-(4-溴苯基)-2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]嘧啶-4-胺

26 N-(4-溴苯基)-2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺

27 2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲基苯基)嘧啶-4-胺

28 N-(1,3-苯并二氧杂环戊烯-5-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

29 N-(2,3-二氢-1,4-苯并二氧杂环己二烯-6-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

30 N-(6-甲氧基吡啶-3-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

31 N^2,N^2-二甲基-N^5-{2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-基}吡啶-2,5-二胺

32 2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

33 2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺

34 N-(3-氟-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

35 N-(3-氯-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

36 N-(3-氯-4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

37 N-(4-乙氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

38 N-[4-(丙-2-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

39 N-[4-(1H-吡唑-1-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

40 N-(3-氯-4-甲氧基苯基)-2-(2-甲基-1*H*-苯并咪唑-1-基)嘧啶-4-胺

41 2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺

42 N-(3-氯-4-甲氧基苯基)-2-[2-(三氟甲基)-1H-苯并咪唑-1-基]嘧啶-4-胺

43 5-氟-N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

44 5-氯-N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

45 N-(4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺

46 2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

47 N-(4-氯苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺

48 2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

49 2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲氧基)苯基]嘧啶-4-胺

50 N-(4-甲氧基苯基)-2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

51 N-[4-(二氟甲氧基)苯基]-2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

52 2-{[6-{[4-(二氟甲氧基)苯基]氨基}-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}乙醇

53 N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺

54 2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺

55 N-[4-(二氟甲氧基)苯基]-2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺

56 N-[4-(三氟甲基)苯基]-2-[2-(三氟甲基)吡唑并[1,5-a]吡啶-3-基]嘧啶-4-胺

57 2-{[2-(2-甲基-1H-苯并咪唑-1-基)-6-{[4-(三氟甲基)苯基]氨基}嘧啶-4-基]氨基}乙醇

58 N^4-(2-甲氧基乙基)-2-(2-甲基-1H-苯并咪唑-1-基)-N^6-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

59 N^4-[4-(二氟甲氧基)苯基]-N^6-(2-甲氧基乙基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

60 N-(4-甲氧基苯基)-2-[2-(三氟甲基)吡唑并[1,5-a]吡啶-3-基]嘧啶-4-胺

61 N-[4-(二氟甲氧基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-胺

62 N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺

63 2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

64 2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

65 N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4,6-二胺

66 2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

67 N-[4-(三氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4,6-二胺

68 2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

69 N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

70 N-[4-(三氟甲基)苯基]-2-(1,3,5-三甲基-1H-吡唑-4-基)嘧啶-4,6-二胺

71 2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

72 N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

73 2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

74 2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

75 2-(2-环丙基-6-氟咪唑并[1,2-a]吡啶-3-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺

76 N-[4-(二氟甲氧基)-3-氟苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

77 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

78 2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺

79 N-[4-(三氟甲基)苯基]-2-(2,5,6-三甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

80 N-[3-氟-4-(三氟甲基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

81 2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

82 2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

83 2-(2-环丙基-5-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

84 [3-(4-氨基-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-6-氟咪唑并[1,2-a]吡啶-2-基]甲醇

85 2-(6-溴-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

86 2-(2,6-二甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

87 2-(6-乙基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

88 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

89 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

90 2-{[2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-6-{[4-(三氟甲基)苯基]氨基}嘧啶-4-基]氨基}乙醇

91 2-(6-乙烯基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

92 2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

93 2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

94 2-(6-氟-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

95 5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

96 2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

97 2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺

98 2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺

99 2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺

100 2-(6-氟-2-甲基咪唑并[1,2-a]嘧啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

101 N-[4-(二氟甲氧基)-3-氟苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

102 N-[4-(二氟甲氧基)苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

103 2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺

104 2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

105 2-(6-氯-2-乙基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

106 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

107 2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

108 5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

109 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

110 N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

111 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

112 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

113 N-[4-(二氟甲氧基)苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

114 2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

115 2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

116 2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

117 2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

118 2-(咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺

119 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

120 2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

121 2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

122 2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

123 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

124 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

125 2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

126 N-[4-(二氟甲氧基)-3-氟苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

127 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

128 N-[4-(二氟甲氧基)-3-氟苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

129 2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

130 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

131 N-[4-(二氟甲氧基)苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

132 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

133 N-[4-(二氟甲氧基)苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

134 5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

135 N-[4-(二氟甲氧基)苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

136 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

137 5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

138 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺

139 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺

140 2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

141 2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

142 2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺

143 2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺

144 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

145 N-[4-(二氟甲氧基)苯基]-2-[2-(二氟甲基)-6-氟-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

146 2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(甲基硫烷基)苯基]嘧啶-4,6-二胺

147 2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

148 N-[4-(二氟甲氧基)苯基]-2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺

149 2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

150 2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

151 2-[2-(丙-2-基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

152 2-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

153 2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

154 2-(2-甲基吡唑并[1,5-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

155 2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

156 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

157 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

158 2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

159 2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

160 2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

161 2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

162 2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

163 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

164 2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

165 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

166 5-氯-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

167 5-氯-2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

168 5-氯-N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

169 5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

170 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

171 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

172 5-甲基-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

173 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)嘧啶-4,6-二胺

174 5-氟-N-[4-(三氟甲基)苯基]-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺

175 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺

176 N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺

177 5-氟-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

178 5-氟-2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

179 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺

180 2-(2-环丙基吡唑并[1,5-a]吡啶-3-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

181 [3-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-5-氟吡唑并[1,5-a]吡啶-2-基]甲醇

182 2-[2-(甲基硫烷基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

183 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[6-(三氟甲基)吡啶-3-基]嘧啶-4,6-二胺

184 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

185 N-(4-氯苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

186 N-[4-(二氟甲氧基)苯基]-2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟嘧啶-4,6-二胺

187 2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

188 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟嘧啶-4,6-二胺

189 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(3-甲氧基苯基)嘧啶-4,6-二胺

190 N-(3-氯苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

191 5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

192 4-{[6-氨基-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈

193 4-{[6-氨基-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲酸甲酯

194 5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-(3-甲基苯基)嘧啶-4,6-二胺

195 5-氟-N-(3-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

196 2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

197 N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

198 N-[4-(二甲基氨基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

199 5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

200 5-氟-N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

201 N-(4-氯苯基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

202 4-{[6-氨基-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈

203 N-(1,3-苯并二氧杂环戊烯-5-基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

204	5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺
205	N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
206	N-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
207	N-(3-氟-4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
208	N-(6-甲氧基吡啶-3-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
209	N-(4-氯苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
210	4-{[6-氨基-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈
211	2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-硝基苯基)嘧啶-4,6-二胺
212	N-(4-溴苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
213	2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺
214	2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺
215	N-(4-氯苯基)-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
216	N-[4-(二氟甲氧基)苯基]-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺
217	5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲基苯基)嘧啶-4,6-二胺
218	5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲氧基苯基)嘧啶-4,6-二胺
219	N-(4-氯苯基)-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺
220	5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺
221	2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺
222	1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈
223	1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈

224 1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈

225 1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈

226 1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈

227 1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

228 1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

229 1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈

230 1-{4-氨基-6-[(4-氯苯基)氨基]-5-氟嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈

231 N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

232 5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

233 5-氟-N-(4-甲氧基苯基)-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

234 N-[4-(二氟甲氧基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

235 N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

236 5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

237 N-(4-氯苯基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

238 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

239 5-氟-N-(4-甲氧基苯基)-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)嘧啶-4,6-二胺

240 N-(1,3-苯并二氧杂环戊烯-5-基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺

241 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺

242 2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺

243 2-(5,7-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

244 5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺

245 N-(4-氯苯基)-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

246 5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺

247 N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

248 5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

249 5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺

250 N-(1,3-苯并二氧杂环戊烯-5-基)-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

251 N-(4-氯苯基)-5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺

252 5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺

253 5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

254 5-氟-2-(2-甲基-5-硝基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺

255 5-氟-N-(4-甲氧基苯基)-2-(2-甲基-5-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

256 2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺

257 2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺

258 2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺

259 N-(4-氯苯基)-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

260 N-(4-氯-3-氟苯基)-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺

261	N-(4-氯-3-氟苯基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
262	N-(4-氯-3-氟苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
263	N-(4-氯苯基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
264	2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺
265	2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺
266	N-[4-(二甲基氨基)苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
267	N-(4-氯-3-氟苯基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
268	2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(3-甲基苯基)嘧啶-4,6-二胺
269	N-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺
270	2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺
271	2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺
272	2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺
273	N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
274	N-(4-氯苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
275	N-(4-氯-3-氟苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
276	2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺
277	2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺
278	2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺
279	N-(4-氯苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
280	N-(4-氯-3-氟苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺
281	5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺
282	5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺
283	5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺, 和
284	2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺;

其中式 (I) 化合物的形式选自其盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对应异构体或互变异构体。

[0101] 术语

上述和贯穿本文说明书使用的化学术语，除非另外具体定义，否则应该被本领域普通技术人员理解为具有以下指定含义。

[0102] 本文中使用的术语“C_{1-8}烷基”是指在直链或支链构型中具有一至八个碳原子的

饱和烃基，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、正己基、正庚基、正辛基等。在一些实施方案中，C_{1-8}烷基包括 C_{1-6}烷基， C_{1-4}烷基等。C_{1-8}烷基基团可以在允许有效化合价的位置被任选取代。

[0103] 本文中使用的术语“C_{2-8}烯基”是指在直链或支链构型中具有二至八个碳原子和其中的一个或多个碳碳双键的部分不饱和的烃基，包括但不限于乙烯基、烯丙基、丙烯基等。在一些实施方案中，C_{2-8}烯基包括 C_{2-6}烯基， C_{2-4}烯基等。C_{2-8}烯基基团可以在允许有效化合价的位置被任选取代的。

[0104] 本文中使用的术语“C_{2-8}炔基”是指在直链或支链构型中具有二至八个碳原子和其中的一个或多个碳碳三键的部分不饱和烃基，包括但不限于乙炔基、丙炔基等。在一些实施方案中，C_{2-8}炔基包括 C_{2-6}炔基炔基、C_{2-4}炔基等。C_{2-8}炔基基团可以在允许有效化合价的位置被任选取代。

[0105] 本文中使用的术语 “C_{1-8}烷氧基”是指具有下式的直链或支链构型的一至八个碳原子的饱和烃基：-O-C_{1-8}烷基，包括但不限于甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、仲丁氧基、叔丁氧基、正戊氧基、正己氧基等。在一些实施方案中，C_{1-8}烷氧基包括 C_{1-6}烷氧基， C_{1-4}烷氧基等。C_{1-8}烷氧基基团可以在允许有效化合价的位置被任选取代。

[0106] 本文中使用的术语“C_{3-14}环烷基”是指饱和单环、双环或多环烃基，包括但不限于环丙基、环丁基、环戊基、环己基、环庚基、环辛基、1H- 茚满基、茚基、2,3- 二氢 -1H- 茚基、四氢 - 萘基等。在一些实施方案中，C_{3-14}环烷基包括 C_{3-8}环烷基， C_{5-8}环烷基， C_{3-10}环烷基等。C_{3-14}环烷基基团可以在允许有效化合价的位置被任选取代。

[0107] 本文中使用的术语“芳基”是指单环、双环或多环芳族碳原子环结构基团，包括但不限于苯基， 萘基 （还称为萘基团）、蒽基、芴基、蒽基、菲基等。芳基基团可以在允许有效化合价的位置被任选取代。

[0108] 本文中使用的术语“杂芳基”是指单环、双环或多环芳族碳原子环结构基团，其中一个或多个碳原子环成员已经在允许结构稳定性的位置被一个或多个杂原子例如 O、S 或 N 原子替代，包括但不限于呋喃基、噻吩基（还称为噻吩基团）， 吡咯基， 吡唑基 （还称为 1H- 吡唑基）， 咪唑基 （还称为 1H- 咪唑基）， 异噁唑基 （还称为 1,2- 噁唑基）， 异噻唑基， 噁唑基， 噻唑基， 三唑基， 噁二唑基， 噻二唑基， 四唑基， 吡喃基， 噻喃基， 吡啶基 （还称为吡啶基团）， 嘧啶基， 吡嗪基， 哒嗪基， 三嗪基， 吲哚基 （还称为 1H- 吲哚基）， 氮杂吲哚基， 吲唑基 （还称为 2H- 吲唑基）， 氮杂吲唑基， 异吲哚基， 吲哚嗪基， 苯并呋喃基， 苯并噻吩基， 苯并咪唑基 （还称为 1H- 苯并咪唑基）， 苯并噻唑基， 苯并噁唑基， 咪唑并 [2,1-b][1,3] 噻唑基， 吡唑并 [1,5-a] 吡啶基， 吡唑并 [1,5-c] 嘧啶基， 咪唑并 [1,2-a] 吡啶基， 1H- 咪唑并 [4,5-b] 吡啶基， 1H- 咪唑并 [4,5-c] 吡啶基， 咪唑并 [1,2-a] 吡嗪基， 咪唑并 [1,2-a] 嘧啶基， 7H- 嘌呤基， 9H- 嘌呤基， 喹啉基， 异喹啉基， 喹唑啉基， 喹喔啉基， 吖啶基等和其相关类似物和位置异构体。杂芳基可以在允许有效化合价的碳或氮原子环成员上被任选取代。

[0109] 本文中使用的术语“杂环基”是指饱和或部分不饱和单环、双环、或多环碳原子环结构基团，其中一个或多个碳原子环成员已经在允许结构稳定性的位置被杂原子例如 O， S 或 N 原子替代，包括但不限于氧杂环丙烷基、氧杂环丁烷基、氮杂环丁烷基、二氢呋喃

基、四氢呋喃基、二氢噻吩基、四氢噻吩基、吡咯啉基、吡咯烷基、二氢吡唑基、吡唑啉基、吡唑烷基、二氢咪唑基、咪唑啉基、咪唑烷基、异噁唑啉基、异噁唑烷基、异噻唑啉基、异噻唑烷基、噁唑啉基、噁唑烷基、噻唑啉基、噻唑烷基、三唑啉基、三唑烷基、噁二唑啉基、噁二唑烷基、噻二唑啉基、噻二唑烷基、四唑啉基、四唑烷基、1,3- 二氧戊环基、二氢 -2H- 吡喃基、四氢 -2H- 吡喃基、二氢 - 吡啶基、四氢 - 吡啶基、二氢 - 嘧啶基、四氢 - 嘧啶基、二氢 - 吡嗪基、四氢 - 吡嗪基、二氢 - 哒嗪基、四氢 - 哒嗪基、哌嗪基、哌啶基、吗啉基、硫代吗啉基、二氢 - 三嗪基、四氢 - 三嗪基、六氢三嗪基、1,4- 二氮杂环庚烷基、二氢 - 吲哚基、二吲哚啉基、四氢 - 吲哚基、二氢 - 吲唑基、四氢 - 吲唑基、二氢 - 异吲哚基、二氢 - 苯并呋喃基、四氢 - 苯并呋喃基、二氢 - 苯并噻吩基、四氢 - 苯并噻吩基、二氢 - 苯并咪唑基、四氢 - 苯并咪唑基、二氢 - 苯并噁唑基、四氢 - 苯并噁唑基、二氢 - 苯并噁嗪基、四氢 - 苯并噁嗪基、苯并 [1,3] 二氧杂环戊烯（还称为 1,3- 苯并二氧杂环戊烯基团）、苯并 [1,4] 二氧杂环己烷基（还称为 1,4- 苯并二氧杂环己烷基或 2,3- 二氢 -1,4- 苯并二氧杂环己二烯基）、苯并 [1,4] 二氧杂环己二烯基 （还称为 1,4- 苯并二氧杂环己二烯基）、4,5,6,7- 四氢 -2H- 吲唑基、5,6,7,8- 四氢咪唑并 [1,2-a] 吡啶基、4,5,6,7- 四氢 -3H- 咪唑并 [4,5-c] 吡啶基、二氢 - 嘌呤基、四氢 - 嘌呤基、二氢 - 喹啉基、四氢 - 喹啉基、二氢 - 异喹啉基、四氢 - 异喹啉基、二氢 - 喹唑啉基、四氢 - 喹唑啉基、二氢 - 喹喔啉基、四氢 - 喹唑啉基等和其相关类似物。杂环基可以在允许有效化合价的碳或氮原子环成员上被任选取代。

[0110] 本文中使用的术语“$B(OR_8)_2$”是指下式基团：当 R_8 为氢时 -B[(-OH)(-OH)]；或，当 R_8 独立地为氢或 C_{1-8} 烷基时 -B[(-OH)(-O-C_{1-8}烷基)]；或，当 R_8 为 C_{1-8} 烷基时 -B[(-O-C_{1-8}烷基)(-O-C_{1-8}烷基)]。

[0111] 本文中使用的术语“C_{1-8}烷氧基 -C_{1-8}烷基”是指下式基团：-C_{1-8}烷基 -O-C_{1-8}烷基。

[0112] 本文中使用的术语“C_{1-8}烷氧基 -C_{1-8}烷基 - 氨基”是指具有下式的基团：-NH-C_{1-8}烷基 -O-C_{1-8}烷基。

[0113] 本文中使用的术语“C_{1-8}烷氧基 -C_{2-8}烯基”是指具有下式的基团：-C_{2-8}烯基 -O-C_{1-8}烷基。

[0114] 本文中使用的术语“C_{1-8}烷氧基 -C_{2-8}炔基”是指具有下式的基团：-C_{2-8}炔基 -O-C_{1-8}烷基。

[0115] 本文中使用的术语“C_{1-8}烷氧基 - 羰基”是指具有下式的基团：-C(O)-O-C_{1-8}烷基。

[0116] 本文中使用的术语“C_{1-8}烷氧基 - 羰基 -C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基 -C(O)-O-C_{1-8}烷基。

[0117] 本文中使用的术语“C_{1-8}烷氧基 - 羰基 - 氨基”是指具有下式的基团：-NH-C(O)-O-C_{1-8}烷基。

[0118] 本文中使用的术语“C_{1-8}烷氧基 - 羰基 - 氨基 -C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基 -NH-C(O)-O-C_{1-8}烷基。

[0119] 本文中使用的术语“C_{1-8}烷氧基 - 亚氨基 -C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基 (=N-O-C_{1-8}烷基)。

[0120] 本文中使用的术语“C_{1-8}烷基 - 氨基”是指具有下式的基团：-NH-C_{1-8}烷基。

[0121] 本文中使用的术语“(C_{1-8}烷基)$_2$- 氨基”是指具有下式的基团：-N(C_{1-8}烷基)$_2$。

[0122] 本文中使用的术语“C_{1-8}烷基 - 氨基 -C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷

基 -NH-C_{1-8}烷基。

[0123] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-C_{1-8}烷基”是指具有下式的基团:-C_{1-8}烷基-N(C_{1-8}烷基)$_2$。

[0124] 本文中使用的术语“C_{1-8}烷基-氨基-C_{1-8}烷基-氨基”是指具有下式的基团:-NH-C_{1-8}烷基-NH-C_{1-8}烷基。

[0125] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-C_{1-8}烷基-氨基”是指具有下式的基团:-NH-C_{1-8}烷基-N(C_{1-8}烷基)$_2$。

[0126] 本文中使用的术语“C_{1-8}烷基-氨基-羰基”是指具有下式的基团:-C(O)-NH-C_{1-8}烷基。

[0127] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-羰基”是指具有下式的基团:-C(O)-N(C_{1-8}烷基)$_2$。

[0128] 本文中使用的术语“C_{1-8}烷基-氨基-羰基-氨基”是指具有下式的基团:-NH-C(O)-NH-C_{1-8}烷基。

[0129] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-羰基-氨基”是指具有下式的基团:-NH-C(O)-N(C_{1-8}烷基)$_2$。

[0130] 本文中使用的术语“C_{1-8}烷基-氨基-磺酰基”是指具有下式的基团:-SO_2-NH-C_{1-8}烷基。

[0131] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-磺酰基”是指具有下式的基团:-SO_2-N(C_{1-8}烷基)$_2$。

[0132] 本文中使用的术语“C_{1-8}烷基-氨基-磺酰基-氨基”是指具有下式的基团:-NH-SO_2-NH-C_{1-8}烷基。

[0133] 本文中使用的术语“(C_{1-8}烷基)$_2$-氨基-磺酰基-氨基”是指具有下式的基团:-NH-SO_2-N(C_{1-8}烷基)$_2$。

[0134] 本文中使用的术语“C_{1-8}烷基-羰基”是指具有下式的基团:-C(O)-C_{1-8}烷基。

[0135] 本文中使用的术语“C_{1-8}烷基-羰基-氨基”是指具有下式的基团:-NH-C(O)-C_{1-8}烷基。

[0136] 本文中使用的术语“C_{1-8}烷基-羰基-氨基-C_{1-8}烷基”是指具有下式的基团:-C_{1-8}烷基-NH-C(O)-C_{1-8}烷基。

[0137] 本文中使用的术语“C_{1-8}烷基-羰基-氧基”是指具有下式的基团:-O-C(O)-C_{1-8}烷基。

[0138] 本文中使用的术语“C_{1-8}烷基-羰基-氧基-C_{1-8}烷基”是指具有下式的基团:-C_{1-8}烷基-O-C(O)-C_{1-8}烷基。

[0139] 本文中使用的术语“C_{1-8}烷基-磺酰基”是指具有下式的基团:-SO_2-C_{1-8}烷基。

[0140] 本文中使用的术语“C_{1-8}烷硫基”是指具有下式的基团:-S-C_{1-8}烷基。

[0141] 本文中使用的术语“氨基”是指具有下式的基团:-NH_2。

[0142] 本文中使用的术语“氨基-C_{1-8}烷基”是指具有下式的基团:-C_{1-8}烷基-NH_2。

[0143] 本文中使用的术语“氨基-C_{1-8}烷基-氨基”是指具有下式的基团:-NH-C_{1-8}烷基-NH_2。

[0144] 本文中使用的术语“氨基-羰基”是指具有下式的基团:-C(O)-NH_2。

[0145] 本文中使用的术语“氨基－羰基－氨基”是指具有下式的基团：-NH-C(O)-NH_2。

[0146] 本文中使用的术语“氨基－磺酰基”是指具有下式的基团：-SO_2-NH_2。

[0147] 本文中使用的术语“氨基－磺酰基－氨基”是指具有下式的基团：-NH-SO_2-NH_2。

[0148] 本文中使用的术语“芳基-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基－芳基。

[0149] 本文中使用的术语“芳基-C_{1-8}烷基－氨基”是指具有下式的基团：-NH-C_{1-8}烷基－芳基。

[0150] 本文中使用的术语“芳基－氨基”是指具有下式的基团：-NH- 芳基。

[0151] 本文中使用的术语“羧基”是指具有下式的基团：-COOH, -C(O)OH 或 -CO_2H。

[0152] 本文中使用的术语“甲酰基”是指具有下式的基团：-C(O)-H。

[0153] 本文中使用的术语“甲酰基－氧基”是指具有下式的基团：-O-C(O)-H。

[0154] 本文中使用的术语“卤代”或“卤素”是指卤素原子基团，包括氟、氯、溴和碘。

[0155] 本文中使用的术语“卤素-C_{1-8}烷氧基”是指具有下式的基团：-O-C_{1-8}烷基－卤素，其中C_{1-8}烷基可以在允许有效化合价的位置被一个或多个卤素原子部分或完全取代。在一些实施方案中，卤素-C_{1-8}烷氧基包括卤素-C_{1-6}烷氧基，卤素-C_{1-4}烷氧基等。

[0156] 本文中使用的术语“卤素-C_{1-8}烷氧基－羰基”是指具有下式的基团：-C(O)-O-C_{1-8}烷基－卤素。

[0157] 本文中使用的术语“卤素-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基－卤素，其中C_{1-8}烷基可以在允许有效化合价的位置被一个或多个卤素原子部分或完全取代。在一些实施方案中，卤素-C_{1-8}烷基包括卤素-C_{1-6}烷基，卤素-C_{1-4}烷基等。

[0158] 本文中使用的术语“卤素-C_{1-8}烷基－羰基”是指具有下式的基团：-C(O)-C_{1-8}烷基－卤素。

[0159] 本文中使用的术语“卤素-C_{1-8}烷基－磺酰基”是指具有下式的基团：-SO_2-C_{1-8}烷基－卤素。

[0160] 本文中使用的术语“卤素-C_{1-8}烷硫基”是指具有下式的基团：-S-C_{1-8}烷基－卤素。

[0161] 本文中使用的术语“杂芳基-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基－杂芳基。

[0162] 本文中使用的术语“羟基-C_{1-8}烷氧基”是指具有下式的基团：-O-C_{1-8}烷基-OH, 其中C_{1-8}烷基可以在允许有效化合价的位置被一个或多个羟基部分或完全取代。

[0163] 本文中使用的术语“羟基-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基-OH, 其中C_{1-8}烷基可以在允许有效化合价的位置被一个或多个羟基部分或完全取代。

[0164] 本文中使用的术语“羟基－氨基”是指具有下式的基团：-NH-OH。

[0165] 本文中使用的术语“羟基-C_{1-8}烷基－氨基”是指具有下式的基团：-NH-C_{1-8}烷基-OH。

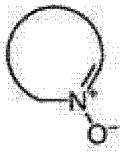
[0166] 本文中使用的术语“羟基-C_{1-8}烷基－氨基-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基-NH-C_{1-8}烷基-OH。

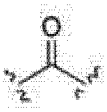
[0167] 本文中使用的术语“羟基-C_{1-8}烷基－氨基-C_{1-8}烷基－氨基”是指具有下式的基团：-NH-C_{1-8}烷基-NH-C_{1-8}烷基-OH。

[0168] 本文中使用的术语“羟基－亚氨基-C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基(=N-OH)。

[0169] 本文中使用的术语“亚氨基”是指具有下式的基团：=NH。

[0170] 本文中使用的术语“亚氨基 -C_{1-8}烷基”是指具有下式的基团：-C_{1-8}烷基 (=NH)。

[0171] 本文中使用的术语“N- 氧化物”是指下式基团：  。

[0172] 本文中使用的术语“氧代”是指下式基团：  。

[0173] 本文中使用的术语“P(O)$(R_7)_2$- 氨基” 是指下式基团：当 R_7独立地为羟基和 (C_{1-8}烷氧基)$_n$时为 -NH-P(O)(-O-C_{1-8}烷基)(OH)，其中 n 为 1；或，当 R_7为羟基时为 -NH-P(O)$(OH)_2$；或，当 R_7为 (C_{1-8}烷氧基)$_n$时 -NH-P(O)(-O-C_{1-8}烷基)$_2$，其中 n 为 1。

[0174] 本文中使用的术语“取代基”是指在指定原子位置被连接的核心分子的原子上的位置变量，在指定原子上替代一个或多个氢原子，条件是连接原子不超过有效化合价或共享化合价，从而使取代导致获得稳定化合物。因此，取代基和 / 或变量的组合是允许的，只要此类组合导致稳定化合物。假定本文中所述或所示具有表现为不满足的化合价水平的任何碳原子和杂原子具有大量氢原子以满足所述或所示化合价。

[0175] 本文中涉及本文中提供的化学术语定义时使用的术语“等”是指可以被本领域技术人员预期的化学结构中的变体，包括但不限于异构体(包括链、支化或位置结构异构体)、环体系水合(包括单环、双环或多环结构的饱和或部分不饱和)和导致稳定化合物的允许有效化合价的全部其他变体。

[0176] 出于本说明书的目的，在式 (I) 化合物的一个或多个取代基变量包括引入式 (I) 化合物的官能团的情况下，在公开的化合物中的任何位置出现的各官能团可以独立地选择，和如果合适的话，被独立地和 / 或任选地取代。

[0177] 本文中使用的术语“独立地选择”或“各自选择”是指在可以在核心分子结构上被多于一次连接的取代基列表中的官能变体，其中取代模式在每次出现时独立于在任何其他出现时的模式。此外，在本文中所述的化合物的核心结构上使用通用取代基变量理解为包括通用取代基被包括在特定类别中的特定取代基替代，例如芳基可以被苯基或萘基等替代，从而所得化合物包括在本文所述化合物范围内。

[0178] 本文中使用的术语“任选取代”是指特定取代基变量、基团、基、或部分表示类别的范围并可以独立地按需要进行选择以替代核心分子的连接的指定原子上的一个或多个氢原子。

[0179] 本文使用的术语“稳定化合物”或“稳定结构”是指足够稳固以被从反应混合物和其制剂中分离成可用程度的纯度的化合物至有效治疗剂中。

[0180] 使用由 ACD Labs 提供的 ACD Labs Index Name 软件和 / 或由 CambridgeSoft 提供的 ChemDraw Ultra 软件获得本文中使用的化合物名称。当本文中公开的化合物名称与描述的结构相矛盾时，所示的结构将取代使用的名称以定义需要的化合物。

[0181] <u>化合物形式</u>

本文中使用的术语“式 (Ia) 化合物，”“式 (II) 化合物，”“式 (IIa) 化合物，”“式 (III) 化合物额，”“式 (IIIa) 化合物，”“式 (IV) 化合”或“式 (IVa) 化合物”是指本文中定义的式 (I) 化合物或其形式的亚类。在某些实施方案中，并非重复式 (I) 化合物的各

种亚类，包括使用术语“式 (I) 化合物或其形式”是指式 (Ia) 化合物或其形式、式 (II) 化合物或其形式、式 (IIa) 化合物或其形式、式 (III) 化合物或其形式 、式 (IIIa) 化合物或其形式、式 (IV) 化合物或其形式或式 (IVa) 化合物或其形式，单独地或一起地。因此，“式 (I) 化合物”的实施方案和涉及内容意在包括式 (Ia) 化合物， 式 (II) 化合物， 式 (IIa) 化合物， 式 (III) 化合物， 式 (IIIa) 化合物， 式 (IV) 化合物和式 (IVa) 化合物。

[0182] 本文中使用的术语“形式”是指式 (I) 化合物，其选自其游离酸、游离碱、盐、酯、水合物、溶剂合物、螯合物、包合物、多晶型物、同位素体、立体异构体、外消旋体、对映异构体、非对映异构体、或互变异构体。

[0183] 在本文所述的某些实施方案中，式 (I) 化合物的形式选自其盐、同位素体、立体异构体、外消旋体、对映异构体、非对映异构体或互变异构体。

[0184] 在本文中所述的某些实施方案中，式 (I) 化合物的形式选自其游离酸、同位素体、立体异构体、外消旋体、对映异构体、非对映异构体或互变异构体。

[0185] 在本文中所述的某些实施方案中，式 (I) 化合物的形式选自其游离碱、同位素体、立体异构体、外消旋体、对映异构体、非对映异构体或互变异构体。

[0186] 在本文中所述的某些实施方案中，式 (I) 化合物的形式为其游离酸、游离碱或盐。

[0187] 在本文中所述的某些实施方案中，式 (I) 化合物的形式为其同位素体。

[0188] 在本文中所述的某些实施方案中，式 (I) 化合物的形式为其立体异构体、外消旋体、对映异构体或非对映异构体。

[0189] 在本文中所述的某些实施方案中，式 (I) 化合物的形式为其互变异构体。

[0190] 在本文中所述的某些实施方案中，式 (I) 化合物的形式为药学上可接受的形式。

[0191] 在本文中所述的某些实施方案中，式 (I) 化合物或其形式分离用于使用。

[0192] 本文中使用的术语“分离”是指式 (I) 化合物或其形式以足以通过本文中所述的或技术人员熟知的标准分析技术可表征的纯度在根据本文中所述的或技术人员熟知的一种或多种分离、分开或纯化方法(例如色谱、重结晶等) 从合成过程(例如从反应混合物) 或天然来源或其组合分离和 / 或分开和 / 或纯化之后的物理状态。

[0193] 本文中使用的术语“保护”是指当式 (I) 化合物经历反应时该化合物或其形式上的官能团处于改性成排除该官能团的不期望的副反应的形式。本领域普通技术人员和参考标准课本例如 T. W. Greene 等人 ， *Protective Groups in Organic Synthesis* (2007), Wiley, New York 意识到合适的保护基团。

[0194] 还考虑本文中所述的式 (I) 化合物或其形式的前药和溶剂合物。

[0195] 本文中使用的术语“前药”是指式 (I) 化合物上的官能团处于在体内转化以获得一种或多种活性式 (I) 化合物或其形式的形式(例如充当活性或非活性药物前体)。所述转化可以通过各种机制(例如通过代谢和 / 或非代谢化学过程) 进行，例如通过血液、肝脏和 / 或其他器官和组织中的水解和 / 或代谢。由 V.J. Stella 等人，“Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards,” American Association of Pharmaceutical Scientists and Springer Press, 2007 提供前药的使用的讨论。

[0196] 在一个实例中，当式 (I) 化合物或其形式含有羧酸官能团时，前药可以包括通过采用官能团例如烷基等替代酸基团的氢原子形成的酯。在另一实例中，当式 (I) 化合物或其形式含有醇官能团时，可以通过用官能团例如烷基或羰基氧基等替代醇基团的氢原子形

式前药。在另一实例中，当式 (I) 化合物或其形式含有胺官能团时，可以通过采用官能团例如烷基或取代羰基替代一个或多个胺氢原子形成的前体。

[0197] 式 (I) 化合物或其形式的药学上可接受的前药包括在合适的情况下被一个或多个以下基团取代的那些化合物：羧酸酯、磺酸酯、氨基酸酯、膦酸酯(例如用于衍生氨基磷酸的氨基磷酸)和进一步被烷基取代的单 -、二 - 或三磷酸酯。如本文所述，本领域普通技术人员理解为一个或多个此类取代基可以用于提供式 (I) 化合物或其形式作为前药。

[0198] 式 (I) 化合物或其形式可以形成盐，其意在包括在本说明书的范围内。关于本文中的式 (I) 化合物或其形式，理解为包括其盐，除非另外指明。本文中使用的术语“盐”是指采用无机和 / 或有机酸形成的酸性盐，和采用无机和 / 或有机碱形成的碱性盐。另外，当式 (I) 化合物或其形式含有碱性基团，例如但不限于吡啶或咪唑，以及酸性基团，例如但不限于羧酸时，可以形成两性离子(“内盐”)并包括在本文中使用的术语“盐”内。

[0199] 本文中使用的术语“药学上可接受的盐”是指安全和有效(即无毒生理学上可接受的)用于哺乳动物并具有生物活性的本文中所述的式 (I) 化合物或其形式的那些盐，不过其他盐也可用。例如可以通过式 (I) 化合物与一定量的酸或碱(例如当量数)在介质例如其中盐沉淀的介质或在水性介质中反应然后冻干形成式 (I) 化合物的盐。

[0200] 药学上可接受的盐包括一种或多种本文中描述的在式 (I) 化合物或其形式中存在的酸性或碱性基团的盐。酸加成盐的实施方案包括但不限于乙酸盐、酸磷酸盐、抗坏血酸盐、苯甲酸盐、苯磺酸盐、硫酸氢盐、酒石酸氢盐、硼酸盐、丁酸盐、氯化物、柠檬酸盐、樟脑酸盐、樟脑磺酸盐、乙磺酸盐、甲酸盐、富马酸盐、gentisinate、葡糖酸盐、葡萄糖醛酸盐(glucaronate)、谷氨酸盐、氢溴酸盐、盐酸盐、二盐酸盐、氢碘酸盐、异烟酸盐、乳酸盐、马来酸盐、甲磺酸盐、萘磺酸盐、硝酸盐、草酸盐、双羟萘酸盐、泛酸盐、磷酸盐、丙酸盐、蔗糖盐、水杨酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐(也称为甲苯基磺酸盐)、三氟乙酸盐、三氟乙酸的盐等。酸加成盐的一个或多个实施方案包括氯化物、盐酸盐、二盐酸盐、三盐酸盐、氢溴酸盐、乙酸盐、二乙酸盐、甲磺酸盐、硫酸盐、三氟乙酸盐、三氟乙酸的盐等。更具体的实施方案包括氯化物、盐酸盐、二盐酸盐、氢溴酸盐、甲磺酸盐、硫酸盐、三氟乙酸盐、三氟乙酸的盐等。

[0201] 在本文所述的式 (I) 化合物或其形式的某些实施方案中，该化合物以盐形式分离，其中所述化合物与该盐以表示成“化合物：盐 (A:B)，”(在非限定性实例中)的比率缀合，其中“A”和“B”代表分离形式的化合物和盐的当量。

[0202] 另外，例如由P. Stahl等人，Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge等人，*Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson等人，*The Practice of Medicinal Chemistry* (1996), Academic Press, New York; 和在 *The Orange Book* (Food & Drug Administration, Washington, D.C. 在它们的网站上)中讨论认为适合从碱性药物化合物形成药学上可使用的盐的酸。这些公开并入本文中作为参考。

[0203] 合适的碱性盐包括但不限于铝、铵、钙、锂、镁、钾、钠、锌和二乙醇胺盐。在本文中描述的某些式 (I) 化合物或其形式也可以与有机碱(例如有机胺)和与各种氨基酸形成药学上可接受的盐，所述有机碱例如但不限于二环己胺、叔丁胺等，所述氨基酸例如但不限于精

氨酸、赖氨酸等。含碱性氮的基团可以与试剂例如低级烷基卤化物(例如甲基、乙基、和丁基氯化物、溴化物和碘化物)、二烷基硫酸酯(例如二甲基、二乙基和二丁基硫酸酯)、长链卤化物(例如癸基、月桂基和硬脂基氯化物、溴化物和碘化物)、芳烷基卤化物(例如苄基和苯乙基溴化物)等季化。

[0204] 全部此类酸盐和碱盐意在包括在本文中所述药学上可接受的盐的范围内。另外，出于本说明书的目的，认为全部此类酸和碱盐等于相应化合物的游离形式。

[0205] 式(I)化合物和其形式可以进一步以互变异构体形式存在。考虑全部此类互变异构体形式并意在包括在本文中所述式(I)化合物或其形式的范围内。

[0206] 式(I)化合物或其形式可以含有不对称或手性中心，因此可以不同的互变异构形式存在。本说明书意在包括式(I)化合物的全部立体异构形式和其混合物，包括外消旋混合物。

[0207] 本文中所述的式(I)化合物或其形式可以包括一个或多个手性中心，因此可以作为外消旋混合物(*R/S*)或基本上纯对映异构体和非对映异构体存在。所述化合物也可以作为基本上纯(*R*)或(*S*)对映异构体存在(当存在一个手性中心时)。在一种实施方案中，在本文中记载的式(I)化合物或其形式为(*S*)异构体并可以作为基本上只包含(*S*)异构体的对映异构体纯组合物存在。在另一实施方案中，在本文中所述的式(I)化合物和其形式为(*R*)异构体并可以作为基本上只包含(*R*)异构体的对映异构体纯组合物存在。本领域技术人员会意识到当存在多于一个手性中心时，本文中所述的式(I)化合物或其形式也可以作为如 *IUPAC* 命名法建议书中定义的(*R,R*)，(*R,S*)，(*S,R*)或(*S,S*)异构体存在。

[0208] 本文中使用的术语“基本上纯的”是指基本上由以大于或等于 90% 的量，以大于或等于 92% 的量，以大于或等于 95% 的量，以大于或等于 98% 的量，以大于或等于 99% 的量，或以等于 100% 的量的单异构体构成的式(I)化合物或其形式。

[0209] 在说明书的一个方面，式(I)化合物或其形式为以大于或等于 90% 的量，以大于或等于 92% 的量，以大于或等于 95% 的量，以大于或等于 98% 的量，以大于或等于 99% 的量，或以等于 100% 的量存在的基本上纯(*S*)对映异构体。

[0210] 在说明书的一个方面，式(I)化合物或其形式为以大于或等于 90% 的量，以大于或等于 92% 的量，以大于或等于 95% 的量，以大于或等于 98% 的量，以大于或等于 99% 的量，或以等于 100% 的量存在的基本上纯(*R*)对映异构体。

[0211] 本文中使用的术语“外消旋体”是指并非“对映异构体纯”的异构形式的任何混合物，包括混合物例如但不限于以约 50/50、约 60/40、约 70/30、或约 80/20、约 85/15 或约 90/10 的比率。

[0212] 另外，本文中描述的式(I)化合物或其形式包括全部几何和位置异构体。例如，如果式(I)化合物或其形式包括双键或稠环，则顺式和反式形式和其混合物包括在本文中所述的式(I)化合物或其形式的范围内。

[0213] 非对映异构混合物可以基于它们的物理化学区别通过本领域那些技术人员熟知的方法例如通过色谱和/或分级结晶分离成它们单个非对映异构体。可以通过使用本领域那些技术人员已知的手性 HPLC 柱或其他色谱方法分离对映异构体。

[0214] 也可以通过与合适的光学活性化合物(例如手性助剂例如手性醇或 Mosher 酰氯)反应使对映异构混合物转化成非对映异构混合物，分离非对映异构体并转化(例如水解)单

个非对映异构体成相应的纯对映异构体分离对映异构体。

[0215] 认为本发明式 (I) 化合物或其形式(包括其盐、溶剂合物、酯和前药和转换的前药),其可以由于各种取代基上的不对称碳(包括对映异构形式(其可以在甚至不存在不对称碳的情况下存在)、旋转异构形式、阿托异构体、非对映异构和区域异构形式) 存在,的全部立体异构体(例如几何异构体、光学异构体等) 在本文说明书的范围内。本文中所述的式 (I) 化合物的单个立体异构体或其形式可以例如基本上不含其它异构体或可以如上所述的外消旋混合物存在。

[0216] 使用术语“盐”、“溶剂合物”、“酯”、“前药”等意在等同于使用本发明化合物的对映异构体、立体异构体、旋转异构体、互变异构体、位置异构体、外消旋体、同位素体或前药的盐、溶剂合物、酯和前药。

[0217] 术语“同位素体”是指富含同位素的式 (I) 化合物或其形式,其等同于本文所述的那些,但尽管一个或多个原子被具有不同于通常在自然界发现的原子量或质量数的原子量或质量数的原子替代的事实。可以并入本文中所述的式 (I) 化合物或其形式中的同位素的实例分别包括氢、碳、氮、氧、磷、氟和氯的同位素,例如H^2, H^3, C^{13}, C^{14}, N^{15}, O^{18}, O^{17}, P^{31}, P^{32}, S^{35}, F^{18}, Cl^{35}和 Cl^{36},其各自还在该说明书的范围内。

[0218] 本文中所述的式 (I) 化合物或其形式的某些富含同位素的形式(例如用H^3和C^{14}标记的那些)可用于化合物和 / 或底物组织分布分析中。氚化 (即 , H^3) 和碳 -14 (即 , C^{14}) 同位素对于它们制备的容易性和检测能力是特别优选的。此外,采用同位素例如氘 (即 , ″富氘 ″) 取代可以赋予由较大代谢稳定性(例如在体内半衰期内增加)、增加溶解度、降低的剂量要求(例如增加的生物利用度) 或降低的毒性(例如减低的代谢酶的抑制) 导致的某些治疗优势并因此在一些环境中可以是优选的。

[0219] 一种或多种本文中描述的式 (I) 化合物或其形式可以与药学上可接受的溶剂例如水、乙醇等的非溶剂化和溶剂化形式存在,并且本文说明书意在包括溶剂化和非溶剂化形式。

[0220] 本文中使用的术语“溶剂合物”是指本文中描述的式 (I) 化合物或其形式与一种或多种溶剂分子的物理缔合。该物理缔合包括改变离子和共价键包括氢键的程度。在某些情况下,溶剂合物能够分离,例如当一种或多种溶剂分子并入结晶固体的晶格中时。本文中使用的“溶剂合物”包括溶液相和可分离溶剂合物两者。合适的溶剂合物的非限定性实例包括乙醇合物、甲醇合物盐等。

[0221] 一种或多种本文中所述的式 (I) 化合物或其盐可以任选转化成溶剂合物。溶剂合物的制备通常是已知的。典型的非限定性方法涉及以高于环境温度下溶解式 (I) 化合物或其形式在需要量的需要溶剂(有机或水或其混合物) 中,和以足以形成晶体(然后通过标准方法分离) 的速率冷却该溶液。分析技术例如红外光谱法示出溶剂(或水) 存在于晶体中作为溶剂合物(或水合物)。

[0222] 本文中使用的术语“水合物”是指其中溶剂分子为水的溶剂合物。

[0223] 式 (I) 化合物和其形式、和式 (I) 化合物或其形式的盐、溶剂合物、酯和前药的多晶型结晶和非晶形式还意在包括在本文所述的式 (I) 化合物或其形式的范围内。

[0224] <u>化合物使用</u>

在 20 世纪 90 年代早期,*Bmi-1*致癌基因首先识别为莫罗尼鼠白血病病毒的关键插入 /

活化区域的一部分（*1-6*）。*Bmi-1*为转录抑制子的多梳家族（PcG）的成员并识别为造血干细胞（HSC）自我更新的必需调节物（*76*, *77*）。Park 发现 Bmi-1 在纯化小鼠和人类 HSC 中高度表达并且不存在 Bmi-1（如 *Bmi-1*敲除小鼠示范的）导致全部造血血统的渐进损失（*76*）。此外，*Bmi-1*$^{-/-}$ 第 14.5 天胎肝细胞移植到致死辐射的普通小鼠示范了该细胞不能重构髓样细胞、B 细胞、和 T 细胞，因为 *Bmi-1*$^{-/-}$ HSC 不能更新（*76*）。

[0225] 除了 *Bmi-1*在 HSC 自我更新的作用之外，发现在小鼠中 *Bmi-1*转基因表达诱导的淋巴瘤（*2*）。还发现 Bmi-1 在很多肿瘤类型包括急性髓性白血病、成神经管细胞瘤、成神经细胞瘤、结肠直肠癌、肺癌和前列腺癌中过度表达并发现随着恶性肿瘤而增加（*34*, *78*, *61*, *79*, *80*, *65*, *43*）。Bmi-1 通过 *Bmi-1*特异性 RNA 干扰（RNAi）在各种人类癌细胞系中的失去示出导致急性细胞死亡和生长抑制，而 Bmi-1 在各种正常细胞系中的失去示出只导致轻微生长抑制而没有显著的细胞死亡（*69*）。因此，Bmi-1 对于癌细胞的存活是必需的但对正常细胞的存活具有最小效果。

[0226] *Bmi-1*已经随后通过实验示出充当致癌基因并且已经证实与 c-myc 一起引发小鼠中的淋巴瘤特别有效（*7*, *8*）。Bmi-1 在淋巴瘤生成中的作用已经部分归于 INK4a 基因座（含有 p16^{INK4A}和 p14^{ARF}基因两者）的转录抑制，导致癌症和肿瘤细胞增殖的维护和分化的抑制（*7*, *9*）。已经广泛研究由于启动子沉默导致的 INK4a 基因座的表达损失并且对于很多类型的血液系统癌症的发展和预知很重要（*10*, *11*）。INK4a 基因座偶尔通过白血病和淋巴瘤中的缺失失去（*12*, *13*）。

[0227] 然而，Bmi-1 已经示出在缺少 INK4a 基因座的模型中的肿瘤发生中起作用，表明在癌症中重要的其他基因座通过该蛋白调节（*14*）。实验结果已经证实 Bmi-1 的失去诱导已知缺少 INK4a 的纤维肉瘤细胞中的生长停滞和衰老（*15*）。还存在 Bmi-1 对于乳腺癌中刺猬信号（Hh）路径重要的证据。Hh 信号传导的活化增加 *Bmi-1*表达，同时向下调节 *Bmi-1*（通过 siRNA）消除 Hh 信号传导对体外微球体形成的效果并抑制小鼠中导管 / 肺泡发育（*16*）。近期工作已经示范 Bmi-1 在 Hox 基因表达调节中的作用。Bmi-1 的敲低导致 H2A 泛素化的球形和基因座特异性丧失、HoxC5 基因的上调、和 HeLa 细胞生长的抑制（*17*）。另一研究示范 E2F6 和 Bmi-1 参与调节 Hox 基因表达（特别是 Hox C10 和 B9）调节，因此影响中轴骨生长，但不抑制 Ink4a-Arf 基因座。这些发现强调 E2F6-Bmi-1 相互作用的显著性并暗示 Hox 和 Ink4a-Arf 基因座或多或少通过不同的 Bmi-1- 依赖性机制调节（*18*）。近期研究暗示 Bmi-1 具有不同的作用，取决于细胞类型和 / 或生长阶段。保持识别由 Bmi-1 调节的其他基因。

[0228] 发现 Bmi-1 在恶性肿瘤例如弥漫性大 B 细胞淋巴瘤（DLBCL）、B 细胞非 Hodgkin 淋巴瘤、Hodgkin 淋巴瘤、急性髓性白血病、结肠癌、肝癌、非小细胞肺癌、乳腺癌和成神经管细胞瘤中高度表达。*Bmi-1*敲除小鼠的研究已经显示 Bmi-1 是白血病和正常造血干细胞的自身更新所需要的。

[0229] 另外，证据为与血瘤类型，特别是 Burkitt 淋巴瘤、套细胞淋巴瘤、Hodgkin 淋巴瘤（*21-23*）、非 Hodgkin 淋巴瘤、一些 T 细胞淋巴瘤（*2*, *24-31*）、急性髓性白血病和 T-ALL（*32-35*）相关的 Bmi-1 含量。Raaphorst 等观察到在 Hodgkin 淋巴瘤中，Reed-Sternberg 细胞（HRS）共表达 Bmi-1, EZH2, 和 Mib-1/Ki-67。因为 HRS 细胞被认为源自表达 Bmi-1 的生发中心淋巴球，所以此类淋巴球应该随着它们分化失去表达 Bmi-1 的能力（和获得表达 EZH2 的能力）。这些观察暗示 Hodgkin 淋巴瘤与这些细胞中的 Bmi-1 和

EZH2 的异常共表达相关(*22*)。van Gosliga 等人的急性髓性白血病干细胞群体的评价(*36*)示出能够通过至少两轮膨胀在骨髓底物上形成白血病 - 鹅卵石群体的 $CD34^+/CD38^-$ 细胞表示极少的细胞群体。其他分析示出该细胞群体表达高含量 *Bmi-1* mRNA 并能够在小鼠中形成侵占性白血病,而具有较低含量 *Bmi-1* mRNA 的那些细胞却不能(*36*)。此类研究涉及肿瘤生长中的 Bmi-1 和细胞存活并暗示肿瘤初发中的中心功能和癌症和肿瘤干细胞的维护。

[0230] Bmi-1 的含量已经示出在很多肿瘤类型中的预后相关性。基于在 64 名患者中评价高 Bmi-1 含量的预后值的研究的结果,该实例在急性髓性白血病中被发现(*32*)。基于 Bmi-1 的中值(54.58%),将患者分成两组并监测存活。当与具有较高含量的 Bmi-1 (>55%, n=31, 分别)的患者比较时,具有低 Bmi-1 阳性(<55%, n=33)的患者具有显著更长的总体存活(P=0.0001)、无复发存活(P=0.0072)和缓解时间(P=0.0065),与年龄组无关(*32*)。类似地,Van Galen 等人(*37*)已经示出 Bmi-1 含量在弥漫性大 B 细胞淋巴瘤(DLBCL)中高度预后的(*37*)。DLBCL 情况下的赘生性细胞源自生发中心 B(GCB)细胞或它们的后代(*38*)。近期微阵列分析已经示出一些 DLBCL 表型类似非赘生 GCB 细胞,而一些示出类似于活化 B 细胞(ABC)的表达特征(*39*)。

[0231] 此外,具有 GCB- 类表型的患者具有比具有 ABC- 类表型的那些好得多的预后(*40*)。*Bmi-1*识别成区别 ABC- 类 DLBCL 的一种基因(*39*),(*41*)。在套细胞淋巴瘤(MCL)、非 Hodgki 淋巴瘤和其他白血病(*22, 26, 27, 29, 42-44*)、以及很多其他肿瘤类型包括成神经细胞瘤、恶性胶质瘤、肝细胞癌、和乳腺癌、结肠直肠癌、前列腺癌、肺癌、胃癌和唾腺癌(*45-57*)中,其他家族具有相关的升高的 Bmi-1 含量和不良预后。从 INK4A 基因座表达丧失已经示出具有预后值(*12, 13*)。加在一起,这些数据主要涉及癌症中的 Bmi-1,并暗示通过在癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞中抑制 Bmi-1 功能和降低 Bmi-1 含量抑制不受控细胞增殖具有对患有多种癌类型的患者特别是罹患血液癌症的那些有利的治疗效果。

[0232] 例如,MCL 是稀有的、侵占性和不能治愈的 B 细胞非 Hodgkin 淋巴瘤,其是难治的(即对常规化疗法具有耐受性)和与不良预后相关。MCL 通过 t(11;14)(q13;q32) 易位表征,导致多梳家族基因 *Bmi-1*的扩大和过度表达,其通常起到造血干细胞的自身更新的作用并当过度表达时具有诱导肿瘤的能力。

[0233] 多发性骨髓瘤为另一致命 B- 细胞恶性疾病,其特征在于在骨髓中异常血浆细胞的累积。用于多发性骨髓瘤的标准疗法类似于 MCL 进程并且通常由通常导致 60-70% 反应率的联合化疗构成。然而,大部分患者最终复发,使患者具有有限的疗法选择。如通过免疫印迹法证实的,相比于正常血浆细胞,近期的多发性骨髓瘤细胞的基因表达谱显示 Bmi-1 的增加的表达。

[0234] *Bmi-1*已经示出由于大量因素包括 SALL4, FoxM1, c-Myc, E2F-1 和 Mel18 得到转录调节。Bmi-1 和 SALL4 为调节干细胞多能性和并在白血病形成(也称为白血病生成)中起作用的假型致癌基因。鼠科 Sal14 还示出在保持 ES (胚胎干细胞)的性能和调整原始内细胞团命运中其关键作用。Yang 等人示范从 *Bmi-1*启动子的转录以剂量 - 依赖性方式被 SALL4 显著活化(*35*)。Forkhead box 转录因子 FoxM1 在增殖细胞中表达并已经示出在通过 c-myc 活化响应于氧化应激中 Bmi-1 在转换 NIH 3T3 细胞中含量的上调(*58*)。*Bmi-1*同系物, Mel18, 在表达 Bmi-1 时充当有效抑制剂。*Bmi-1*启动子区域含有功能 E-box, c-Myc 和 Mel-18 通过其可以调节 *Bmi-1*表达。由于 Mel18 下调 c-Myc 表达和 *Bmi-1*为 c-Myc 靶,

这些数据暗示 Mel18 通过在细胞衰老期间抑制 c-Myc 调节 Bmi-1 的表达并因此连接 c-Myc 和多梳功能 (*59*)。类似地,近期报道暗示 E2F-1 也可能调节成神经细胞瘤中 Bmi-1 的含量 (*60*)。*Bmi-1*启动子含有由 E2F-1 构建的 *Bmi-1*启动子 - 依赖性报道子活化需要的假型 E2F 结合位点。尚未报道产生 Bmi-1 的转录后或翻译后控制。

[0235] 在不受理论限定的情况下,在本文中所述的式 (I) 化合物或其形式活化凋亡通路,如通过膜联蛋白 -V 表达、以及聚 (ADP- 核糖) 聚合酶 (PARP) 和半胱天冬酶 -9 和半胱天冬酶 -7 的裂解测定的。采用这些式 (I) 化合物或其形式处理的细胞的细胞周期分析还示范在 G_2/M 阶段阻断然后形成多倍体。这些发现暗示 Bmi-1 也可以在 DNA 修复和 / 或有丝分裂的调节中起作用。本文中所述的式 (I) 化合物或其形式是 Bmi-1 功能的有用抑制剂并导致 Bmi-1 蛋白含量降低并因此为过度表达 Bmi-1 的任何癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞的潜在疗法。另外,本文中所述的式 (I) 化合物或其形式抑制 Bmi-1 功能并降低癌症干细胞和肿瘤干细胞环境中 Bmi-1 含量,并因此可用于靶向已经示出对当前疗法(例如使用大和小分子化疗剂的那些和放射疗法,以及通过任意的破坏有丝分裂细胞进行主要作用的靶向疗法)具有耐受性的癌细胞群体。

[0236] 本文中使用的“*Bmi-1*,”的斜体形式,除非另外指明或从说明书上下文清楚看出,是指 *Bmi-1*基因。“Bmi-1,”的常规形式,“BMI-1”的大写形式或术语“Bmi-1 蛋白”,除非另外指明或从说明书上下文清楚看出,全部是指 Bmi-1 蛋白。

[0237] 本文中使用的术语“Bmi-1 抑制剂”或短语(或其变体)“抑制 Bmi-1 功能并降低 Bmi-1 含量”是指 Bmi-1 蛋白功能的翻译后抑制和随后的降解,导致在肿瘤环境中存在的 Bmi-1 蛋白含量降低,包括但不限于体外和体内环境,包括癌症干细胞或肿瘤干细胞或癌症干细胞和肿瘤干细胞。

[0238] 根据本说明书,抑制 Bmi-1 功能并降低 Bmi-1 含量的式 (I) 化合物或其形式还抑制体外和体内肿瘤细胞的增殖并提高固有耐受性群体(例如“癌症干细胞”“肿瘤干细胞”或两者)对化疗的敏感性。已经报道人类 Bmi-1 在多发性癌症样品和癌细胞系中的升高的表达 (*2, 42, 51, 56, 61-68*)。申请人已经识别抑制 Bmi-1 功能并降低体内和体外 Bmi-1 含量的式 (I) 化合物或其形式,具有在体内肿瘤细胞生长和异种移植物生长的并发抑制。

[0239] 本文中所述的一个实施方案涉及抑制 Bmi-1 功能和降低 Bmi-1 含量以对有此需要的对象治疗由 Bmi-1 介导的癌症的方法,包括使来自所述对象的具有升高的 Bmi-1 含量的细胞与一定量的式 (I) 化合物或其形式接触,其中所述细胞选自癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞,确定抑制细胞中 Bmi-1 功能的式 (I) 化合物或其形式的有效量,随后对该对象给予该有效量的式 (I) 化合物或其形式。

[0240] 本文所述的另一实施方案涉及抑制 Bmi-1 功能并降低 Bmi-1 含量以对有此需要的对象治疗由 Bmi-1 介导的癌症的方法,包括对该对象给予有效量的式 (I) 化合物或其形式。

[0241] 本文所述的另一实施方案涉及对有此需要的对象治疗由 Bmi-1 介导的癌症的方法,包括使来自所述对象的具有升高的 Bmi-1 含量的细胞与一定量的式 (I) 化合物或其形式接触,其中所述细胞选自癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞。

[0242] 本文所述的另一实施方案涉及还包括使来自所述对象的具有升高的 Bmi-1 含量的细胞与一定量的式 (I) 化合物或其形式接触的方法,其中所述细胞选自癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞,确定抑制细胞中 Bmi-1 功能的式 (I) 化合物或其形式的有效

量，并随后对该对象给予该有效量的式（I）化合物或其形式。

[0243] 本文所述的另一实施方案涉及其中被确定为抑制接触的细胞中 Bmi-1 功能的有效量的式（I）化合物或其形式降低了接触的细胞中 Bmi-1 含量。

[0244] 本文所述的方法的一个实施方案包括给予有效量的式（I）化合物或其形式以在癌细胞中在体内或体外、在肿瘤细胞中在体内或体外、在癌症干细胞群体中在体内或体外、或在肿瘤干细胞群体中在体内或体外抑制 Bmi-1 功能。

[0245] 本文所述的方法的一个实施方案包括给予有效量的式（I）化合物或其形式以在癌细胞中在体内或体外、在肿瘤细胞中在体内或体外、在癌症干细胞群体中在体内或体外、或在癌症干细胞群体在体内或体外降低 Bmi-1 含量。

[0246] 本文中所述的方法的一个实施方案包括给予有效量的式（I）化合物或其形式以抑制癌细胞增殖、肿瘤细胞增殖、癌症干细胞增殖或肿瘤干细胞增殖。

[0247] 本文中所述的实施方案包括式（I）化合物或其形式在制备药物中的用途，该药物用于抑制 Bmi-1 功能并降低 Bmi-1 含量以对有此需要的对象治疗由 Bmi-1 介导的癌症，包括对该对象给予有效量的所述药物。

[0248] 在不受理论限制的情况下，由过度表达的 Bmi-1 的存在调节或取决于其的任何类型的癌症都可以根据本文所述的式（I）化合物或其形式的意图使用治疗。

[0249] 本文中使用的术语“癌症”是指其中 Bmi-1 异常表达或过度表达的细胞并且该细胞取决于用于存活或增殖的Bmi-1。在不受理论限制的情况下，该细胞可以为干细胞类或更加分化的，但该细胞依赖于 Bmi-1 以能够获得不受控细胞分裂和形成对细胞毒素的化疗剂的耐受性。

[0250] 在另一实施方案中，术语“由 Bmi-1 介导的癌症”是指特征在于相比于来自无癌症患者(即没有可检测的癌症的患者，如通过常规技术 MRI， CAT 扫描等测定的）的细胞过度表达 Bmi-1 的来自癌症患者的细胞或一部分细胞的癌症。或者，该术语是指相对于来自周围正常组织的癌症患者细胞，表达相差为至少 2%， 4%， 8%， 10%， 15%， 20%， 25%， 30%， 35%， 40%， 45%， 50%， 55%， 60%， 65%， 70%， 75%， 80%， 85%. 90%， 或 95% 或更多的 Bmi-1 含量的来自癌症患者的细胞或一部分细胞，如通过本领域中常规使用的任何方法检测的或在本文中描述的，例如在 ELISA 中。

[0251] 可以采用本文所述的意图用途治疗的由 Bmi-1 介导的癌症的非限定性实例：白血病，例如但不限于急性白血病， 急性淋巴细胞白血病， 急性髓细胞白血病， 例如成髓细胞、早幼粒细胞、髓单核细胞、单核细胞和红白血病和骨髓增生异常综合症； 慢性白血病，例如但不限于慢性髓细胞（粒细胞）白血病， 慢性淋巴细胞白血病， 毛细胞白血病； 红细胞增多； 淋巴瘤例如但不限于 Hodgkin 淋巴瘤， 非 Hodgkin 淋巴瘤； 多发性骨髓瘤例如但不限于郁积多发性骨髓瘤， 非分泌骨髓瘤、骨硬化骨髓瘤、placancer 细胞白血病、solitary placancercytoma 和髓外 placancercytoma; Waldenström 巨球蛋白血； 未测定显著性的单克隆丙种球蛋白病；良性单克隆丙种球蛋白病； 重链疾病； 骨和结缔组织肉瘤例如但不限于骨肉瘤、成骨肉瘤、软骨肉瘤、Ewing 肉瘤、恶性巨细胞瘤、骨纤维肉瘤、脊索瘤、骨膜肉瘤、软组织肉瘤、血管肉瘤（血管内皮瘤）、纤维肉瘤、Kaposi 肉瘤、平滑肌肉瘤、脂肪肉瘤、淋巴管肉瘤、神经鞘膜瘤、横纹肌肉瘤、滑膜肉瘤；神经胶质脑瘤（即神经胶质瘤） 例如但不限于星形细胞瘤、室管膜瘤、少突神经胶质瘤、脑干胶质瘤、视神经胶质瘤、

弥漫固有脑桥胶质瘤、混合胶质瘤（即， 少突星形细胞瘤）、恶性胶质瘤、多形性成胶质细胞瘤、nonglial 肿瘤、听神经瘤、颅咽管瘤、成神经管细胞瘤、脑膜瘤、成松果体细胞瘤、松果体母细胞瘤、原发性脑淋巴瘤；乳腺癌包括但不限于导管癌、腺癌、小叶（癌细胞）癌、管内癌、髓质乳腺癌、粘液性乳腺癌、管状乳腺癌、乳突乳腺癌、Paget 病和炎性乳腺癌；肾上腺癌例如但不限于嗜铬细胞瘤和肾上腺皮质癌；甲状腺癌例如但不限于乳突或滤泡甲状腺癌、骨髓甲状腺癌和甲状腺未分化癌；胰腺癌例如但不限于胰岛癌、胃泌素瘤、胰高血糖毒瘤、舒血管肠肽瘤、生长激素抑制素分泌瘤、和良性肿瘤或胰岛细胞瘤；脑垂体癌例如但不限于 Cushing 病、催乳素分泌肿瘤、肢端肥大症、和尿崩症；眼癌例如但不限于眼黑素瘤例如虹膜黑素瘤、脉络膜黑素瘤、和睫状体黑素瘤、和成视网膜细胞瘤；阴道癌例如鳞状细胞癌、胰癌、和黑素瘤；外阴癌例如鳞状细胞癌、黑素瘤、腺癌、基底细胞癌、肉瘤和 Paget 病；宫颈癌例如但不限于鳞状细胞癌、和腺癌；子宫癌例如但不限于子宫内膜癌和子宫肉瘤；卵巢癌例如但不限于卵巢上皮癌、边线肿瘤、生殖细胞瘤、和间质瘤；食管癌例如但不限于鳞状癌、腺癌、腺样囊性癌、粘液表皮样癌、腺鳞瘤、肉瘤、黑素瘤、placancercytoma、疣状癌、和燕麦细胞（癌细胞）癌、胃癌例如但不限于腺癌、真菌样生长（息肉状）、溃疡、表面传播、扩散传播、恶性淋巴瘤、脂肪肉瘤、纤维肉瘤、和癌肉瘤；结肠癌；直肠癌；肝癌例如但不限于肝细胞癌和肝母细胞癌；胆囊癌例如腺癌；胆管细胞癌例如但不限于乳突、结节状和扩散；肺癌例如非小细胞肺癌、鳞状细胞癌（表皮样癌）、腺癌、大细胞癌和小细胞肺癌；睾丸癌例如但不限于生发肿瘤、精原细胞瘤、退行发育性、经典性(典型性)、精母细胞性、非精原细胞、胚胎性癌、畸胎瘤、绒毛膜癌（卵黄囊肿瘤）、前列腺癌例如但不限于前列腺上皮肉瘤、腺癌、平滑肌肉瘤、和横纹肌肉瘤；penal cancers；口腔癌例如但不限于鳞状细胞癌；基底细胞癌；唾腺癌例如但不限于腺癌、粘液表皮样癌、和腺样囊性癌；咽癌例如但不限于鳞状细胞癌、和疣性；皮肤癌例如但不限于基底细胞癌、鳞状细胞癌和黑素瘤、表面扩散黑素瘤、结节状黑素瘤、雀斑恶性黑素瘤、肢端雀斑黑素瘤；肾肿瘤例如但不限于肾细胞癌、腺癌、肾上腺样瘤、纤维肉瘤、移行性细胞癌（肾盂和／或 uterer)； Wilms 肿瘤；膀胱癌例如但不限于移行性细胞癌鳞状细胞癌、腺癌、癌肉瘤。另外，癌症包括粘液肉瘤、骨原性肉瘤、内皮肉瘤、lymphangioendotheliosarcoma、间皮瘤、滑膜瘤、成血管细胞瘤、上皮细胞癌、囊腺癌、支气管癌、汗腺癌、皮脂腺癌、乳头状癌和乳突腺癌（对于回顾此类疾病，参见Fishman 等人， 1985, *Medicine*, 第 2 版， J.B. Lippincott Co., Philadelphia and Murphy 等人., 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America)。

[0252] 式 (I) 化合物或其形式也可以用于治疗、预防和／或管理由 Bmi-1 介导的各种癌症或其他异常增殖性疾病（其中，此类疾病通过过度表达的 Bmi-1 或的升高含量的 Bmi-1 介导），包括（但不限于）以下：癌，包括但不限于膀胱、乳房、结肠、肾、肝、肺、卵巢、胰腺、胃、宫颈、甲状腺和皮肤；包括鳞状细胞癌；淋巴血统造血肿瘤，包括白血病、急性淋巴细胞白血病、急性成淋巴细胞性白血病、B- 细胞淋巴瘤、T 细胞淋巴瘤、Burkitt 淋巴瘤；骨髓血统的造血肿瘤，包括急性和慢性骨髓性白血病和前骨髓细胞癌；间叶源肿瘤，包括纤维肉瘤和 rhabdomyoscarcoma；其他肿瘤，包括黑素瘤、精原细胞瘤、tetratocarcinoma、成神经细胞瘤；中枢和外周神经系统肿瘤，包括星形细胞癌、成神经细胞瘤、胶质瘤和 Schwannomas；

间叶细胞源肿瘤，包括纤维肉瘤、rhabdomyoscarama、和骨肉瘤；和其他肿瘤，包括黑素瘤、着色性干皮病、keratoactanthoma、精原细胞瘤、甲状腺滤泡癌和畸胎癌。在一些实施方案中，根据本文所述方法治疗与细胞凋亡中畸变相关的癌症。此类癌症可以包括但不限于滤泡性淋巴瘤、具有 p53 突变的癌症、乳房、前列腺和卵巢的激素依赖性肿瘤和癌前病变例如家族性腺瘤性息肉病和骨髓增生异常综合症。在特定实施方案中，根据本文所述的方法治疗皮肤、肺、肝、骨、脑、胃、结肠、乳房、前列腺、膀胱、肾、胰腺、卵巢和／或子宫的恶性或异型增殖变化（例如化生和发育不良）、或增生过多。在其他具体实施方案中，如本文所述治疗肉瘤或黑素瘤。

[0253] 在具体实施方案中，如本文所述治疗的由 Bmi-1 介导的癌症为白血病、淋巴瘤或骨髓瘤（例如多发性骨髓瘤）。可以采用本文中所述的方法治疗的由 Bmi-1 介导的白血病和其他血源性癌症的非限定实例包括急性成淋巴细胞白血病 (ALL)、急性淋巴母细胞 B 细胞白血病、急性成淋巴细胞 T 细胞白血病、急性成髓细胞白血病 (AML)、急性早幼粒细胞白血病 (APL)、急性单核细胞性白血病、急性红白血病、急性巨核细胞白血病、急性髓单核细胞白血病、急性非淋巴细胞白血病、急性未分化白血病、慢性髓细胞性白血病 (CML)、慢性淋巴细胞白血病 (CLL)、和毛细胞白血病。

[0254] 可以根据本文中所述的方法治疗的由 Bmi-1 介导的淋巴瘤的非限定性实例包括 Hodgkin 淋巴瘤、非 Hodgkin 淋巴瘤、多发性骨髓瘤、Waldenström 巨球蛋白血、重链疾病、和真性红细胞增多症。

[0255] 在另一实施方案中，如本文中所述治疗的由 Bmi-1 介导的癌症为实体瘤。可以根据本文中所述的方法治疗的实体瘤的实例包括但不限于纤维肉瘤、粘液肉瘤、脂肪肉瘤、软骨肉路、骨原性肉瘤、脊索瘤、血管肉瘤、内皮肉瘤、淋巴管肉瘤、lymphangioendotheliosarcoma、滑膜瘤、间皮瘤、Ewing 肿瘤、平滑肌肉瘤、横纹肌肉瘤、结肠癌、结肠直肠癌、肾肿瘤、胰腺癌、骨癌、乳腺癌、卵巢癌、前列腺癌、食管癌、胃癌、口腔癌、鼻癌、喉癌、鳞状细胞癌、基底细胞癌、腺癌、汗腺癌、皮脂腺癌、乳头状癌、乳突腺癌、囊腺癌、髓样癌、支气管源癌、肾细胞癌、肝癌、胆道癌、绒毛膜癌、精原细胞瘤、胚胎性癌、Wilms 肿瘤、宫颈癌、子宫癌、睾丸癌、小细胞肺癌、膀胱癌、肺癌、上皮细胞癌、胶质瘤、多形性成胶质细胞瘤、星形细胞瘤、成神经管细胞瘤、颅咽管瘤、室管膜瘤、松果体瘤、成血管细胞瘤、听神经瘤、少突神经胶质瘤、脑膜瘤、皮肤癌、黑素瘤、成神经细胞瘤、和成视网膜细胞瘤。

[0256] 在某些实施方案中，由 Bmi-1 介导的癌症包括但不限于脑癌、胃癌、血液系统癌、肺癌、非小细胞肺癌、胰腺癌、前列腺癌、唾腺癌、结肠直肠癌、肝细胞癌、肝癌、乳腺癌或肉瘤、食管癌或肉瘤、胃癌或肉瘤、纤维肉瘤、恶性胶质瘤、扩散固有脑桥胶质瘤、成神经管细胞瘤、成神经细胞瘤、弥漫性大 B 细胞淋巴瘤、B 细胞非 Hodgkin 淋巴瘤、Hodgkin 淋巴瘤或慢性或急性髓性白血病。

[0257] 在某些实施方案中，由 Bmi-1 介导的癌症包括但不限于在治疗(即使改进的外科和辐射技术)之后复发的肿瘤。肿瘤复发可以出于很多理由发生，一种貌似可信的解释是在肿瘤群体中存在癌症干细胞 (CSC) 或肿瘤干细胞(肿瘤引发细胞)。CSC 定义为相对于任何类型的血液癌症、实体瘤癌或转移癌的干细胞群体。肿瘤干细胞是具体在肿瘤中找到的那些。两者都具有类似于正常干细胞的特征。如正常干细胞，CSC 和肿瘤干细胞具有自身更新的潜力。与正常干细胞不同，尽管由于持续存在高含量 Bmi-1，CSC 和肿瘤干细胞不能在

末端未加抑制地分化和增殖。它们的改进的 DNA 修复能力也能够使它们对设计成杀死癌细胞和肿瘤细胞的细胞毒素的化疗药物具有耐受性。因此，靶向过度表达 Bmi-1 的 CSC 和肿瘤干细胞对于有效癌症治疗可以是一种途径。一种另外的途径是靶向导致维护 CSC 的自身更新能力的各种转录因子和肿瘤干细胞。

[0258] 本文中使用的术语“治疗 (treat)”、“治疗 (treatment)”或“治疗 (treating)”是指 (i) 预防在可能患有疾病、障碍和 / 或病症但尚未诊断成具有所示疾病、障碍和 / 或病症的对象中发生的疾病、障碍和 / 或病症 ;(ii) 抑制疾病、障碍和 / 或病症，即阻止其发展 ;和 / 或 (iii) 减轻疾病、障碍和 / 或病症，即导致疾病、障碍和 / 或病症的退化。

[0259] 本文中使用的术语“对象”是指人类、马、猪、牛、鼠、家鼠、犬和猫类成员。在一些实施方案中，所述对象为哺乳动物或温血脊椎动物。在其他实施方案中，所述对象为人类。本文中使用的术语“患者”可以与“对象”和“人类”互换使用。

[0260] 在某些实施方案中，所述对象为 0 至 6 月龄，6 至 12 月龄，6 至 18 月龄，18 至 36 月龄，1 至 5 岁龄，5 至至 10 岁龄，10 至 15 岁龄，15 至 20 岁龄，20 至 25 岁龄，25 至 30 岁龄，30 至 35 岁龄，35 至 40 岁龄，40 至 45 岁龄，45 至 50 岁龄，50 至 55 岁龄，55 至 60 岁龄，60 至 65 岁龄，65 至 70 岁龄，70 至 75 岁龄，75 至 80 岁龄，80 至 85 岁龄，85 至 90 岁龄，90 至 95 岁龄或 95 至 100 岁龄的人类。在一些实施方案中，所述对象为人类婴儿。在其他实施方案中，所述对象为人类幼童。在其他实施方案中，所述对象为人类为孩童。在其他实施方案中，所述对象为人类成年人。在其他实施方案中，所述对象为老年人。

[0261] 本文中使用的术语“老年人”是指 65 岁或更大年龄的人类，术语“成年人”是指 18 岁或更大年龄的人类 ;术语“孩童”是指 1 岁至 18 岁龄的人类 ;术语“婴儿”是指新生至 1 岁龄人类 ;并且术语“幼童” 是指 1 岁至 3 岁龄的人类。

[0262] 在某些实施方案中，所述对象处于免疫功能不全状态或抑制免疫状态或有成为免疫功能不全或抑制免疫的危险。在某些实施方案中，所述对象接受免疫抑制治疗或由免疫抑制治疗恢复。在某些实施方案中，所述对象具有或处于患癌症、AIDS 或细菌感染的危险。在某些实施方案中，所述对象经历、将或已经经历外科手术、化疗和 / 放疗。在某些实施方案中，所述对象具有囊胞性纤维症、肺纤维化或影响肺的另一病症。在某些实施方案中，所述对象具有、将具有或已经具有组织移植。

[0263] 在一些实施方案中，对象的癌症，由于 Bmi-1 在其癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞中的过度表达，已经证实对于传统的“护理标准 (standard of care)”疗法是难治的(排除采用式 (I) 化合物或其形式治疗)，从而患者中断了传统治疗。在一种实施方案中，在不受理论限制的情况下，术语“难治”是指至少某一显著部分的癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞由于 Bmi-1 过度表达继续增殖，即使进行治疗。所述癌症对于特定疗法是否难治的测定可以在体内或体外通过本领域已知的任何方法使用在此类背景下本领域接受的“难治”的含义进行，所述方法用于分析疗法对癌细胞、肿瘤细胞、癌症干细胞或肿瘤干细胞的效果。在某些实施方案中，具有由于 Bmi-1 的过度表达导致的难治癌症的患者为其中癌症对于传统或“护理标准”疗法无响应或具有耐受性的患者。在某些实施方案中，具有难治癌症的患者具有进展中的由 Bmi-1 介导的癌症。病程进展，由于缺少对疗法的临床响应，证实该肿瘤或赘生物尚未显著摆脱和 / 或症状尚未显著减轻。患者是否具有由

Bmi-1 介导的难治癌症的测定可以在体内或体外通过本领域已知的任何方法使用在此类背景下的本领域接受的“难治”的含义进行，所述方法用于分析所述疗法用于治疗所述癌症的效果。

[0264] 在某些实施方案中，待根据本文中所述方法治疗的患者为已经采用抗生素、抗病毒、抗真菌、或其他生物疗法、免疫疗法或抗癌疗法治疗的患者。在这些患者中，为患有由 Bmi-1 介导的难治癌症的患者或对于传统疗法过于年轻的患者。在一些实施方案中，治疗中的患者为治疗初期，之前尚未接受任何治疗。在任何上述实施方案中，待治疗的患者可能接受小分子疗法。

[0265] 在一些实施方案中，式 (I) 化合物或其形式可以预防性地给予患者以预防在处于形成癌症危险的患者中开始由 Bmi-1 介导的癌症。在一些实施方案中，式 (I) 化合物或其形式可以治疗性地给予易受对传统疗法产生负面反应的患者。在一些实施方案中，被给予一种或多种式 (I) 化合物或其形式的对象之前尚未接受治疗。在其他实施方案中，对之前已经接受治疗的对象给予一种或多种式 (I) 化合物或其形式。在一些实施方案中，被给予式 (I) 化合物或其形式的对象由于从该治疗没有获得益处、从该治疗获得负面效果或不可接受的毒性水平而已经中断之前的治疗。

[0266] 在一些实施方案中，被给予一种或多种式 (I) 化合物或其形式的对象将会或已经经历外科手术、化疗、抗体治疗、激素治疗和 / 或放射疗法。在某些实施方案中，患者已经经历外科手术以除去肿瘤或赘生物。在某些实施方案中，所述对象将会或已经或正在经历组织或器官移植。

[0267] 本文使用的术语“有效量”、“预防有效量”或“治疗有效量”是指对于有此需要的患者的由 Bmi-1 介导的癌症在抑制 Bmi-1 蛋白功能和降低 Bmi-1 蛋白的含量(如本文所述)和因此产生期望的预防、治疗、改善、抑制或防止效果中有效的式 (I) 化合物或其形式的量。

[0268] 在给予患者式 (I) 化合物或其形式的背景下，本文使用的术语“有效量”是指在患者或患者细胞中(作为可适用的)有效实现至少一种或多个以下效果的式 (I) 化合物或其形式的量：(i) 抑制 Bmi-1 蛋白功能；(ii) 降低 Bmi-1 蛋白的水平或量；(iii) 降低或改善由 Bmi-1 介导的癌症或与其相关的症状的严重度；(iv) 预防由 Bmi-1 介导的癌症或与之相关的症状的发展；(v) 复原由 Bmi-1 介导的癌症或与之相关的症状；(vi) 预防由 Bmi-1 介导的癌症或与之相关的症状的发展或开始；(vii) 预防由 Bmi-1 介导的癌症或与由 Bmi-1 介导的癌症相关的症状的再发生；(viii) 降低与由 Bmi-1 介导的癌症相关的症状的持续时间；(ix) 降低或消除癌症干细胞或肿瘤干细胞群体；(x) 降低或消除过度表达 Bmi-1 的肿瘤或赘生物的生长；(xi) 降低或消除癌细胞或肿瘤细胞的增殖；(xii) 降低或消除过度表达 Bmi-1 的肿瘤或赘生物的形成；(xiii) 消除或控制由 Bmi-1 介导的原发性、局部和 / 或转移癌；(xiv) 降低患者死亡率；(xv) 增加缓解期中患者数；(xvi) 增加患者中缓解期时间长度；(xvii) 保持或控制过度表达 Bmi-1 的肿瘤或赘生物的尺寸从而使该尺寸在给予标准给药之后不增加或增加少于肿瘤尺寸，如通过本领域技术人员可获得的传统方法例如 MRI, X-ray 和 CAT 扫描测量的；(xviii) 增加病程进展的延时；(xix) 增加患者存活；(xx) 降低患者住院的发生；(xxi) 降低患者住院的时间长度；(xxii) 改善或提高另一治疗的预防或治疗效果；(xxiii) 降低与由 Bmi-1 介导的癌症相关的症状的数量；(xxiv) 增加患者的无癌症存活；和 / 或 (xxv) 增加癌症患者的无症

状存活。

[0269] 一般而言，术语“有效量”还包括给予患者的式 (I) 化合物或其形式的如下范围的量：约 0.001 mg/Kg/ 天至约 500 mg/Kg/ 天、或约 0.01 mg/Kg/ 天至约 500 mg/Kg/ 天、或约 0.1 mg 至约 500 mg/Kg/ 天、或约 1.0 mg/ 天至约 500 mg/Kg/ 天，对于体重为约 40 至约 200 Kg 的患者或对象而言单一、分开或连续剂量（该剂量可以调节成适合高于或低于这个范围的患者或对象，特别是低于 40 Kg 的孩童）。预期典型的成年对象具有约 60 至约 100 Kg 范围内的中值体重。对于所述对象的有效量还取决于各种因素，包括该对象的体重、尺寸和健康。可以根据临床医师的技术和判断确定对于给定患者的有效量。

[0270] 在另一实施方案中，在基于对象或患者体重调节日剂量的情况下，本文中所述的式 (I) 化合物或其形式可以以约 0.02, 0.025, 0.03, 0.05, 0.06, 0.075, 0.08, 0.09, 0.10, 0.20, 0.25, 0.30, 0.50, 0.60, 0.75, 0.80, 0.90, 1.0, 1.10, 1.20, 1.25, 1.50, 1.75, 2.0, 5.0, 10, 20 或 50 mg/Kg/ 天配制用于递送。基于所述对象或患者体重调节的日剂量可以单一、分开或连续剂量形式给予。在给予式 (I) 化合物或其形式每天多于一次的剂量的情况下的实施方案中，可以每天给予所述剂量一次、两次、三次或更多次。在另一实施方案中，给予对象一个或多个有效量的式 (I) 化合物或其形式的剂量，其中对于每个剂量所述有效量可能不同。

[0271] 本文中所述的另一实施方案包括约 0.001 mg/Kg/ 天至约 500 mg/Kg/ 天的有效量的式 (I) 化合物或其形式。

[0272] 在本文所述的范围内，在制备药物或用于对有此需要的对象治疗由 Bmi-1 介导的癌症的方法中使用的式 (I) 化合物或其形式的“有效量”意在包括如下范围的量：每日给予约 0.1 ng 至约 3500 mg; 每日给予约 0.1 μg 至约 3500 mg; 每日给予约 0.1 mg 至约 3500 mg; 每日给予约 1 mg 至约 3500 mg; 每日给予约 1 mg 至约 3000 mg; 每日给予约 0.05 mg 至约 1500 mg; 每日给予约 0.5 mg 至约 1500 mg; 每日给予约 1 mg 至约 1500 mg; 每日给予约 5 mg 至约 1500 mg; 每日给予约 10 mg 至约 600 mg; 每日给予约 0.5 mg 至约 2000 mg; 或每日给予约 5.0 mg 至约 1500 mg 范围的量。

[0273] 本文所述的另一实施方案包括约 0.1 ng 至约 3500 mg 范围内的有效量的式 (I) 化合物或其形式。

[0274] 对于任何式 (I) 化合物或其形式，可以通过来自细胞培养分析或来自相关动物模型例如小鼠、黑猩猩、狨猴或绢毛猴动物模型的结果初始评价有效量。相关动物模型也可以用于确定给药的合适浓度范围和途径。此类信息然后可以用于确定对于人类给药的有用剂量和途径。可以通过标准药制药程序在细胞培养或实验动物中测定治疗效果和毒性，例如 ED_{50}（在 50% 群体中治疗有效的剂量）和 LD_{50}（对于 50% 群体致命的剂量）。有毒和治疗效果之间的剂量比率称为治疗指标，并可以表示成比率 LD_{50}/ED_{50}。在一些实施方案中，所述有效量使得获得大治疗指标。在其他实施方案中，剂量在包括几乎没有或没有毒性的 ED_{50} 的血浆浓度范围内。所述剂量可以在该范围内变化，取决于使用的剂型、患者敏感度、和给药途径。

[0275] 更具体地，关于式 (I) 化合物或其形式观察到的浓度 - 生物效果（药效的）关系暗示约 0.001 μg/mL 至约 50 μg/mL、约 0.01 μg/mL 至约 20 μg/mL、约 0.05 μg/mL 至约 10 μg/mL、或约 0.1 μg/mL 至约 5 μg/mL 的目标血浆浓度。为了实现此类血浆浓度，本文中所

述的式 (I) 化合物或其形式可以在 0.001 μg 至 100,000 mg 内变化的剂量给药,取决于体重为约 40 至约 100 kg 患者的单一、分开或连续剂量的途径(该剂量可以调节成适合高于或低于该体重范围的患者,特别是对于低于 40 kg 的孩童)。

[0276] 由从业者鉴于与对象相关的因素确定确切的剂量。可以调节剂量和给药以提供足够含量的活性剂或保持期望的效果。可以考虑的给药因素包括疾病状况的严重度、对象的一般健康状况、对象的种族、年龄、体重、和性别、饮食、给药的时间和频率、药物组合、反应敏感性、对于与药物代谢相关的毒性的耐受性、与其他癌症治疗和方案相关的经历、和对此类治疗和方案的耐受性 / 响应。可以每 2、3 或 4 天、每周一次、或每两周一次给予长效药物组合物,取决于特定制剂的半衰期和清除率。

[0277] 通过本领域中已知的任何药物递送途径可以对所述对象给予本文中所述的式 (I) 化合物或其形式。非限定性实例包括口服、经眼、经直肠、舌下、局部、经鼻、眼科、皮下、肌肉内、静脉内(大药丸和输注)、大脑内、经皮、和经肺给药途径。

[0278] 化合物代谢物

还落入本文所述的范围内的是式 (I) 化合物或其形式的体内代谢产物。此类产物可以例如来自给予的式 (I) 化合物或其形式的氧化、还原、水解、酰胺化、葡萄苷酸化、酯化等,主要由于酶加工。因此,本文所述的式 (I) 化合物或其形式包括通过包括使本文所述的式 (I) 化合物或其形式与哺乳动物组织或哺乳动物接触足以获得其代谢产物的时间段的过程制备的那些。

[0279] 通常通过制备本文所述的放射标记的 (例如 C^{14}或 H^{3}) 式 (I) 化合物或其形式,以可检测的剂量(例如大于约 0.5 mg/kg)将其给予哺乳动物例如大鼠、小鼠、豚鼠、猴或人,能够进行代谢足够时间(通常约 30 秒至 30 小时),和从尿、血液或其他生物样品分离其转化产物,从而识别此类产物。这些产物由于它们被标记而容易分离(通过使用能够结合在代谢物中存活的表位的抗体分离其他产物)。以传统方式例如通过 MS 或 NMR 分析测定代谢物结构。一般而言,可以与对本领域那些技术人员熟知的常规药物代谢研究相同的方式进行代谢物分析。转化产物,只要它们没有以另外方式在体内发现,可以在诊断分析用于本文所述的式 (I) 化合物或其形式的治疗给药,即使它们本身没有生物活性。

[0280] 组合治疗

对有此需要的对象治疗由 Bmi-1 介导的癌症的方法,除了本文前述那些之外,还包括对有此需要的对象给予有效量的一种或多种式 (I) 化合物或其形式,单独地或与一种或多种附加试剂的组合,所述附加试剂选自 :抗癌剂, 抗增殖剂, 化疗剂, 免疫调节剂, 抗血管生成剂, 抗炎剂, 烷基化剂, 甾族和非甾族抗炎剂, 镇痛剂, 白三烯拮抗剂, β 2- 激动剂, 抗胆碱剂, 激素试剂, 生物制剂, 微管蛋白结合剂, 糖皮质激素, 皮质甾类试剂, 抗菌剂, 抗组胺药, 抗疟疾试剂, 抗病毒剂, 抗生素等 ; 和任选与放射疗法组合。

[0281] 在另一实施方案中,可以对所述对象给予单独的一种或多种式 (I) 化合物或其形式或与一种或多种附加试剂的组合,其与扶持性疗法、疼痛缓解疗法、或对于由 Bmi-1 介导的癌症没有效果的其他疗法组合。

[0282] 在一些实施方案中,本文中所述的一种或多种式 (I) 化合物或其形式和本文中所述的一种或多种附加试剂作为同一药物组合物给予。在某些实施方案中,本文中所述的一

种或多种式 (I) 化合物或其形式和本文中所述的一种或多种附加试剂在不同的药物组合物中给予。在某些实施方案中,本文中所述的一种或多种式 (I) 化合物或其形式和本文中所述的一种或多种附加试剂通过同样的给药途径给药。在某些实施方案中,本文中所述的一种或多种式 (I) 化合物或其形式和本文所述的一种或多种附加试剂通过不同的给药途径给药。

[0283] 在其他实施方案中,一种或多种式 (I) 化合物或其形式与在治疗由 Bmi-1 介导的癌症中使用的一种或多种附加试剂在组合产品中给药。技术人员意识到各种活性成分可以与本文中所述的式 (I) 化合物或其形式组合给药,从而该产品可以用于增加或协同改善本文所述的附加试剂和式 (I) 化合物或其形式的任一或两者的抗癌活性。

[0284] 本文中使用的术语“协同”是指本文中所述的组合产品的给药效果,其比任何两种或更多种单一试剂的加和效果更有效。在具体实施方案中,组合产品的协同效果允许对患有由 Bmi-1 介导的癌症的对象使用较低剂量的一种或多种试剂和 / 或较低频率给予所述试剂。在某些实施方案中,使用较低剂量试剂和 / 或较低频率给予所述试剂的能力降低与为对象给予所述试剂相关的毒性而没有降低所述试剂在预防或治疗由 Bmi-1 介导的癌症的效果。在一些实施方案中,协同效果导致每种试剂在治疗由 Bmi-1 介导的癌症中的改善效果。在一些实施方案中,试剂组合的协同效果避免或降低与使用任何单一试剂相关的负面或不希望的副作用。可以将在此类产品中的试剂组合在相同的药物组合物中给予对象。或者,可以将所述试剂在分开的药物组合物中同时给予对象。可以通过相同或不同的给药途径为对象给予所述试剂。在特定实施方案中,至少一种试剂为本文中所述的式 (I) 化合物或其形式。

[0285] 也可以组合本文中所述的任何式 (I) 化合物或其形式与可用于治疗由 Bmi-1 介导的癌症的此类附加试剂,包括本文所述的式 (I) 化合物或其形式,以意在同时或相继给予需要治疗的患者的单一剂型或分开剂型。当相继给药时,可以在两次或更多次给药中给予所述组合。在替代的实施方案中,可以通过不同途径给予本文中所述的一种或多种式 (I) 化合物或其形式和本文中所述的一种或多种附加试剂。

[0286] 根据本文所述的方法,组合产品可以包括活性成分的组合,其可以 :(1) 在组合制剂中共同配制和同时给药或递送 ;(2) 以分开制剂形式相继或平行递送 ;或 (3) 通过本领域中已知的任何其他组合方案。当在替代疗法中以分开制剂递送时,本文中所述方法可以包括给予或递送,例如但不限于分开溶液剂、乳液剂、混悬剂、片剂、丸剂或胶囊剂、或通过在分开注射中的不同的注射。一般而言,在以替代方式给药时,连续给予有效剂量的各活性成分,一次给药在另一次给药之后。相比之下,在平行或同时给药中,一起给予有效剂量的两种或更多种活性成分。还可以使用间歇相继或平行组合给药的各种替代组合。

[0287] 此类试剂的特定实例包括但不限于免疫调节剂 (例如干扰素、青霉胺等), 抗血管生成剂, 抗炎剂 (例如肾上腺类固醇、皮质类固醇 (例如倍氯米松、布地奈德、氟尼缩松、氟替卡松、去炎松、甲基氢化波尼松、氢化波尼松、强的松、氢化可的松)、糖皮质激素、甾族和非甾族抗炎药 (例如阿司匹林、布洛芬、双氯芬酸、和 COX-2 抑制剂))、镇痛剂、白三烯拮抗剂 (例如孟鲁斯特、甲基黄嘌呤、扎鲁司特、和齐留通)、β 2- 激动剂 (例如沙丁胺醇、biterol、非诺特罗、isoetharie、奥西那林、吡布特罗、柳丁氨醇、特布他林、福莫特罗、沙美特罗和柳丁氨醇特布他林)、抗胆碱剂 (例如异丙托溴铵和氧托溴铵)、抗菌剂 (例如柳氮

磺胺吡啶、氨苯砜等）、抗组胺药、抗疟疾试剂（例如羟化氯喹）、抗病毒剂（例如核苷类似物（例如齐多夫定、阿昔洛韦、gangcyclovir、阿糖腺苷、碘苷、曲氟尿苷、病毒唑、膦甲酸、金刚烷胺、金港湾乙胺、沙奎那韦、茚地那韦、利托那韦和 AZT）和抗生素（例如放线菌素 D（原先放射菌素）、争光霉素、红霉素、盘尼西林、光神霉素、和安茴霉素 (AMC)）。

[0288] 在本文中描述的可以与式 (I) 化合物或其形式组合使用的附加试剂的特定实例包括但不限于：阿西维辛；阿柔比星；盐酸阿考达唑；阿克罗宁；阿多来新；阿地白介素；六甲蜜胺；二霉素；醋酸阿美蒽醌；氨基多睡丹；安丫啶；阿那曲唑；安血丁酯剂；安茴霉素；天冬酰胺酶；曲林霉素；阿扎胞苷；阿扎替派；阿佐霉素；巴马斯他；苄替哌；比卡鲁胺；盐酸比生群；双萘法德；二膦酸盐（例如氨羟二磷酸二钠 (Aredria®)、氯膦酸钠 (Bonefos®)、唑来膦酸 (Zometa®)、阿仑膦酸盐 (Fosamax®)、依替膦酸盐、伊班膦酸盐、英卡膦酸盐、利塞膦酸盐、和 tiludromate)；比折来新；硫酸博来霉素；布喹那钠；溴匹立明；白消安、放射菌素；卡普睾酮；卡醋胺；卡贝替姆；卡铂；卡莫司汀；盐酸卡米诺霉素；卡折来新；西地芬戈；瘤可宁；西罗霉素；顺铂；克拉屈滨；甲磺酸克雷斯托；环磷酰胺；阿糖胞苷、达卡巴嗪、放射菌素 D；盐酸道诺霉素；地西他滨；脱甲基剂；右奥马铂；地扎胍宁；甲磺酸地扎胍宁；亚丝醌；多西他赛；阿霉素；盐酸阿霉素；屈洛昔芬；柠檬酸屈洛昔芬；丙酸曲他雄酮；打佐霉素；依达曲沙；盐酸依洛尼塞；EphA2 抑制剂；依沙芦星；恩洛铂；恩普氨酯；依匹哌啶；盐酸表柔比星；厄布洛唑；盐酸依索比星；雌氮芥；雌氮芥磷酸钠；依他硝唑；依托泊苷；依托泊苷磷酸盐；艾托卜宁；盐酸法倔唑；法扎拉滨；芬维 A 胺；氟脲苷；磷酸氟脲苷；5- 氟尿嘧啶；fluorocitabine；磷喹酮；福司曲星；吉西他滨；盐酸吉西他滨；组蛋白脱乙酰酶抑制剂；羟基脲；盐酸去甲氧基柔红霉素；异环磷酰胺；伊莫福斯；甲磺酸马替尼；白介素 II（包括重组白介素 II，或 rIL2)、干扰素 α-2a；干扰素 α-2b；干扰素 α-n1；干扰素 α-n3；干扰素 β-I a；干扰素 γ-I b；异丙铂；盐酸伊立替康；醋酸兰瑞肽；来那度胺；来曲唑；醋酸亮丙瑞林；盐酸利阿唑；洛美曲索；环己亚硝脲；盐酸洛索蒽醌；马索罗酚；美登素；二氯甲基二乙胺；抗 -CD2 抗体；醋酸甲地孕酮；醋酸美仑孕酮；美法仑；美诺里尔；巯嘌呤；甲氨蝶呤；甲氨蝶呤钠；氯苯氨啶；美妥替哌；米丁度胺；mitocarcin；丝裂红素；米托洁林；米托马星；丝裂霉素；丝裂帕菌素；米托坦；盐酸米托蒽醌；霉酚酸；诺考达唑；诺加霉素；奥马铂；亚磺酰吡啶；紫杉醇；培门冬酶；培利霉素；戊氮芥；硫酸培洛霉素；培磷酰胺；胍血生；嗪消安；盐酸罗蒽醌；普卡霉素；普洛美坦；卟吩姆钠；紫菜霉素；泼尼氮芥；盐酸甲基苄肼；嘌呤霉素；盐酸嘌呤霉素；吡唑霉素；利波腺苷；罗谷亚胺；沙芬戈；盐酸沙芬戈；司莫司汀；辛曲秦；磷乙酰天冬氨酸钠；司帕霉素；盐酸螺旋锗；洛莫司汀；螺铂；链黑菌素；链脲菌素；磺氯苯脲；他利霉素；替可加兰钠；喃氟啶；盐酸替洛蒽醌；替莫卟吩；替尼泊苷；替罗昔隆；睾内酯；硫脒嘌呤；硫鸟嘌呤；噻替派；噻唑羧胺核苷；替拉扎明；柠檬酸托瑞米芬；醋酸曲托龙；磷酸曲西瑞宾；三甲曲沙；葡萄糖醛酸三甲曲沙；曲普瑞林；盐酸妥卜氯唑；乌拉莫司汀；乌瑞替派；伐普肽；维替泊芬；硫酸长春花碱；硫酸长春新碱；长春地辛；硫酸长春地辛；硫酸长春匹定；硫酸长春苷酯；硫酸长春罗新；酒石酸长春瑞滨；硫酸长春罗定；硫酸长春利定；沃利替尼；伏氯唑；折尼铂；净司他丁；盐酸佐柔比星等。

[0289] 治疗由 Bmi-1 介导的癌症的其他实例包括采用抗癌或抗增殖试剂进行的治疗，其中所述抗癌或抗增殖试剂选自但不限于：20-Epi-1,25- 二氢维生素 D3 (MC 1288, MC 1301, KH 1060)；5- 乙炔基尿嘧啶；阿比特龙；阿柔比星；酰基富烯；腺环戊醇；阿多

来新；阿地白介素；ALL-TK 拮抗剂；六甲蜜胺；氨莫司汀；氯杀螨；氨磷汀；氨基乙酰丙酸；氨柔比星；安吖啶；阿那格雷；阿那曲唑；雄茸交酯；血管生成抑制剂；拮抗剂 D；拮抗剂 G；安雷利克斯；抗背部化形态蛋白 -1；抗雄激素，抗雌激素；抗肿瘤物质；反义寡核苷酸；甘氨酸阿非迪霉素；细胞凋亡基因调节剂；细胞凋亡调节剂；无嘌呤酸；ara-CDP-DL-PTBA（O- 棕榈酰 -1- 硫基甘油）；精氨酸脱氨酶；asulacrine；阿他美坦；阿莫司汀；axinastatin 1；axinastatin 2；axinastatin 3；阿扎司琼；阿扎毒素；重氮酪氨酸；浆果赤霉素 III 衍生物；balanol；巴马司他；BCR/ABL 拮抗剂；benzochlorins；苯甲酰十字孢碱；β 内酰胺衍生物；β-alethine；betaclamycin B；桦木酸；bFGF 抑制剂；比卡鲁胺；比生群；双吖丙啶基精胺；双萘法的；bistratene A；比折来新；breflate；溴匹立明；布朵替坦；丁硫氨酸亚砜胺；钙泊三醇；卡弗他丁 C；喜树碱衍生物；金丝雀痘 IL-2；希罗达；甲酰胺 - 氨基 - 三唑 (CaRest M3)；CARN 700；软骨衍生的抑制剂；卡折来新；酪蛋白激酶抑制剂 (ICOS)；栗树精胺；杀菌肽 B；西曲瑞克；chlorlns；氯代喹喔啉胺磺酰；西卡前列素；顺式卟啉；克拉屈滨；氯米芬类似物；克霉唑；collismycin A；collismycin B；康普立停 A4；康普立停类似物；conagenin；crambescidin 816；克雷斯托；念珠藻素 8；念珠藻素 A 衍生物；curacin A；环戊蒽醌；环铂 (cycloplatam)；cypemycin；阿糖胞苷烷磷酯 (YNK01 或 Starasid®)；溶细胞因子；细胞抑制剂；达西单抗；地西他滨；脱氢膜海鞘素 B；德舍瑞林；地塞米松；dexifosfamide；右丙亚胺；右维拉帕米；亚丝醌；膜海鞘素 B；didox；二乙基去甲精胺；二氢 -5- 氮胞苷；二氢紫杉酚，dioxamycin；二苯基螺莫司汀；多西他赛；二十二醇；多拉司琼；去氧氟尿苷；屈洛昔芬；屈大麻酚；倍癌霉素 SA（duocarmycin SA）；依布硒啉；依考莫司汀；依地福新；依决洛单抗；依洛尼塞；榄香烯；乙嘧替氟；表柔比星；爱普列特；雌氮芥类似物；雌激素激动剂；雌激素拮抗剂；依他硝唑；磷酸依托泊苷；依西美坦；法倔唑；法扎拉滨；芬维 A 胺；非格司亭；非那雄胺；弗拉平度；氟卓斯汀；fluasterone；氟达拉滨；盐酸 fluorodaunorunicin；福酚美克；福美司坦；福司曲星；福莫司汀；gadolinium texaphyrin；硝酸镓；加洛他滨；加尼瑞克；白明胶酶抑制剂；吉西他滨；谷胱甘肽抑制剂；HMG CoA 还原酶抑制剂（例如阿托伐他汀、西立伐他汀、氟伐他汀、来适可、lupitor、洛伐他汀、罗素伐他汀、和辛伐他汀）；hepsulfam；调蛋白；六亚甲基双乙酰胺；金丝桃素；伊班膦酸；伊达比星；艾多昔芬；伊决孟酮；伊莫福新；伊洛马司他；咪唑并吖啶酮；咪喹莫特；免疫刺激剂多肽；类胰岛素生长因子 -1 受体抑制剂；干扰素激动剂；干扰素；白介素；碘苄胍；碘阿霉素；甘薯苦醇，4- 伊洛普拉；伊索拉定；isobengazole；isohomohalicondrin B；伊他司琼；jasplakinolide；kahalalide F；卡螺素 -N 三乙酸盐；兰瑞肽；leinamycin；来格司亭；硫酸香菇多糖；leptolstatin；来曲唑；白血病抑制因子；白血球 α 干扰素；亮丙瑞林 / 雌激素 / 黄体酮组合；亮丙瑞林；左旋咪唑；LFA-3TIP（参见国际公开 No. WO93/0686 和美国专利 No. 6,162,432)；利阿唑；线性多胺类似物；亲脂二糖肽；亲脂铂化合物；lissoclinamide 7；洛铂；蚯蚓磷脂；洛美曲索；氯尼达明；洛索蒽醌；洛伐他汀；洛索立宾；勒托替康；lutetium texaphyrin；lysofylline；细胞溶素肽；美坦辛；mannostatin A；马马司他；马索罗酚；乳腺丝抑蛋白；基质溶解因子抑制剂；基质金属蛋白酶抑制剂；美诺利尔；merbarone；阿伏瑞林；蛋氨酸酶；胃

复安；MIF 互变异构酶抑制剂；米非司酮；米替福新；米立司亭；配错双链 RNA；米托胍腙；二溴卫矛醇；丝裂霉素类似物；米托萘胺；迈托霉素纤维母细胞生长因子－皂草素；米托蒽醌；莫法罗汀；莫拉司亭；单克隆抗体，人绒毛膜促性腺激素；单磷酰基脂质 A/ 分支杆菌细胞壁骨架 (CWS/MPL)；莫哌达醇；多重抗药基因抑制剂；多重肿瘤抑制 1- 基疗法；氮芥抗癌剂；mycaperoxide B；分支杆菌细胞壁提取物；myriaporone；N- 乙酰基地那林；N- 取代苯甲酰胺；那法瑞林；nagrestip；纳洛酮 / 镇痛新组合；napavin；naphterpin；那托司汀；奈达铂；萘莫柔比星；奈立膦酸；中性肽链内切酶；尼鲁米特；nisamycin；一氧化氮调节剂；硝基氧抗氧化剂；nitrullyn；06- 苄基鸟嘌呤；奥曲肽；okicenone；寡核苷酸；奥那司酮；oracin；口服细胞因子诱导物；奥马铂；奥莎特隆；奥沙利铂；oxaunomycin；紫杉醇；紫杉醇类似物；紫杉醇衍生物；palauamine；palmitoylrhizoxin；帕米膦酸；人参炔三醇；巴罗米特；parabactin；泊泽尼普定；培门冬酶；peldesine (BCX-34)；戊聚糖多硫酸钠；喷司他丁；pentrozole；全氟溴烷；培磷酰胺；紫苏醇脱氢酶；phenazinomycin；苯基乙酸酯；磷酸酶抑制剂；溶链菌制剂；盐酸毛果芸香碱；吡柔比星；吡曲克辛；placetin A；placetin B；纤溶酶原激活物抑制剂；铂络合物；铂化合物；铂三胺络合物；卟吩姆钠；紫菜霉素；强的松；丙基双吖啶酮；前列腺素 J2；蛋白酶体抑制剂；蛋白 A- 基免疫调节剂；蛋白激酶 C 抑制剂，微藻类；蛋白酪氨酸磷酸酶抑制剂；嘌呤核苷磷酸化酶；红紫素；甲氧基吡唑啉吖啶；pyridoxylated 血红蛋白聚氧乙烯缀合物；raf 拮抗剂；雷替曲塞；雷莫司琼；ras 法呢基蛋白转移酶抑制剂；ras 抑制剂；ras-GAP 抑制剂；去甲基化瑞替普汀；依替膦酸铼 Re 186；根霉素；酶性核酸；RII 维甲酸；罗谷亚胺；罗西吐碱；罗莫肽；罗喹美克；rubiginone B1；ruboxyl；沙芬戈；saintopin；SarCNU；sarcophytol A；沙格司汀；Sdi 1 模仿物；司莫司汀；衰老衍生的抑制剂 1；义寡核苷酸；信号传导抑制剂；信号传导调节剂；单链抗原结合蛋白；西佐喃；索布佐生；硼卡钠；苯基乙酸钠；solverol；生长调节素结合蛋白；索纳明；斯帕磷酸；spicamycin D；螺莫司汀；斯耐潘定；spongistatin 1；角鲨胺；干细胞抑制剂；干细胞分裂抑制剂；stipiamide；溶基质素；sulfinosine；超活性血管活性肠肽拮抗剂；suradista；苏拉明；苦马豆素；合成葡糖氨基葡聚糖；他莫司汀；5- 氟尿嘧啶；亚叶酸；三苯氧胺甲碘化物；牛磺莫司汀；他扎罗汀；替可加兰钠；喃氟啶；tellurapyrylium；端粒酶抑制剂；替莫卟吩；替莫唑胺；替尼泊苷；tetrachlorodecaoxide；tetrazomine；thaliblastine；噻可拉林；促血小板生成素；促血小板生成素模拟物；胸腺法新；促胸腺生成素受体激动剂；胸腺曲南；促甲状腺激素；tin ethyl etiopurpurin；替拉扎明；环戊二烯钛；topsentin；托瑞米芬；全能干细胞因子；翻译抑制剂；维甲酸；三乙酰基尿苷；曲西立滨；三甲曲沙；曲普瑞林；托烷司琼；妥罗雄脲；酪氨酸激酶抑制剂；酪氨酸磷酸化抑制剂；UBC 抑制剂；乌苯美司；尿生殖窦－衍生的生长抑制因子；尿激酶受体拮抗剂；伏普肽；variolin B；向量系统，红细胞基因疗法；萨利多胺；维拉雷索；藜芦胺；维尔丁；维替泊芬；长春瑞滨；vinxaltine；沃利替尼；伏氯唑；扎诺特隆；折尼铂；亚苄维；净司他丁斯酯等。

[0290] 在一些实施方案中，与本文中所述的式 (I) 化合物或其形式组合使用的附加试剂为一种或多种免疫调节剂。免疫调节剂的非限定性实例包括蛋白质试剂例如细胞因子、肽

模拟物、和抗体(例如人、人化、嵌合体、单克隆、多克隆、Fvs, ScFvs, Fab 或 $F(ab)_2$片段或表位结合片段)、核酸分子(例如反义核酸分子和三倍螺旋)、癌症分子、有机化合物、和无机化合物。

[0291] 具体地,可以与本文中所述的式 (I) 化合物或其形式组合使用的一种或多种免疫调节剂包括但不限于甲氨蝶呤、来氟米特、环磷酰胺、环磷酰胺、环孢霉素 A、二甲胺四环素、咪唑硫嘌呤 (Imuran®)、抗生素 (例如 FK506 (他克莫司))、甲基氢化波尼松 (MP)、皮质类固醇、类固醇、霉酚酸酯、雷帕霉素 (西罗莫司)、咪唑立宾、脱氧精胍菌素、布喹那、malononitriloamindes (例如 leflunamide)、T 细胞受体调节剂、细胞因子受体调节剂、和调节剂肥大细胞调节剂。

[0292] 在一种实施方案中,所述免疫调节剂为化疗剂。在替代的实施方案中,所述免疫调节剂为并非化疗剂的免疫调节剂。在一些实施方案中,本文中所述使用的附加试剂不是免疫调节剂。

[0293] 在一些实施方案中,可以与本文中所述的式 (I) 化合物或其形式组合使用的附加试剂为一种或多种抗血管生成剂。抗血管生成剂的非限定性实例包括蛋白、多肽、肽、融合蛋白、抗体(例如其人、人化、嵌合体、单克隆、多克隆、Fvs、ScFvs、Fab 片段、$F(ab)_2$片段、和抗原结合片段)例如免疫特异性结合至 TNF-α、核酸分子 (例如反义分子或三倍螺旋)、有机分子、无机分子、和降低或抑制血管生成的癌症分子的抗体。在其他实施方案中,本文中所述的附加试剂不是抗血管生成试剂。

[0294] 在一些实施方案中,可以与本文中所述的式 (I) 化合物或其形式组合使用的附加试剂为一种或多种抗炎试剂。抗炎剂的非限定性实例包括可用于治疗炎性疾病的任何抗炎剂。抗炎剂的非限定性实例包括非甾族抗炎药 (NSAID)、甾族抗炎药、抗胆碱能类 (例如硫酸阿托品、甲基硝酸阿托品、和溴化异丙托品 (ATROVENT®), β2- 激动剂 (例如沙丁胺醇 (VENTOLIN®和 PROVENTIL®)、比托特罗 (TORNALATE®)、左旋沙丁胺醇 (XOPONEX®)、奥西那林 (ALUPENT®)、吡布特罗 (MAXAIR®)、terbutlaine (BRETHAIRE®和 BRETHINE®)、沙丁胺醇 (PROVENTIL®, REPETABS®, 和 VOLMAX®)、福莫特罗 (FORADIL AEROLIZER®)、沙美特罗 (SEREVENT®和 SEREVENT DISKUS®))、甲基黄嘌呤 (例如茶碱 (UNIPHYL®、THEO-DUR®、SLO-BID®、和 TEHO-42®)) 等。NSAID 的实例包括但不限于阿司匹林、布洛芬、塞来昔布 (CELEBREX®)、双氯芬酸 (VOLTAREN®)、依托度酸 (LODINE®)、非诺洛芬 (NALFON®)、消炎痛 (INDOCIN®)、ketoralac (TORADOL®)、奥沙普秦 (DAYPRO®)、nabumentone (RELAFEN®)、苏灵大 (CLINORIL®)、托美丁 (TOLECTIN®)、罗非考昔 (VIOXX®)、萘普生 (ALEVE®, NAPROSYN®)、酪洛芬 (ACTRON®)、纳布美通 (RELAFEN®) 等。此类 NSAID 通过抑制环氧合酶 (例如 COX-1 和 / 或 COX-2) 起作用。甾类抗炎药的实例包括但不限于糖皮质激素、地塞米松 (DECADRON®)、皮质类固醇 (例如甲基氢化泼尼松 (MEDROL®))、可的松、氢化可的松、强的松 (PREDNISONE® 和 DELTASONE®)、氢化波尼松 (PRELONE®和 PEDIAPRED®)、去炎松、柳氮磺胺吡啶、类花生酸抑制剂 (例如前列腺素、凝血噁烷和白细胞三烯) 等。

[0295] 在某些实施方案中,可以与本文中所述式 (I) 化合物或其形式组合使用的附加试剂为烷基化剂、亚硝基脲、抗代谢物、安血定制剂、拓扑异构酶 II 抑制剂、有丝分裂抑制剂等。烷基化剂包括但不限于白消安、顺铂、卡铂、瘤可宁、环磷酰胺、异环磷酰胺、达卡巴嗪二氯甲基二乙胺、美法仑、替莫唑胺等。亚硝基脲包括但不限于卡莫司汀 (BiCNU®)、环己亚硝

脲 (CeeNU®) 等。抗代谢物包括但不限于 5- 氟尿嘧啶、希罗达、甲氨蝶呤、吉西他滨、阿糖胞苷、氟达拉滨等。安血定制剂包括但不限于道诺霉素、阿霉素、表柔比星去甲氧基柔红霉素、米托蒽醌等。拓扑异构酶 II 抑制剂包括但不限于拓扑替康、伊立替康、依托泊苷 (VP-16)、替尼泊苷等。有丝分裂抑制剂包括但不限于紫杉烷（紫杉醇、多西他赛）、和长春花生物碱（长春花碱、长春新碱、和长春瑞滨）等。

[0296] 在更具体的实施方案中，与本文中所述的式 (I) 化合物或其形式组合使用的附加抗癌剂、抗增殖剂或化疗剂包括但不限于阿柏西普、安丫啶、争光霉素、白消安、希罗达、卡铂、卡莫司汀、瘤可宁、顺铂、克拉屈滨、crisantaspase、环磷酰胺、阿糖胞苷、达卡巴嗪、放线菌素 D、道诺霉素 (IV 和脂质体）、多西他赛、阿霉素 (IV 和脂质体）、enzastaurin、表柔比星、依托泊苷、氟达拉滨、5- 氟尿嘧啶 (5-FU)、吉西他滨、gliadel 植入物、羟基尿素、去甲氧基柔红霉素、异环磷酰胺、甲磺酸伊马替尼、伊立替康、兰瑞肽、来那度胺、亚叶酸、环己亚硝脲、美法仑、巯嘌呤、美司钠、甲氨蝶呤、丝裂霉素、米托蒽醌、奥曲肽、奥沙利铂、紫杉醇、培美曲塞、喷司他丁、甲基苄肼、雷替曲塞、赛特铂、索拉非尼、链脲菌素、舒尼替尼、喃氟啶 - 尿嘧啶、替莫唑胺、替尼泊苷、萨利多胺、噻替派、硫鸟嘌呤、拓扑替康、苏消安、瓦塔拉尼、长春花碱、长春新碱、长春地辛、长春新碱、长春地辛、长春瑞滨、沃利替尼、ZD6474、单克隆抗体（例如贝伐单抗、西妥昔单抗、IMC-A12、IMC-1121B、medi-522、利妥昔单抗等）、激素试剂（例如阿那曲唑、比卡鲁胺、布舍瑞林、环丙孕酮、二乙基己烯雌酚、依西美坦、氟他米特、戈舍瑞林（乳房和前列腺）、来曲唑、亮丙瑞林、甲羟孕酮、醋酸甲地孕酮、三苯氧胺、托瑞米芬、曲普瑞林等）、生物制剂（例如干扰素、白介素 -12 等）、血管生成受体酪氨酸激酶 (RTK) 抑制剂（例如 AE-941、血管抑制因子、羧胺三唑、西仑吉肽、内皮抑制素、氢溴酸卤夫酮、2- 甲氧基雌二醇、乳酸角鲨胺、SU6668 等）、微管蛋白结合剂（例如磷酸康普瑞汀 A4 等）、基质金属蛋白酶抑制剂（例如 BMS-275291 等）和 / 或丝氨酸 / 苏氨酸 / 酪氨酸激酶抑制剂和任选非甾类或 COX-2 抗炎剂（例如塞来昔布等）或皮质类固醇（例如强的松等）。

[0297] 在更具体的实施方案中，可以与本文中所述的式 (I) 化合物或其形式组合使用的一种或多种附加抗癌剂、抗增殖剂或化疗剂选自贝伐单抗、卡铂、顺铂、多西他赛、阿霉素、依西美坦、吉西他滨、5- 氟尿嘧啶、伊马替尼、伊立替康、索拉非尼、舒尼替尼、替莫唑胺、沃利替尼或其组合。

[0298] 在一些实施方案中，与放射疗法组合使用本文中所述的式 (I) 化合物或其形式和一种或多种附加抗癌剂、抗增殖剂或化疗剂，所述放射疗法包括使用破坏癌细胞或肿瘤细胞的 X 射线、γ 射线和其他辐射源。在具体实施方案中，以外部束辐射或远距放疗形式给予放射疗法，其中所述辐射源自远程源。在其他实施方案中，以内部疗法或短距离放疗形式给予辐射疗法，其中将放射源置于癌细胞、肿瘤细胞和 / 或肿块附近。

[0299] 单独或组合的当前可获得的抗癌剂、抗增殖剂或化疗剂、它们的剂量方案、给药途径和推荐的用途是本领域中已知的并且记载于文献例如 *Physician's Desk Reference* 中。

[0300] 可以与本文中所述的式 (I) 化合物或其形式组合使用任何抗癌剂、抗增殖剂、或化疗剂或已知可用于或已经用于或当前用于治疗由 Bmi-1 介导的癌症的任何抗癌疗法。参见例如 Gilman 等人，Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 第 10 版，McGraw-Hill, New York, 2001; The Merck Manual of Diagnosis and Therapy, Berkow, M.D 等人．（编），第 17 版，Merck Sharp & Dohme

Research Laboratories, Rahway, NJ, 1999; Cecil Textbook of Medicine, 第 20 版, Bennett and Plum (编), W.B. Saunders, Philadelphia, 1996, 和涉及癌症治疗的信息的医师案头参考(例如使用预防性或治疗性试剂),其已经或当前用于预防、治疗和/或管理由 Bmi-1 介导的癌症。

[0301] 药物组合物

本说明书还涉及包含有效量式 (I) 化合物或其形式与药学上可接受的赋形剂的混合的药物组合物。

[0302] 本文中所述的实施方案包括由混合式 (I) 化合物或其形式与药学上可接受的赋形剂的方法制备的药物组合物。所述药物组合物还可以配制成获得生理学上相容的约 pH 7,约 pH 3 至约 pH 11 的 pH。

[0303] 本发明的另一实施方案包括药物组合物中式 (I) 化合物或其形式用于治疗由 Bmi-1 介导的癌症的用途,所述组合物包含有效量的式 (I) 化合物或其形式与药学上可接受的赋形剂的混合。

[0304] 本文中使用的术语“组合物”是指包含特定量的特定成分的产品、以及直接或间接由特定量的特定成分的组合获得的任何产品。

[0305] 在另一实施方案中,所述药物组合物可以包含本文中所述的一种或多种式 (I) 化合物或其形式的组合和一种或多种治疗由 Bmi-1 介导的癌症的附加试剂例如抗癌剂、抗增殖剂、化疗剂或生化疗剂。

[0306] 术语“药学上可接受的赋形剂”是指配制用于与活性药物试剂例如本文中所述的式 (I) 化合物或其形式一起给药的药理学上不活泼的物质。该术语是指可以在没有异常毒性的情况下给药的任何药物赋形剂。药学上可接受的赋形剂可以部分通过给予特定组合物以及通过特定模式的给药和/或剂型确定。药学上可接受的赋形剂的非限定性实例包括载体、溶剂、稳定剂、助剂、稀释剂等。因此,存在本文中所述的药物组合物的宽范围的合适制剂(参见,例如雷明顿的药物科学)。

[0307] 合适的赋形剂可以为包括大的、缓慢代谢的大分子的载体分子,例如蛋白、多糖、聚乳酸、聚乙醇酸、聚合氨基酸、氨基酸共聚物、和不活泼病毒颗粒。其他示例性赋形剂包括抗氧化剂例如抗坏血酸;螯合剂例如 EDTA;糖类例如糊精、羟烷基纤维素、羟烷基甲基纤维素、硬脂酸;液体例如油、水、盐水、甘油和乙醇;润湿剂或乳化剂;pH 缓冲物质等。脂质体也包含在药学上可接受的赋形剂的定义内。

[0308] 本文中所述的药物组合物可以适合期望的给药方法的任何形式配制。用于口服给药的合适的制剂包括固体、液体溶液、乳液和悬浮液,同时用于肺部给药的合适的可吸入制剂包括液体和粉末。替代的制剂包括糖浆、乳油、软膏、片、和冻干固体,其可以在给药之前与生理学上相容的溶剂重组。

[0309] 当意在用于口服使用时,可以制备例如片剂、糖锭、锭剂、水性或油性混悬剂、无水溶液、分散性粉末或颗粒(包括微粒化颗粒或纳米颗粒)、乳液、硬质或软质胶囊、糖浆剂或酏剂。可以根据用于制备药物组合物的技术领域已知的任何方法制备意在用于口服的组合物,并且此类组合物可以含有一种或多种试剂,包括甜味剂、调味剂、着色剂和防腐剂,从而提供可口配制品。

[0310] 适合采用片剂的药学上可接受的赋形剂包括例如惰性填料,例如纤维素、碳酸钙

或碳酸钠、乳糖、磷酸钙或磷酸钠；崩解剂，例如交联羧甲基纤维素钠、交联聚维酮、玉米淀粉、或藻酸；结合剂，例如聚维酮、淀粉、明胶或阿拉伯树胶；和润滑剂，例如硬脂酸镁、硬脂酸或滑石。片剂可以为未涂布的或可以通过已知技术涂布，包括微胶囊化以延迟分解和吸附在胃肠道并从而经较长时间提供持久作用。

[0311] 用于口服使用的制剂也表现为硬质明胶胶囊，其中所述活性成分与惰性固体稀释剂例如纤维素、乳糖、磷酸钙或高岭土混合，或表现为软质明胶胶囊，其中所述活性成分与无水或油性介质例如甘油、丙二醇、聚乙二醇、花生油、液体石蜡或橄榄油混合。

[0312] 在其他实施方案中，本文中所述的药物组合物可以配制成包含本文中所述的与至少一种适合制备混悬剂的药学上可接受的赋形剂混合的式 (I) 化合物或其形式的悬浮液。在其他实施方案中，本文中所述的药物组合物可以配制成适合通过添加一种或多种赋形剂制备悬浮剂的可分散粉末和颗粒。

[0313] 适合用于混悬剂的赋形剂包括悬浮剂，例如羧甲基纤维素钠、甲基纤维素、羧丙基甲基纤维素、海藻酸钠、聚乙烯吡咯烷酮、黄蓍胶、阿拉伯树胶、分散剂或润湿剂例如天然产生的磷脂（例如卵磷脂）、环氧乙烷与脂肪酸的缩合产物（例如聚氧乙烯硬脂酸酯）、环氧乙烷与长链脂肪醇的缩合产物（例如 heptadecacthyleneoxycethanol)、环氧乙烷与衍生自脂肪酸和己糖醇酐的局部酯的缩合产物（例如聚氧乙烯脱水山梨糖醇单油酸酯）；和增稠剂，例如卡波姆、蜂蜡、硬质石蜡或鲸蜡醇。所述混悬剂还含有一种或多种防腐剂，例如乙酸、甲基和 / 或正丙基对羟基 - 苯甲酸酯；一种或多种着色剂；一种或多种调味剂；和一种或多种甜味剂例如蔗糖或糖精。

[0314] 本文中所述的药物组合物也可以为水包油乳液形式。油相可以为植物油，例如橄榄油或花生油、矿物油，例如液体石蜡或它们的混合物。合适的乳化剂包括天然产生的树胶，例如阿拉伯树胶和黄蓍胶；天然产生的磷脂，例如大豆卵磷脂、衍生自脂肪酸的酯或局部酯；己糖醇酐，例如脱水山梨糖醇单油酸酯；和这些局部酯与环氧乙烷的缩合产物例如聚氧乙烯脱水山梨糖醇单油酸酯。所述乳液可以还含有甜味剂和调味剂。糖浆和酏剂可以与甜味剂，例如甘油、山梨醇或蔗糖一起配制。此类制剂可以还含有缓和剂、防腐剂、调味剂或着色剂。

[0315] 另外，本文中所述的药物组合物可以为无菌可注射配制品的形式，例如无菌可注射水性乳液或油质悬浮液。可以根据已知技术使用上述那些合适的悬浮剂或润湿剂和悬浮剂配制此类乳液或悬浮液。所述无菌可注射配制品也可以为在无毒肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液，例如 1,2- 丙 - 二醇中的溶液。所述无菌可注射配制品也可以制备成冻干粉末。在可以使用的可接受的媒介物和溶剂中，为水、Ringer 溶液、等渗氯化钠溶液等。另外，可以溶剂或悬浮介质形式使用无菌固定油。出于该目的，可以使用任何无味固定油，包括合成甘油单酯或甘油二脂。另外，脂肪酸例如油酸可以同样用于制备可注射物。

[0316] 本文中所述的式 (I) 化合物或其形式基本上可以通过化学或生物化学基团的取代或加成，例如通过酯化、糖基化、聚乙二醇化等改性(例如增加溶解性、生物活性、适口性，降低不良反应等)，这使它们更适合递送。

[0317] 在一些实施方案中，本文中所述的式 (I) 化合物或其形式配制成在提高此类式 (I) 化合物或其形式的口服生物利用度的制剂中用于口服给药。因此，本文中所述的药物组

合物可以包含有效量的式 (I) 化合物或其形式，和与至少一种药学上可接受的赋形剂(选自中链脂肪酸或其丙二醇酯等（例如可食用脂肪酸例如辛和癸脂肪酸的丙二醇酯））和药学上可接受的表面活性剂(例如聚乙二醇 40 氢化蓖麻油等)一起。

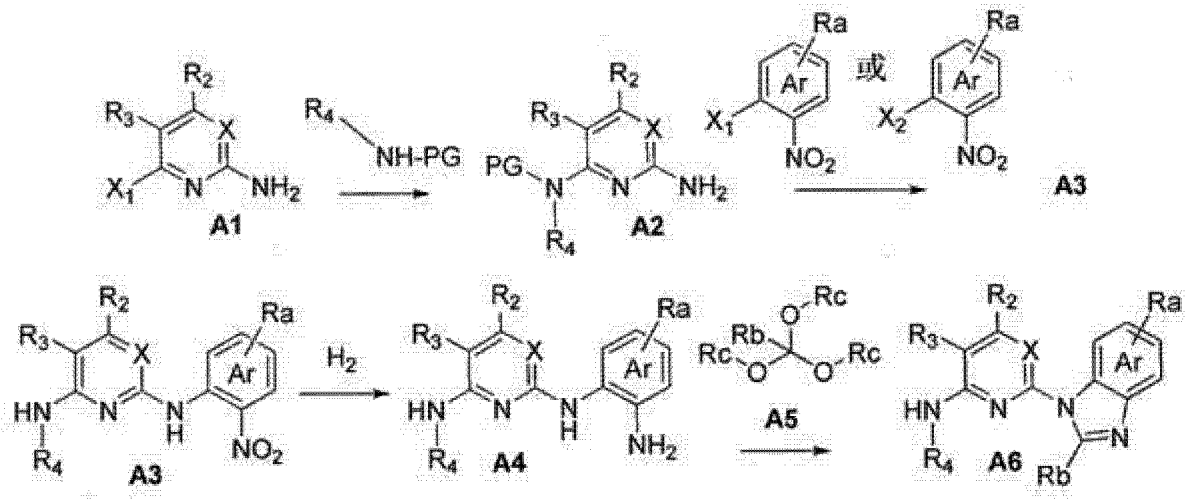
[0318] 在其他实施方案中，可以通过使用粒度优化技术包括但不限于使用本领域那些技术人员已知的技术制备纳米颗粒或纳米悬浮液提高式 (I) 化合物或其形式的生物利用度。存在于此类配制品中的化合物形式包括非晶、部分非晶、部分结晶或结晶形式。

[0319] 在替代的实施方案中，所述药物组合物可以还包含一种或多种水溶解性改进剂，例如环糊精。环糊精的非限定性实例包括 α-, β-, 和 γ-环糊精的羟丙基、羟乙基、葡糖基、麦芽糖基和麦芽三塘基衍生物和羟丙基-β-环糊精 (HPBC)。在一些实施方案中，所述药物组合物还包含约 0.1% 至约 20%、约 1% 至约 15%、或约 2.5% 至约 10% 的 HPBC。所使用的溶解性改进剂的量可以取决于组合物中活性药物成分的量。

[0320] <u>一般合成实施例</u>

如本文中公开的，制备本文中所述的式 (I) 化合物或其形式的方法通常使用标准、熟知的合成方法。很多起始原料是可商购的或可以按照使用本领域技术人员已知的技术在具体合成实施例中制备。也可以在化学上可行的位置进行修饰取代基的官能转换，并被认为包括在通常方案和本领域普通技术人员的知识的范围内。可以如以下方案中所述制备式 (I) 化合物或其形式。

[0321] 方案 A 苯并咪唑取代的嘧啶化合物



在强碱(例如 KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS 等)存在下在溶剂(例如 THF, DMF 等)中使胺取代的化合物 A1 （其中 X_1代表选自溴、氯或碘的卤素原子）与各种取代的芳基，杂芳基或杂环基胺（其中 PG 代表在胺上单取代的任选存在的保护基）偶联以提供化合物 A2。

[0322] 当 R_2和 R_3的一个或两个任选为卤素时，获得位置异构体混合物形式的产物化合物 A2，其中术语“Sep”是指使用本领域普通技术人员已知的分离技术分离待从混合物获得的期望的化合物 A2异构体，然后脱保护。

[0323] 或者，可以通过在膦基配体：钯源的混合物的存在下（其中钯源选自 $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3, Q-Phos, XPhos 等；或者可以使用可商购的催化剂例如 $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$等），使化合物 A1与各种取代芳

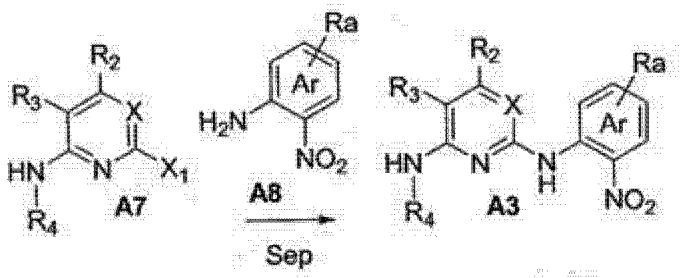
基，杂芳基或杂环基胺（其中不存在保护基）反应，然后按需要分离制备化合物 A2。

[0324] 可以通过在过渡金属催化剂（例如含有选自铜、钯等的金属的催化剂）存在下使化合物 A2与取代的邻－卤素－硝基苯（其中 X_1代表选自溴、氯或碘的卤素原子）反应制备化合物 A3。

[0325] 或者，可以通过在强碱（例如 KOtBu，NaOtBu，NaO^tAm，NaH，NaHMDS 等）存在下在溶剂（例如 THF，DMF 等）中使化合物 A2与取代的邻－卤素－硝基苯（其中 X_2代表选自溴、氯、氟或碘的卤素原子）反应制备化合物 A3。

[0326] 通过在氢气和催化剂（例如碳载镍、铂、钯等）存在下使化合物 A3反应制备化合物 A4。

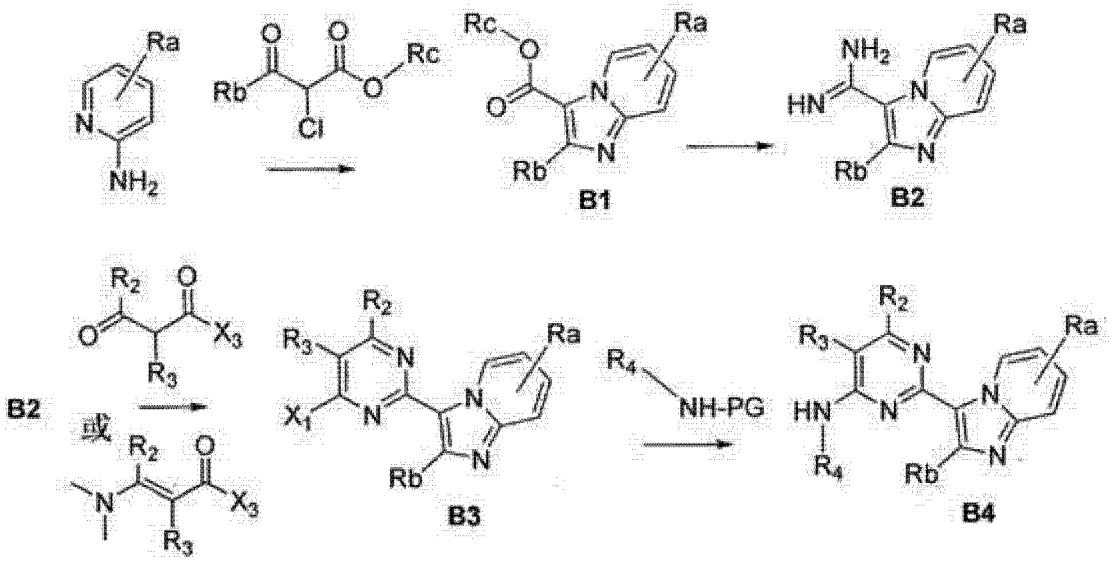
[0327] 通过化合物 A4与原酸酯化合物 A5缩合制备化合物 A6（其中 Rb 代表另外的任选 R_5取代基和 Rc 代表 C_{1-3}烷基）。也可以通过将化合物 A4与各种反应物环化获得任选 R_5取代基的加成以制备化合物 A6。例如，反应物可以为 TCDI，其中另外的任选 R_5取代基为可以进一步取代的硫代－羰基。



[0328] 或者，通过使用膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$，$PdCl_2(allyl)$，$PdCl_2(ACN)$，$[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3，Q-Phos，XPhos 等；或者，可以使用可商购催化剂例如 $Pd(dppf)Cl_2$，$Pd(PPh_3)_4$等）的混合物经由钯催化的交联反应使化合物 A7（其中 X_1 代表选自溴、氯或碘的卤素原子）与硝基取代的胺化合物 A8（其中 Ar 代表芳族或杂芳族环；其中 Ra 代表一个、两个或三个任选的 R_5取代基）交联制备化合物 A3。

[0329] 当 R_2和 R_3的一个或两个任选为卤素时，获得位置异构体混合物形式的产物化合物 A3，其中术语“Sep”是指使用本领域普通技术人员已知的分离技术分离待从混合物获得的期望的化合物 A3异构体。

[0330] 方案 B 咪唑并 [1,2-a] 吡啶取代的嘧啶化合物



通过取代的2-氨基-吡啶（其中Ra代表一个、两个或三个任选的R_5取代基）与α-卤化酮基酯（其中Rb代表另外的任选R_5取代基和Rc代表C_{1-3}烷基）的缩合制备化合物B1。

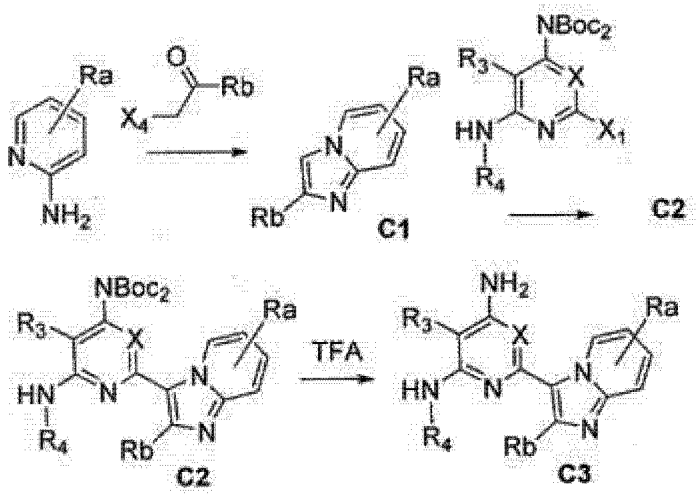
[0331] 通过在有机铝试剂(例如甲苯中$AlMe_3$等)存在下采用氨源(例如NH_4Cl，NH_3等)处理化合物B1制备化合物B2。

[0332] 通过在卤化试剂（例如$POCl_3$，$POBr_3$等）存在下使化合物B2与取代的烷基酯（例如在溶剂例如苯基醚等中的β-酮基酯或取代的丙烯酸酯；其中X_3代表离去基，例如C_{1-3}烷氧基、苯氧基或卤素）缩合然后回流制备化合物B3（其中X_1代表选自溴、氯或碘的卤素原子）。

[0333] 通过在强碱（例如KOtBu，NaOtBu，NaO^tAm，NaH，NaHMDS等）存在下在溶剂（例如THF，DMF等）中使化合物B3与各种取代的芳基，杂芳基或杂环基胺（其中PG代表任选存在的在胺上单取代的保护基）偶联制备化合物B4。

[0334] 或者，可以通过使用膦基配体：钯源（其中钯源选自$Pd_2(dba)_3$，$PdCl_2(allyl)$，$PdCl_2(ACN)$，$[Pd(OAc)_2]_3$等，膦基配体选自PCy_3，Q-Phos，XPhos等；或者可以使用可商购催化剂例如$Pd(dppf)Cl_2$，$Pd(PPh_3)_4$等）混合物经由钯催化的交联反应使化合物B3与取代的芳基，杂芳基或杂环基胺（其中不存在保护基）反应制备化合物B4。

[0335] 方案C 4,6-二氨基取代的嘧啶化合物

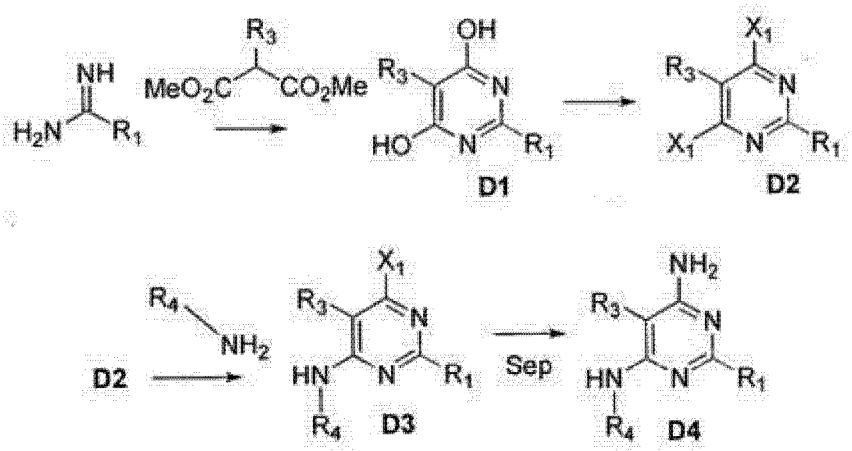


通过在有机溶剂（例如乙腈等）中在回流下使取代的 2- 氨基 - 吡啶 （其中 Ra 代表一个、两个或三个任选 R_5取代基）与 α - 卤化酮（其中 X_4代表离去基例如氯或溴，Rb 代表另外的任选 R_5取代基）的缩合制备化合物 C1。

[0336] 通过在有机溶剂（例如二甲基乙酰胺等）中使用膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3, Q-Phos, XPhos 等；或者可以使用可商购催化剂例如 $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$等）与至少 2 当量碱（例如乙酸铯等）经由钯催化的交联反应使化合物 C1与取代嘧啶化合物（其中 X_1 代表选自溴、氯或碘的卤素原子）反应制备化合物 C2经历 Heck 偶联。所述反应可以在升高的温度最多至 100℃下进行。

[0337] 通过在环境温度或升高的温度下用脱保护试剂（例如 20-40% TFA 在 DCM 等中）处理化合物 C2制备化合物 C3。

[0338] 方案 D 4,6- 二氨基取代的嘧啶化合物



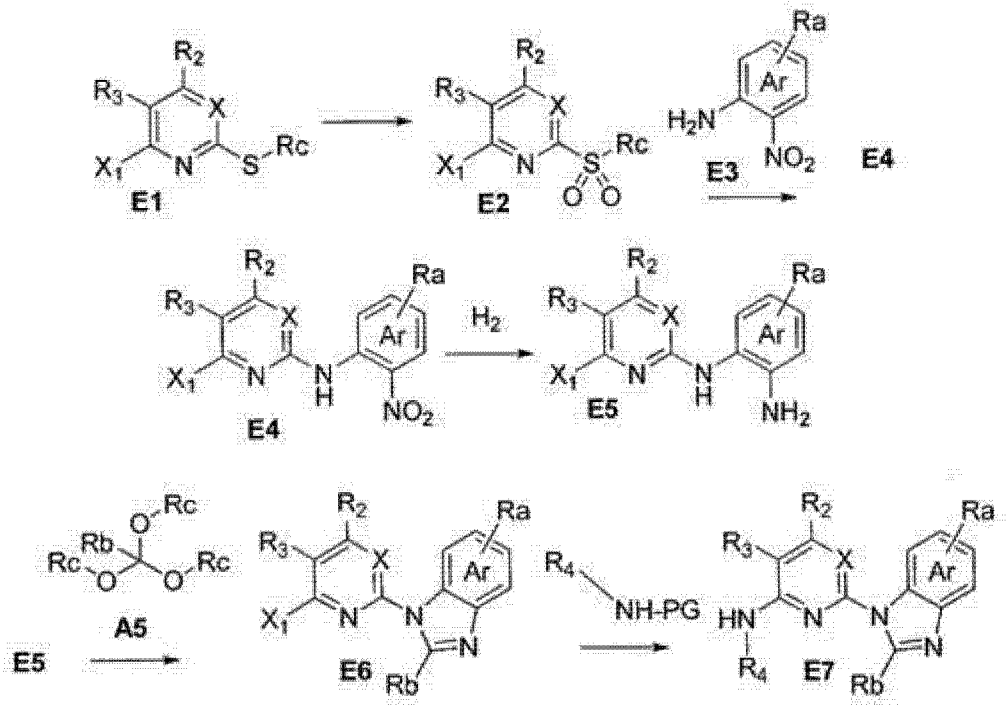
通过在含有烷醇钠 - 溶剂混合物（例如在 MeOH 中的 NaOMe 或在 EtOH 中的 NaOEt 等）的溶液中取代的丙二酸酯化合物与酰胺化 R_1基团的缩合反应制备化合物 D1。

[0339] 通过在卤化试剂（例如 $POCl_3$, $POBr_3$等）存在下通过回流化合物 D1制备化合物 D2 （其中 X_1代表选自溴、氯或碘的卤素原子）。

[0340] 通过在溶剂（其中溶剂选自 EtOH, THF, DMF, 其混合物等）中使化合物 D2与各种取代的芳基，杂芳基或杂环基胺单胺化制备化合物 D3。

[0341] 通过在含有溶剂（其中溶剂选自 CH_3CN, DMSO, 其混合物等）的混合物中采用氨水源处理化合物 D3制备化合物 D4。

[0342] 方案 E 苯并咪唑取代的嘧啶化合物



通过在溶剂（例如 CH_2Cl_2等）中在合适温度下使 2- 甲硫基取代的嘧啶化合物 E1 （其中 X_1代表选自溴、氯或碘的卤素原子，Rc 代表 C_{1-3}烷基）与氧化剂（例如 mCPBA, MPS 等）反应制备 2- 甲基磺酰基取代的化合物 E2。

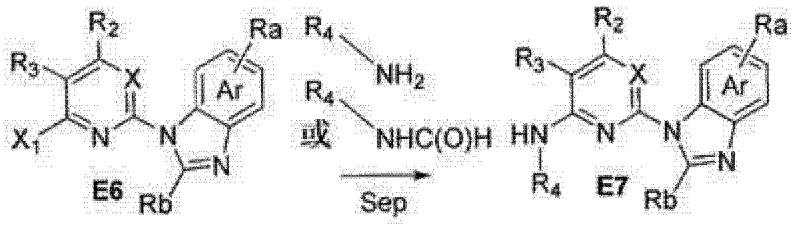
[0343] 通过在强碱（例如 KOtBu, NaOtBu, NaO^{t}Am, NaH, NaHMDS 等）存在下在溶剂（例如 THF, DMF 等）中使化合物 E2与硝基取代胺化合物 E3 （其中 Ar 代表芳族或杂芳族环；其中 Ra 代表一个、两个或三个任选 R_5取代基）反应制备化合物 E4。在化合物 E3上的胺取代基可以任选在胺上被保护基单取代。

[0344] 通过在氢气和催化剂(例如碳载镍、铂、钯等)存在下使化合物 E4反应制备化合物 E5。

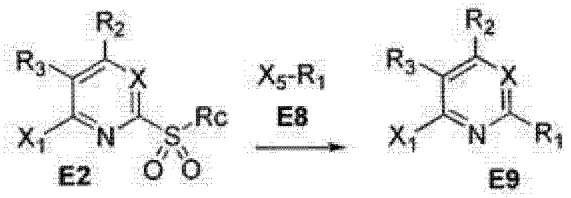
[0345] 通过化合物 E5与原酸酯化合物 A5 （其中 Rb 代表另外的任选 R_5取代基，Rc 代表 C_{1-3}烷基）的缩合制备化合物 E6。也可以通过化合物 E5与各种反应物环化以获得任选 R_5取代基的加成制备化合物 E6。例如，反应物可以为 TCDI，其中另外的任选 R_5取代基为硫代 - 羰基，其可以被进一步取代。

[0346] 可以通过在溶剂（其中溶剂选自 EtOH, THF, DMF, 其混合物等）中使化合物 E6 与各种取代的芳基，杂芳基或杂环基胺反应制备化合物 E7。

[0347] 当 R_3为任选的卤素时，获得位置异构体混合物形式的产物化合物 E7，其中术语“Sep”是指使用本领域普通技术人员已知的分离技术分离待从混合物获得的期望的化合物 E7异构体，然后脱保护。

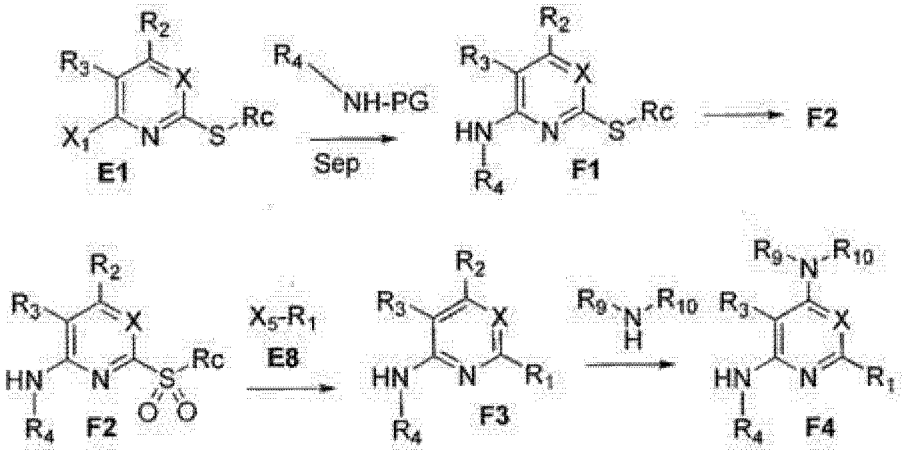


[0348] 或者，可以通过使用膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$，$PdCl_2(allyl)$，$PdCl_2(ACN)$，$[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3，Q-Phos，XPhos 等；或者可以使用可商购催化剂例如 $Pd(dppf)Cl_2$，$Pd(PPh_3)_4$等）混合物经由钯催化的交联反应使化合物 E6与取代的芳基，杂芳基或杂环基胺或酰胺反应（其中不存在保护基）制备化合物 E7。



[0349] 可以在强碱（例如 KOtBu，NaOtBu，NaO^tAm，NaH，NaHMDS 等）存在下使化合物 E2与化合物 E8（例如具有酸性质子基团的 R_1取代基，其中 X_5代表反应性氢原子）反应直接制备化合物 E9。化合物 E9可以代替化合物 E6以提供式（I）化合物。

[0350] 方案 F 取代的嘧啶化合物



通过在强碱（例如 KOtBu，NaOtBu，NaO^tAm，NaH，NaHMDS 等）存在下在溶剂（例如 THF，DMF 等）中在合适温度下使化合物 E1（其中 X_1代表选自溴、氯或碘的卤素原子，Rc 代表 C_{1-3}烷基）与取代芳基，杂芳基或杂环基胺（其中 PG 代表任选存在的在胺上单取代的保护基）反应制备化合物 F1。

[0351] 当 R_3为任选的卤素时，获得位置异构体混合物形式的产物化合物 F1，其中术语“Sep”是指使用本领域普通技术人员已知的分离技术分离待从混合物获得的期望的化合物 F1异构体。

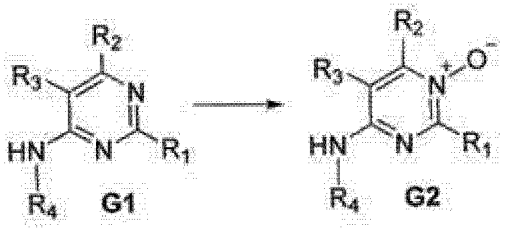
[0352] 或者，通过使用膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$，$PdCl_2(allyl)$，$PdCl_2(ACN)$，$[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3，Q-Phos，XPhos 等；或者可以使用可商购催化剂例如 $Pd(dppf)Cl_2$，$Pd(PPh_3)_4$等）经由钯催化的交联反应使化合物 E1与取代的芳基，杂芳基或杂环基胺或酰胺（其中不存在保护基）反应制备化合物 F1。

[0353] 通过在溶剂（例如 CH_2Cl_2等）中使化合物 F1与氧化剂（例如 mCPBA，MPS 等）反应制备化合物 F2。

[0354] 可以在强碱（例如 KOtBu，NaOtBu，NaO^tAm，NaH，NaHMDS 等）存在下使化合物 F2与化合物 E8（例如具有酸性质子基团的 R_1取代基，其中 X_5代表反应性氢原子）反应提供化合物 F3，式（I）化合物的代表。

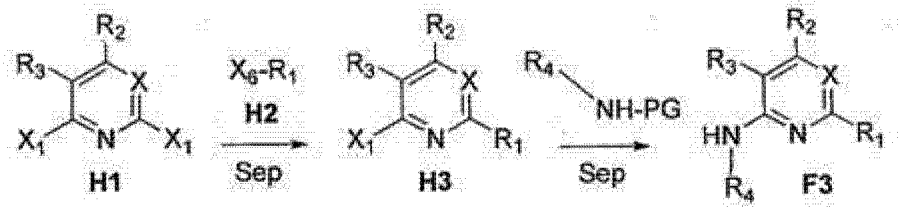
[0355] 当 R_2为卤素时，可以在含有溶剂（其中溶剂选自 CH_3CN, DMSO, 其混合物等）的混合物中采用取代胺处理化合物 F3以提供化合物 F4，式（III）化合物的代表。

[0356] 方案 G 氧化物取代的嘧啶化合物



可以使化合物 G1与氧化剂（例如 mCPBA, MPS 等）反应以提供化合物 G2，式（IV）化合物的代表。

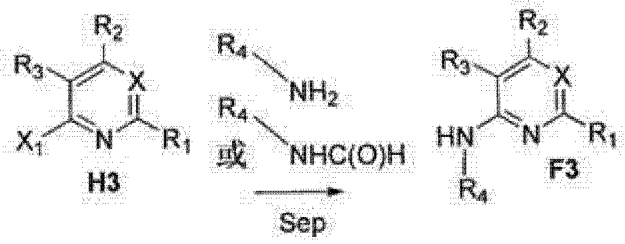
[0357] 方案 H 取代的嘧啶化合物



通过在膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3, Q-Phos, XPhos 等；或者可以使用可商购催化剂例如 $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$等）混合物存在下使化合物 H1（其中 X_1代表选自溴、氯或碘的卤素原子）与化合物 H2（其中 R_1为取代的杂芳族或杂环单环或二环体系，X_6代表连接至 R_1的碳原子的反应性基团例如硼酸、硼酸酯、三烷基锡、氯化锌等）反应制备化合物 H3。

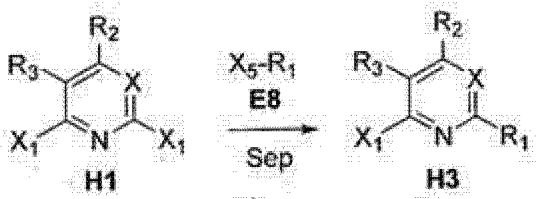
[0358] 当 R_2和 R_3中的一个或两个任选为卤素时，可以获得位置异构体混合物形式的产物化合物 H3，其中术语“Sep”是指使用本领域普通技术人员已知的分离技术分离待从混合物获得的期望的化合物 H3异构体。

[0359] 通过在溶剂（其中 PG 代表任选存在的在胺上单取代的保护基；其中溶剂选自 EtOH, THF, DMF, 其混合物等）中使化合物 H3与各种取代的芳基，杂芳基或杂环基胺反应，然后按需要分离和脱保护制备化合物 F3。

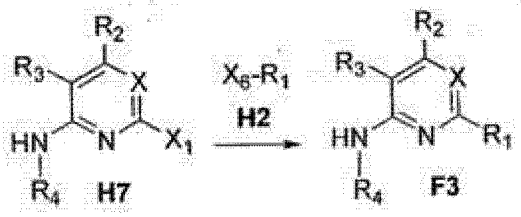


[0360] 或者，通过在膦基配体：钯源（其中钯源选自 $Pd_2(dba)_3$, $PdCl_2(allyl)$, $PdCl_2(ACN)$, $[Pd(OAc)_2]_3$等，膦基配体选自 PCy_3, Q-Phos, XPhos 等；或者，可以使用可商购催化剂例如 $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$等）混合物存在下使化合物 H3与各种取代的芳基，杂芳基或杂环基胺或酰胺反应制备化合物 F3。当化合物 H3与酰胺反应时，所得中间体产物在碱性条件下采用试剂（例如 NaOH, KOH, LiOH 等）在合适的温度下水解，然后按需要分

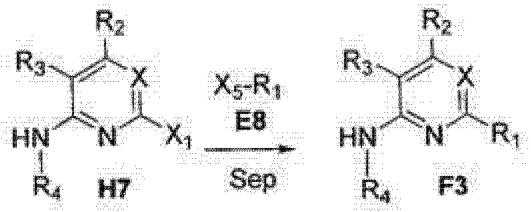
离获得产物化合物 F3。



[0361] 或者，经由化合物 H1与化合物 E8的 Heck 反应制备化合物 H3，然后按需要分离。

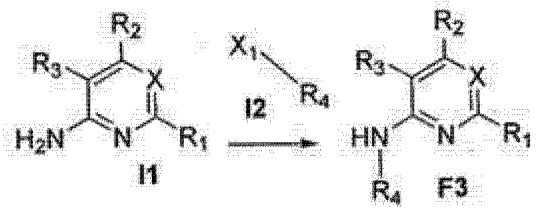


[0362] 或者，通过使化合物 H7与取代的化合物 H2（其中 R_1为取代的杂芳族或杂环单环或二环体系，X_6代表连接至 R_1的碳原子的反应性基团，例如硼酸、硼酸酯、三烷基锡、氯化锌等）反应制备化合物 F3。

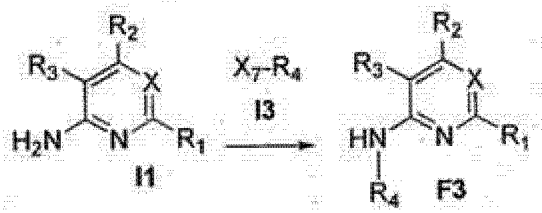


[0363] 或者，经由化合物 H7与化合物 E8（其中 X_5代表反应性氢基团）的 Heck 反应制备化合物 F3，然后按需要分离。

[0364] 方案 I 取代的嘧啶化合物



通过在过渡金属催化剂（例如含选自铜、钯等的金属的催化剂）存在下使取代的化合物 I1与化合物 I2（例如各种取代的芳基，杂芳基或杂环基环体系，其中 X_1 代表选自溴、氯或碘的卤素原子）反应制备化合物 F3。



[0365] 通过在硼氢化物（例如 $NaCNBH_3$或 $NaBH(OAc)_3$等）存在下使取代的化合物 I1与

化合物 I3（例如各种取代的芳基，杂芳基或杂环基环体系，其中 X_7 代表酮或醛离去基）反应制备化合物 F3。

[0366] 具体合成实施例

为了帮助理解本文中所述的式 (I) 化合物或其形式的范围，包括以下具体实施例。涉及本文中所述式 (I) 化合物或其形式的实验当然不应该理解为具体限定本文中所述的式 (I) 化合物或其形式的范围，并且理解为目前已知或稍后形成的本文中所述的式 (I) 化合物或其形式的此类变体（其在本领域技术人员理解范围内）落入本文中所述和后文中要求保护的范围内。

[0367] 除了实施例之外，除非有相反指明，否则说明书和权利要求中使用的表达成分、反应条件、实验数据等的量的全部数字都理解为被术语“约”修饰。因此，全部此类数字代表可以根据试图通过反应或由于可变实验条件获得的期望的性质变化的近似值。因此，在实验再现性的期望范围内，所得数据的上下文中的术语“约”是指可以根据与平均值的标准偏差变化提供的数据范围。而且，对于提供的实验结果，所得数据可以四舍五入以一致性地表达数据，而没有损失有效数字。至少，并且并非意图将等同物的概念的使用限制到权利要求范围，各数字参数应该理解成考虑有效数字和常规四舍五入技术。

[0368] 尽管述及本文中所述的式 (I) 化合物或其形式的特征的数字范围和参数是近似值，但实施例中述及的数值尽量精确地报道。然而，任何数值固有地含有从在相应测试中出现的标准偏差必然产生的某些误差。

[0369] 本文中提供的式 (I) 化合物或其形式更具体地参考以下非限定性实施例描述，其更全面地示例本文中所述的式 (I) 化合物或其形式的范围，但并非理解成限制其范围。实施例示例了本文中所述的式 (I) 化合物或其形式的制备，以及这些式 (I) 化合物或其形式在体外和 / 或体内的测试。本领域那些技术人员会理解为这些实施例中所述的合成技术代表落入具有化学领域中普通技术的那些的实践内的技术，并如此构成用于其实践的优选模式。然而，应该理解成本领域技术人员应该，鉴于本公开，理解为在本文中公开的具体方法中可以进行很多变化，同时仍然获得相似或类似的结果，而不脱离本文中所述的精神和范围。

[0370] 试剂和溶剂如购买时的使用（从多个供应商），除非存在注释。在适用的情况下，以下实施例中示出的术语“Celite”用于代表商标 CELITE®（硅藻土品牌）。在适用的情况下，使用通常可例如通过使用 ISCO CombiFlash® Rf 系统获得的技术和仪器进行色谱分离。在适用的情况下，使用通常可例如使用 Bruker Avance III^{500} 分光仪和氘代溶剂例如 DMSO-d_6 或残留溶剂作为标准的技术和仪器获得 NMR 波谱。在适用的情况下，使用通常可例如使用 SRS OptiMelt® MPA100（没有修正 / 校准地获得的值）测定熔点。在适用的情况下，使用通常可例如使用 Aldrich 254 nm 玻璃背板的板 (60 Å, 250 μm) 获得的技术和仪器进行 TLC 分析（使用 UV 和 I_2 着色观察）。在适用的情况下，使用通常可例如使用 ACQUITY UPLC® 系统获得的技术和仪器获得 ESI 质谱，其中值视为 $[M+H]^+$ 或 $[M-H]^-$，除非另外指明。在适用的情况下，通过 2D NOESY (Nuclear Overhauser SpectroscopY) 实验获得产品结构。

[0371] 提供以下缩写以确保本文中使用的术语对于本领域技术人员是清楚的：

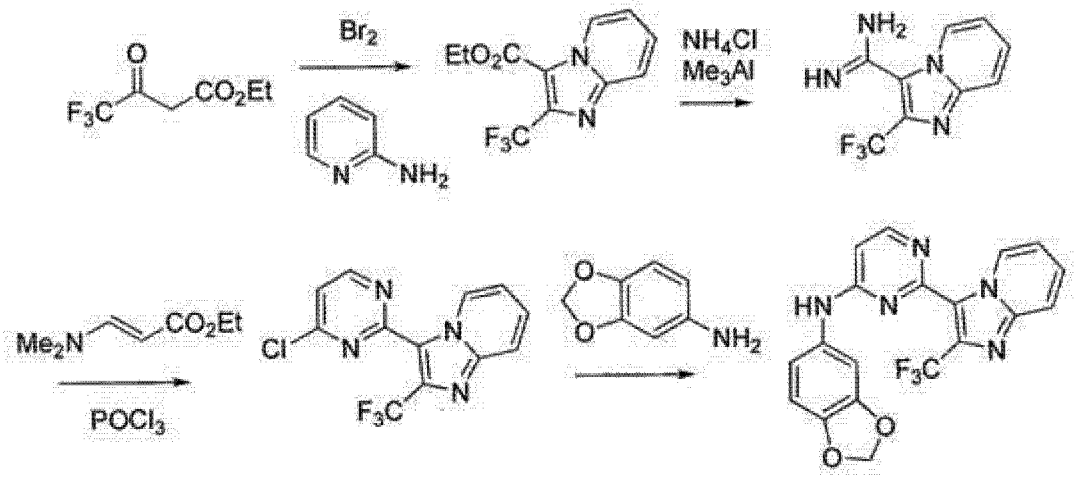
缩写	含义
AcOH 或 HOAc	乙酸

CAN 或 MeCN	乙腈
$AlMe_3$	三甲基铝
APC	烯丙基氯化钯 (II) 二聚物
Boc	叔丁氧羰基
CsOAc	乙酸铯
DCM 或 CH_2Cl_2	二氯甲烷
DME	二甲醚
DMF	二甲基甲酰胺
DMA	二甲基乙酰胺
DMAP	4- 二甲基氨基吡啶
DMSO	二甲亚砜
EtOAc	乙酸乙酯
EtOH	乙醇
HPLC	高效液相色谱
h, hr, min, s	小时 (h 或 hr), 分钟 (min), 秒 (s)
iPrMgCl*LiCl	异丙基氯化镁氯化锂复合物
iPrOAc	乙酸异丙酯
K_2CO_3	碳酸钾
K_3PO_4	磷酸钾
KOtBu 或 t-BuOK	叔丁醇钾
LC/MS, LCMS 或 LC-MS	液相色谱 - 质谱
MeOH	甲醇
$MeNH_2$x HCl	甲胺盐酸盐
MS	质谱
m.p.	熔点 (以℃表示)
MPS	过一硫酸钾 ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)
NaH	氢化钠
$NaHCO_3$	碳酸氢钠
NaHMDS	六甲基二硅基氨基钠
$NaIO_4$	高碘酸钠
NaOH	氢氧化钠
NaOtAm	叔戊醇钠
NaOMe	甲醇钠
NaOEt	乙醇钠
NaOtBu	叔丁醇钠
NCS	N- 氯代琥珀酰亚胺
NH_4Cl	氯化铵
NH_4OH	氢氧化铵
NIS	N- 碘代琥珀酰亚胺
NMP	N- 甲基吡咯烷酮
NMR	核磁共振
Oxone	过一硫酸钾
PCl_5	高氯化磷或五氯化磷
PCy_3	三环己基膦
[Pd]	钯
Pd/C°	碳载钯
$Pd_2(dba)_3$或 Pd_2dba_3	三 (二苄叉基丙酮) 二钯 (0)
$Pd(dppf)Cl_2$	[1,1'- 双 (二苯基膦基) 二茂铁] 二氯化钯 (II)
$PdCl_2(ACN)$	双 (乙腈) 二氯化钯 (II)
$PdCl_2(allyl)$	氯烯丙基钯 (II) 二聚物
$[Pd(OAc)_2]_3$	乙酸钯 (II)
$Pd(PPh_3)_4$	四 (三苯基膦) 钯

$POCl_3$	三氯氧磷
PPh_3	三苯基膦
psi	每平方英寸磅压力
Pt/C	碳载铂
PTSA	对甲苯磺酸
Q-Phos 或 QPhos	1,2,3,4,5- 五苯基 -1'-(二叔丁基膦基) 二茂铁
RT	室温
TBSO 或 OTBS	*叔丁基*二甲基甲硅烷基氧基
TCDI	1,1'- 硫代羰基联咪唑
t-Bu	叔丁基
TEA, NEt_3, Et_3N	三乙胺
TFA	三氟乙酸
TFAA	三氟乙酸酐
THF	四氢呋喃
TsOH X H_2O	对甲苯磺酸一水合物
UPLC	超效液相色谱
Xphos 或 XPhos	2- 二氯己基膦基 -2',4',6'- 三异丙基联苯

[0372] 实施例 1

N-(1,3- 苯并二氧杂环戊烯 -5- 基)-2-[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 嘧啶 -4- 胺 (Cpd 28)



步骤 1. 向 4,4,4- 三氟 -3- 氧代丁酸乙酯 (9.0 g, 48.9 mmol) 在 CH_2Cl_2 (50 mL) 中的溶液中加入溴 (2.5 mL, 49 mmol)。将反应混合物在室温下搅拌 15 小时,然后在干氮气下浓缩。向在乙醇 (30 mL) 中的粗材料中添加吡啶 -2- 胺 (5.2 g, 55 mmol)。将反应混合物在 60℃下加热 3 小时。蒸发乙醇,残余物在 EtOAc 和水之间分配。干燥有机层,通过硅胶短塞过滤,然后在减压下浓缩,并通过硅胶层析法纯化以提供白色固体形式的 2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 甲酸乙酯 (5.3 g, 42 %)。

[0373] 步骤 2. 在 0℃下经约 5 分钟时间向 NH_4Cl (2.67 g, 50 mmol) 在甲苯 (20 mL) 中的悬浮液中添加 $AlMe_3$(2M 甲苯中溶液 , 25 mL, 50 mmol),然后气体逸出。在 0℃下搅拌所述悬浮液 5 分钟,然后温热至室温。将 2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 甲酸乙酯 (2.58 g, 10 mmol) 在甲苯 (50 mL) 中的溶液添加至所述悬浮液。在 80℃下加热该反应混合物 72 小时,然后在冰浴中冷却,用 MeOH (100 mL) 和 NaOH (2 g, 50 mmol) 淬火。通过 Celite 过滤混合物,并浓缩以提供褐色固体形式的粗 2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 甲脒 (2.3 g)。

[0374] 步骤 3. 将 2-(三氟甲基)咪唑并[1,2-a]吡啶-3-甲脒(2.3 g, 10 mmol)和 3-(二甲基氨基)丙烯酸乙酯(7.2 g, 50 mmol)在二苯醚(10 mL)中的混合物在 160℃下加热 1 小时。将该混合物冷却至室温并用已烷(200 mL)稀释。将沉淀物过滤并用已烷洗涤以提供浅褐色固体形式的 2-(2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基)嘧啶-4(3H)-酮。将固体溶解在乙腈(10 mL)中并向该混合物中添加 $POCl_3$(1.9 mL, 20 mmol)。将反应混合物加热至 100℃,持续 30 分钟,冷却至冰水浴中,然后用二氯甲烷(100 mL)稀释,用 $NaHCO_3$ 水溶液洗涤。干燥有机层,然后通过 Celite 过滤并通过硅胶层析法纯化以提供浅黄色固体材料形式的 3-(4-氯嘧啶-2-基)-2-(三氟甲基)咪唑并[1,2-a]吡啶(1.09 g, 37%,经 3 步)。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.61 (d, J = 6.9 Hz, 1H), 9.00 (d, J = 5.0 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 5.4 Hz, 1H), 7.69 (ddd, J = 8.7, 7.1, 1.3 Hz, 1H), 7.37 (td, J = 7.0, 1.1 Hz, 1H).

[0375] 步骤 4. 在 0℃下向 3-(4-氯嘧啶-2-基)-2-(三氟甲基)咪唑并[1,2-a]吡啶(75 mg, 0.25 mmol)和苯并[d][1,3]二氧杂环戊烯-5-胺(69 mg, 0. 5 mmol)在 THF(1 mL)中的溶液中添加 KOtBu(1M 在 THF 中的溶液, 1 mL, 1 mmol)。在 10 分钟之后,用 HOAc 淬火该反应混合物,然后在 EtOAc 和水之间分配。干燥有机层,然后浓缩,将残余物通过硅胶层析法纯化以提供黄褐色固体形式的标题化合物(58 mg, 58 %)。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.70 (s, 1H), 9.43 (d, J = 6.6 Hz, 1H), 8.43 (d, J = 5.7 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.58 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.37 (br. s., 1H), 7.17 (td, J = 6.9, 0.9 Hz, 1H), 6.95 (dd, J = 8.2, 1.9 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 6.0 Hz, 1H), 6.03 (s, 2H); MS *m/z* 400 $[M+H]^+$.

[0376] 可以根据实施例 1 的程序通过代替合适的起始原料、试剂和反应条件制备本文中所述的另外的式(I)化合物或其形式。

Cpd	名称 & 数据
2	**N-(2,3-二氢-1,4-苯并二氧杂环己二烯-6-基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (dt, J = 6.9, 0.9 Hz, 1H), 9.45 (br. s, 1H), 8.36 (d, J = 5.7 Hz, 1H), 7.60 (dt, J = 8.8, 0.9 Hz, 1H), 7.38 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.95 - 6.98 (m, 2H), 6.87 (dd, J = 4.4, 3.5 Hz, 1H), 6.54 (d, J = 6.0 Hz, 1H), 4.25 - 4.30 (m, 4H), 2.75 (s, 3H); MS *m/z* 360 $[M+H]^+$

Cpd	名称 &数据
3	**2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 (br. s, 1H), 9.81 (dt, J = 6.9, 1.1 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.63 (dt, J = 8.8, 1.1 Hz, 1H), 7.42 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.03 (td, J = 6.9, 1.3 Hz, 1H), 6.74 (d, J = 5.7 Hz, 1H), 2.78 (s, 3H); MS *m/z* 370 [M+H]$^+$
4	**N-(4-甲氧基苯基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.84 (d, J = 6.6 Hz, 1H), 9.44 (br. s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 7.59 (dt, J = 8.8, 0.9 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.37 (ddd, J = 8.9, 6.9, 1.3 Hz, 1H), 6.97 - 7.00 (m, 2H), 6.95 (td, J = 6.9, 0.9 Hz, 1H), 6.52 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 2.73 (s, 3H); MS *m/z* 332 [M+H]$^+$
5	**N-(4-氯苯基)-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.81 (d, J = 6.9 Hz, 1H), 9.78 (br. s, 1H), 8.45 (d, J = 5.7 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.44 (s, 2H), 7.40 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.01 (td, J = 6.9, 1.3 Hz, 1H), 6.64 (d, J = 6.0 Hz, 1H), 2.74 (s, 3H); MS *m/z* 336 [M+H]$^+$
6	**2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-苯基嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (dt, J = 6.9, 0.9 Hz, 1H), 9.65 (br. s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.59 - 7.64 (m, 3H), 7.36 - 7.43 (m, 3H), 7.11 (tt, J = 7.4, 0.9 Hz, 1H), 6.98 (ddd, J = 7.5, 5.5, 0.9 Hz, 1H), 6.63 (d, J = 6.0 Hz, 1H), 2.75 (s, 3H); MS *m/z* 302 [M+H]$^+$
7	**2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.36 (d, J = 6.9 Hz, 1H), 8.59 (d, J = 5.7 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 9.1 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.60 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.21 (td, J = 6.9, 1.3 Hz, 1H), 6.92 (d, J = 5.7 Hz, 1H); MS *m/z* 424 [M+H]$^+$
8	**N-(4-氯苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.95 (br. s., 1H), 9.37 (d, J = 6.9 Hz, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 6.8 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 390 [M+H]$^+$
9	**N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.75 (br. s, 1H), 9.41 (d, J = 6.6 Hz, 1H), 8.45 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 6.9 Hz, 2H), 6.77 (d, J = 5.7 Hz, 1H), 2.31 (s, 3H); MS *m/z* 370 [M+H]$^+$
10	**N-(4-溴苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.97 (br. s, 1H), 9.37 (d, J = 6.9 Hz, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 8.0, 6.9 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 6.9 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 435 [M+H]$^+$

Cpd	名称 & 数据
11	**N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.52 (dt, J = 7.3, 0.9 Hz, 1H), 8.38 (d, J = 6.0 Hz, 1H), 7.72 (dt, J = 9.1, 0.9 Hz, 1H), 7.30 - 7.37 (m, 3H), 7.11 (d, J = 8.8 Hz, 2H), 6.93 (td, J = 6.9, 1.3 Hz, 1H), 6.87 (br. s., 1H), 6.54 (d, J = 6.0 Hz, 1H), 6.46 (t, J = 73.8 Hz, 1H); MS *m/z* 422 $[M+H]^+$
12	**N-(4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.63 (dt, J = 7.3, 0.9 Hz, 1H), 8.40 (d, J = 6.0 Hz, 1H), 7.79 (dt, J = 9.1, 0.9 Hz, 1H), 7.41 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.24 - 7.33 (m, 2H), 7.00 (td, J = 6.9, 0.9 Hz, 1H), 6.94 - 6.98 (m, 2H), 6.91 (br. s, 1H), 6.50 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H); MS *m/z* 386 $[M+H]^+$
13	**2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s., 1H), 9.56 - 9.72 (m, 1H), 8.60 (d, J = 5.4 Hz, 1H), 7.83 - 7.98 (m, 3H), 7.63 - 7.74 (m, 3H), 6.90 (d, J = 5.4 Hz, 1H); MS *m/z* 458 $[M+H]^+$
14	**2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲氧基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.72 - 9.82 (m, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.65 - 7.77 (m, 1H), 7.46 (dd, J = 9.0, 2.7 Hz, 2H), 7.39 (dd, J = 9.6, 2.0 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 6.84 (br. s, 1H), 6.64 (d, J = 6.0 Hz, 1H); MS *m/z* 474 $[M+H]^+$
15	**N-(4-溴苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.96 (br. s, 1H), 9.60 (dd, J = 2.0, 0.8 Hz, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.92 (dd, J = 9.6, 0.8 Hz, 1H), 7.66 (dd, J = 9.6, 2.0 Hz, 1H), 7.61 - 7.64 (m, 2H), 7.50 - 7.55 (m, 2H), 6.81 (d, J = 6.0 Hz, 1H); MS *m/z* 469 $[M+H]^+$
16	**2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.60 - 9.78 (m, 1H), 8.40 (dd, J = 6.0, 0.9 Hz, 1H), 7.66 (dd, J = 9.5, 0.6 Hz, 1H), 7.34 (dd, J = 8.8, 2.5 Hz, 2H), 7.31 (dd, J = 9.6, 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.76 (br. s, 1H), 6.54 (d, J = 6.0 Hz, 1H), 6.46 (t, J = 74.4 Hz, 1H); MS *m/z* 456 $[M+H]^+$
17	**N-(4-氯苯基)-2-[6-氯-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.59 - 9.75 (m, 1H), 8.41 (dd, J = 6.0, 0.9 Hz, 1H), 7.66 (dd, J = 9.6, 0.8 Hz, 1H), 7.23 - 7.36 (m, 5H), 6.74 (br. s, 1H), 6.55 (dd, J = 6.0, 1.3 Hz, 1H); MS *m/z* 425 $[M+H]^+$

Cpd	名称 &数据
18	**2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (br. s, 1H), 10.26 (s, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.88 (d, J = 11.0 Hz, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 6.0 Hz, 1H), 2.86 (s, 3H); MS *m/z* 438 $[M+H]^+$
19	**N-(4-溴苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.30 (s, 1H), 10.07 (br. s, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.87 - 7.96 (m, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 6.0 Hz, 1H), 2.83 (s, 3H); MS *m/z* 449 $[M+H]^+$
20	**N-(4-甲基苯基)-2-[2-甲基-6-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.28 (s, 1H), 9.83 (br. s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 6.70 (d, J = 6.0 Hz, 1H), 2.81 (s, 3H), 2.30 (s, 3H); MS *m/z* 384 $[M+H]^+$
21	**2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲基苯基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.78 (s, 1H), 9.63 (br. s, 1H), 8.44 (d, J = 6.0 Hz, 1H), 7.94 (dd, J = 10.1, 5.4 Hz, 1H), 7.70 (ddd, J = 10.7, 7.9, 2.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.8 Hz, 1H), 2.30 (s, 3H); MS *m/z* 388 $[M+H]^+$
22	**2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (br. s, 1H), 8.41 (d, J = 5.7 Hz, 1H), 7.94 (dd, J = 9.9, 5.2 Hz, 1H), 7.69 (ddd, J = 10.0, 7.8, 2.4 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.75 - 6.82 (m, 1H), 6.68 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H); MS *m/z* 404 $[M+H]^+$
23	**2-[5氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 8.27 (d, J = 6.3 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.56 (br. s, 1H), 7.26 (dd, J = 8.5, 1.9 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.73 - 6.80 (m, 2H), 6.42 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H); MS *m/z* 433 $[M+H]^+$
24	**2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]-N-[4-(二氟甲氧基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.47 (br. s, 1H), 8.47 (d, J = 6.6 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.50 (dd, J = 8.8, 1.9 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 74.4 Hz, 1H), 6.90 (d, J = 6.3 Hz, 1H), 4.00 (s, 3H); MS *m/z* 469 $[M+H]^+$

Cpd	名称 &数据
25	**N-(4-溴苯基)-2-[5-氯-1-甲基-2-(三氟甲基)-1H-吲哚-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s, 1H), 8.49 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.43 - 7.52 (m, J = 8.5 Hz, 3H), 6.87 (d, J = 6.0 Hz, 1H), 4.00 (s, 3H); MS *m/z* 482 [M+H]$^+$
26	**N-(4-溴苯基)-2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.75 (br. s., 1H), 9.55 (d, J = 3.2 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 7.83 (dd, J = 8.8, 5.0 Hz, 1H), 7.67 (d, J = 7.9 Hz, 2H), 7.57 (td, J = 9.1, 1.6 Hz, 1H), 7.31 - 7.46 (m, J = 7.6 Hz, 3H), 7.01 - 7.21 (m, 4H), 6.72 (d, J = 5.7 Hz, 1H); MS *m/z* 461 [M+H]$^+$
27	**2-(6-氟-2-苯基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲基苯基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.88 (br. s, 1H), 9.49 - 9.61 (m, 1H), 8.37 (d, J = 6.0 Hz, 1H), 7.90 (dd, J = 9.9, 5.2 Hz, 1H), 7.66 - 7.75 (m, 3H), 7.39 - 7.49 (m, 3H), 7.14 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 6.3 Hz, 1H), 2.23 (s, 3H); MS *m/z* 396 [M+H]$^+$
29	**N-(2,3-二氢-1,4-苯并二氧杂环己二烯-6-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm9.63 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.84 (dt, J = 9.1, 0.9 Hz, 1H), 7.58 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.22 (br. s., 1H), 7.15 (td, J = 6.9, 1.3 Hz, 0H), 7.01 (dd, J = 8.5, 2.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 6.0 Hz, 1H), 4.20 - 4.29 (m, 4H); MS *m/z* 410 [M+H]$^+$
30	**N-(6-甲氧基吡啶-3-基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.53 (d, J = 6.9 Hz, 1H), 8.34 (d, J = 5.7 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.69 (dt, J = 9.1, 0.9 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.32 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 6.91 (td, J = 7.0, 1.3 Hz, 2H), 6.75 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 6.0 Hz, 1H), 3.90 (s, 3H); MS *m/z* 387 [M+H]$^+$
31	**N^2,N^2-二甲基-N^5-{2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-基}吡啶-2,5-二胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.55 (d, J = 6.9 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.51 (br. s, 1H), 7.32 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 6.92 (td, J = 6.9, 0.9 Hz, 1H), 6.81 (br. s, 0H), 6.51 (d, J = 9.1 Hz, 1H), 6.35 (d, J = 5.4 Hz, 1H), 3.08 (s, 6H); MS *m/z* 400 [M+H]$^+$
32	**2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.66 (dd, J = 1.9, 0.9 Hz, 1H), 8.60 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.87 (dd, J = 9.6, 0.8 Hz, 1H), 7.74 (dd, J = 9.5, 1.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 6.0 Hz, 1H); MS *m/z* 503 [M+H]$^+$

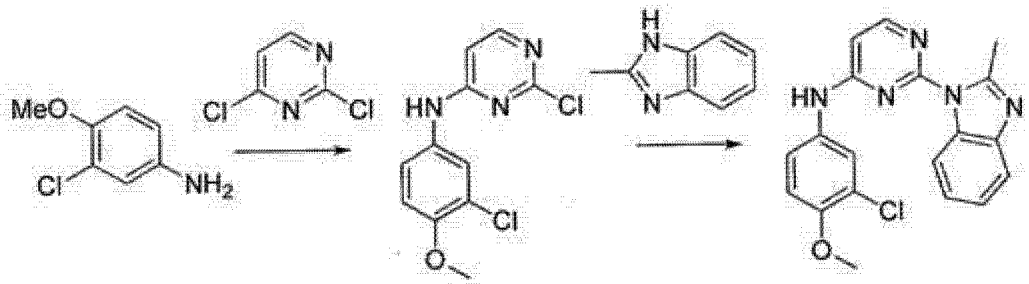
Cpd	名称 &数据
33	**2-[6-溴-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-(4-甲氧基苯基)嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -*d*) δ ppm 9.70 - 9.86 (m, 1H), 8.32 (d, J = 4.7 Hz, 1H), 7.60 (d, J = 9.5 Hz, 1H), 7.40 (dd, J = 9.6, 1.7 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.47 (br. s, 1H), 3.78 (s, 3H); MS *m/z* 465 $[M+H]^+$
34	**N-(3-氟-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.77 (s, 1H), 9.35 (d, J = 6.9 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 13.6 Hz, 1H), 7.53 (ddd, J = 9.1, 6.9, 1.3 Hz, 1H), 7.17 - 7.23 (m, 1H), 7.13 (td, J = 6.9, 1.1 Hz, 1H), 7.13 (td, J = 6.9, 0.9 Hz, 1H), 7.10 (t, J = 9.1 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H); MS *m/z* 404 $[M+H]^+$
35	**N-(3-氯-4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.80 (s, 1H), 9.40 (d, J = 6.9 Hz, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.88 - 7.92 (m, 1H), 7.85 (dt, J = 9.1, 1.0 Hz, 1H), 7.59 (ddd, J = 9.1, 6.6, 1.3 Hz, 1H), 7.43 (dd, J = 8.8, 2.8 Hz, 1H), 7.18 (td, J = 6.9, 1.3 Hz, 1H), 7.15 (d, J = 9.1 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H), 3.85 (s, 3H); MS *m/z* 420 $[M+H]^+$
36	**N-(3-氯-4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 9.38 (d, J = 7.3 Hz, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.86 (dt, J = 9.1, 1.1 Hz, 1H), 7.59 (ddd, J = 9.1, 6.9, 1.3 Hz, 1H), 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.20 (td, J = 6.9, 1.3 Hz, 1H), 6.80 (d, J = 5.7 Hz, 1H), 2.30 (s, 3H); MS *m/z* 404 $[M+H]^+$
37	**N-(4-乙氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.64 (br. s, 1H), 9.43 (br. s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 7.84 (dt, J = 9.1, 1.3 Hz, 1H), 7.57 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.16 (t, J = 6.5 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 6.0 Hz, 1H), 4.02 (q, J = 6.9 Hz, 2H), 1.34 (t, J = 6.9 Hz, 3H); MS *m/z* 400 $[M+H]^+$
38	**N-[4-(丙-2-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.76 (s, 1H), 9.41 (d, J = 6.9 Hz, 1H), 8.45 (d, J = 6.0 Hz, 1H), 7.85 (dt, J = 9.1, 0.9 Hz, 1H), 7.58 (ddd, J = 8.8, 6.6, 1.3 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.16 (td, J = 6.9, 0.9 Hz, 1H), 6.77 (d, J = 6.0 Hz, 1H), 2.89 (spt, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 7H); MS *m/z* 398 $[M+H]^+$
39	**N-[4-(1H-吡唑-1-基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.98 (s, 1H), 9.42 (d, J = 7.3 Hz, 1H), 8.51 (d, J = 5.7 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 7.86 (td, J = 9.1, 1.3 Hz, 1H), 7.76 - 7.84 (m, J = 3.5 Hz, 4H), 7.73 (d, J = 1.6 Hz, 1H), 7.59 (ddd, J = 9.0, 6.8, 1.3 Hz, 1H), 7.20 (td, J = 6.9, 1.3 Hz, 1H), 6.84 (d, J = 6.0 Hz, 1H), 6.54 (t, J = 1.9 Hz, 1H); MS *m/z* 422 $[M+H]^+$

Cpd	名称 &数据
45	**N-(4-甲氧基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.53 (br. s., 1H), 9.16 (d, J = 1.3 Hz, 1H), 8.81 (s, 1H), 8.38 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 4.7 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.70 (dd, J = 8.2, 2.5 Hz, 1H), 3.79 (s, 3H); MS *m/z* 387 $[M+H]^+$
46	**2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.41 - 9.49 (m, 1H), 9.20 (br. s, 1H), 8.49 (dd, J = 6.0, 2.2 Hz, 1H), 8.02 - 8.12 (m, 1H), 7.83 - 7.92 (m, 2H), 7.58 (d, J = 8.5 Hz, 2H), 6.93 - 7.32 (m, 2H); MS *m/z* 425 $[M+H]^+$
47	**N-(4-氯苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.53 (dd, J = 4.9, 1.4 Hz, 1H), 9.25 (d, J = 1.3 Hz, 1H), 9.20 (br. s., 1H), 8.55 (d, J = 6.0 Hz, 1H), 8.15 (d, J = 4.7 Hz, 1H), 7.70 - 7.81 (m, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 6.0 Hz, 1H); MS *m/z* 391 $[M+H]^+$
48	**2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.31 (br. s, 1H), 9.02 (d, J = 2.5 Hz, 1H), 8.65 (d, J = 5.7 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 10.4 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 9.8, 2.5 Hz, 1H), 6.95 (d, J = 6.0 Hz, 1H), 3.66 (s, 3H); MS *m/z* 454 $[M+H]^+$
49	**2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲氧基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.65 (br. s, 1H), 8.96 - 9.06 (m, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.76 (d, J = 9.8 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.36 (dd, J = 9.6, 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H); MS *m/z* 470 $[M+H]^+$
50	**N-(4-甲氧基苯基)-2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.04 (br. s, 1H), 8.97 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.75 - 7.79 (m, 3H), 7.38 (dd, J = 9.1, 2.2 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 6.0 Hz, 1H), 3.59 (s, 3H), 3.33 (s, 3H); MS *m/z* 416 $[M+H]^+$
51	**N-[4-(二氟甲氧基)苯基]-2-[6-甲氧基-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.90 (br. s, 1H), 8.98 (d, J = 1.9 Hz, 1H), 8.50 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.37 (dd, J = 9.8, 2.5 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.19 (t, J = 74.4 Hz, 1H), 6.78 (d, J = 5.7 Hz, 1H), 3.61 (s, 3H); MS *m/z* 452 $[M+H]^+$
53	**N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.74 (dd, J = 4.9, 1.4 Hz, 1H), 9.44 (d, J = 1.6 Hz, 1H), 9.30 (br. s., 1H), 8.72 (d, J = 6.0 Hz, 1H), 8.32 (d, J = 4.7 Hz, 1H), 7.89 - 8.00 (m, 2H), 7.42 - 7.52 (m, 2H), 7.07 (dd, J = 6.0, 1.6 Hz, 1H), 7.20 (t, J = 74.4 Hz, 1H); MS *m/z* 423 $[M+H]^+$

Cpd	名称 &数据
54	**2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.25 (br. s, 1H), 9.58 (ddd, J = 5.7, 1.9, 0.9 Hz, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.97 (ddd, J = 9.8, 5.4, 0.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.73 (ddd, J = 9.9, 7.7, 2.5 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 6.0 Hz, 1H); MS *m/z* 442 [M+H]$^+$
55	**N-[4-(二氟甲氧基)苯基]-2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.75 (dd, J = 5.5, 2.0 Hz, 1H), 9.10 (br. s, 1H), 8.51 (d, J = 5.7 Hz, 1H), 7.84 (ddd, J = 9.8, 5.4, 0.9 Hz, 1H), 7.71 - 7.76 (m, 2H), 7.60 (ddd, J = 10.0, 7.6, 2.5 Hz, 1H), 7.22 - 7.26 (m, 2H), 6.99 (t, J = 74.1 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H); MS *m/z* 440 [M+H]$^+$
56	**N-[4-(三氟甲基)苯基]-2-[2-(三氟甲基)吡唑并[1,5-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -d) δ ppm 10.03 (br. s, 1H), 8.48 (d, J = 6.9 Hz, 1H), 8.21 - 8.36 (m, 1H), 8.00 - 8.15 (m, 1H), 7.65 - 7.73 (m, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.06 - 7.12 (m, 1H), 7.03 (t, J = 6.8 Hz, 1H); MS *m/z* 424 [M+H]$^+$
60	**N-(4-甲氧基苯基)-2-[2-(三氟甲基)吡唑并[1,5-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿 -d) δ ppm 8.49 (d, J = 6.6 Hz, 1H), 8.03 - 8.31 (m, 2H), 7.30 - 7.55 (m, 3H), 7.00 - 7.12 (m, 2H), 6.79 - 6.87 (m, 3H), 3.76 (s, 3H); MS *m/z* 386 [M+H]$^+$
62	**N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡嗪-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.58 (d, J = 3.8 Hz, 1H), 9.23 (d, J = 1.6 Hz, 1H), 8.95 (br. s., 1H), 8.48 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 4.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 6.0 Hz, 1H), 2.37 (s, 3H); MS *m/z* 371 [M+H]$^+$
118	**2-(咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.10 (s, 1H), 9.92 (d, J = 7.3 Hz, 1H), 8.51 (app. s, 1H), 8.48 (d, J = 5.7 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.75 - 7.86 (m, 3H), 7.46 (ddd, J = 9.1, 6.6, 0.9 Hz, 1H), 7.14 (td, J = 6.9, 1.1 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H); MS *m/z* 356 [M+H]$^+$

[0377] 实施例 2

N-(3- 氯 -4- 甲氧基苯基)-2-(2- 甲基 -1*H*- 苯并咪唑 -1- 基) 嘧啶 -4- 胺 (Cpd 40)



步骤 1. 将 3- 氯 -4- 甲氧基苯胺 (2.07 g, 13.1 mmol), 2,4- 二氯嘧啶 (1.95 g, 13.1 mmol) 和三乙胺 (2.1 mL, 15 mmol) 混合在异丙醇 (10 mL) 中。将该混合物在 100℃ 下加热 13 小时,然后部分浓缩,用水稀释,并用 K_2CO_3获得碱性。过滤沉淀物,然后用水洗涤,然后用已烷洗涤。将主要异构体,2- 氯 -N-(3- 氯 -4- 甲氧基苯基) 嘧啶 -4- 胺 (2.07 g, 59 %) 从甲醇中作为白色固体重结晶。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.99 (br. s, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.73 (br. s., 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 5.7 Hz, 1H), 3.85 (s, 3H).

[0378] 步骤 2. 将 2- 氯 -N-(3- 氯 -4- 甲氧基苯基) 嘧啶 -4- 胺 (84 mg, 0.31 mmol), 2- 甲基 -1H- 苯并 [d] 咪唑 (82 mg, 0.62 mmol) 和 K_2CO_3 (86 mg, 0.62 mmol) 混合在 DMF (2 mL) 中。并将该反应混合物在 120℃下加热 3 天,然后冷却,在水和 EtOAc 之间分配,并通过硅胶层析法纯化以提供白色固体形式的标题化合物 (29 mg, 26%)。

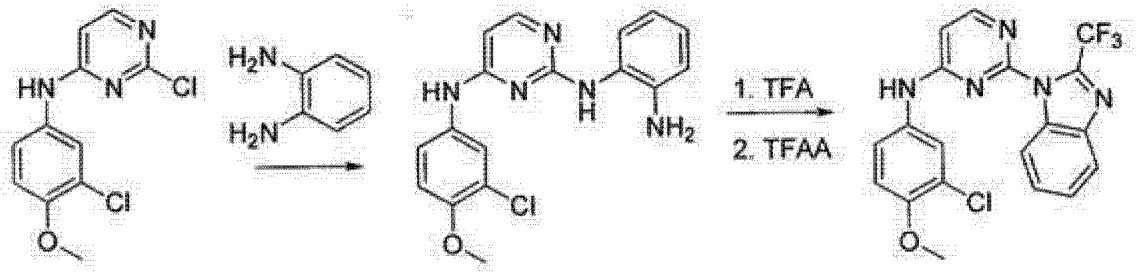
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.94 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 8.03 - 8.10 (m, 1H), 7.82 - 7.90 (m, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.40 - 7.45 (m, 1H), 7.20 - 7.29 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 5.7 Hz, 1H), 3.86 (s, 3H), 2.79 (s, 3H); MS *m/z* 366 $[M+H]^+$.

[0379] 可以根据实施例 2 的步骤通过代替合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 &数据
1	**N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.79 (br. s., 1H), 8.36 (d, J = 5.4 Hz, 1H), 7.95 - 8.17 (m, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.42 - 7.54 (m, 2H), 7.17 - 7.33 (m, 2H), 6.96 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 5.0 Hz, 1H), 3.76 (s, 3H), 2.77 (s, 3H); MS *m/z* 332 $[M+H]^+$
41	**2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4-胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.37 (s, 1H), 8.55 (d, J = 5.7 Hz, 1H), 8.01 - 8.06 (m, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.61 - 7.65 (m, 1H), 7.26 (app. quind, J = 7.3, 1.4 Hz, 2H), 6.91 (d, J = 5.7 Hz, 1H), 2.81 (s, 3H); MS *m/z* 370 $[M+H]^+$
61	**N-[4-(二氟甲氧基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.32 (1H, d, J = 5.5 Hz), 8.06 (1H, d, J = 8 Hz), 7.59 (3H, d, J = 8 Hz), 7.26 (2H, m), 7.14 (2H, d, J = 8 Hz), 7.0 (1H, t, J = 74 Hz), 6.69 (1H, d, J = 6 Hz), 2.82 (3H, s); MS *m/z* 368 $[M+H]^+$

[0380] 实施例 3

N-(3- 氯 -4- 甲氧基苯基)-2-[2-(三氟甲基)-1H- 苯并咪唑 -1- 基] 嘧啶 -4- 胺 (Cpd 42)



将 2- 氯 -N-(3- 氯 -4- 甲氧基苯基) 嘧啶 -4- 胺 (280 mg, 1.03 mmol) 和苯 -1,2- 二胺 (540 mg, 5 mmol) 在异丙醇 (5 mL) 中的混合物在微波炉中在 160℃下加热 10 分钟。用水稀释反应混合物,用 EtOAc 萃取,然后通过硅胶短塞过滤,并浓缩以提供第一粗中间体 N^2-(2- 氨基苯基)-N^4-(3- 氯 -4- 甲氧基苯基) 嘧啶 -2,4- 二胺。将第一粗中间体溶解在二氯甲烷 (5 mL) 中,然后将三氟乙酸酐分两份添加(每份 0.5 mL)。用 $NaHCO_3$水溶液洗涤反应混合物,并通过硅胶层析法纯化以提供第二粗中间体 N-(2-(4-(3- 氯 -4- 甲氧基苯基

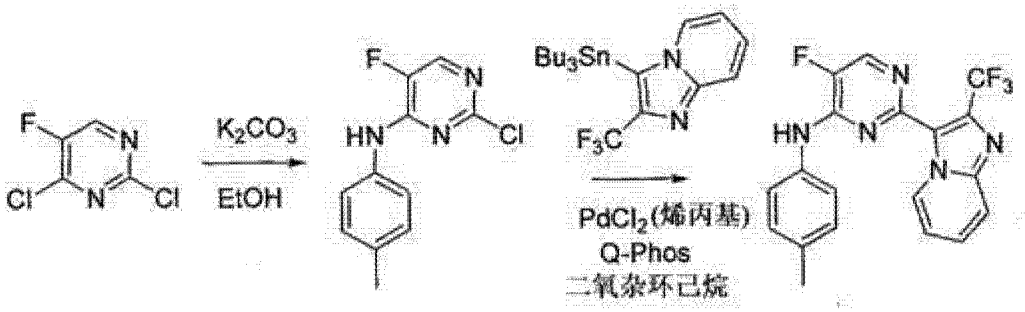
氨基)-嘧啶-2-基氨基)苯基)-2,2,2-三氟乙酰胺。

[0381] 向第二粗中间体(71 mg, 0.16 mmol)在乙腈(2 mL)中的溶液中添加三氟乙酸(0.5 mL)。在微波炉中在180℃下加热该混合物1小时45分钟,之后UPLC示出完全转化。通过硅胶层析法纯化最终产物以提供白色固体形式的标题化合物(40 mg, 59%)。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 - 10.18 (m, 1H), 8.45 (d, J = 5.7 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.83 - 7.90 (m, 1H), 7.52 - 7.56 (m, J = 8.2, 8.2, 1.3 Hz, 1H), 7.50 (td, J = 7.9, 1.3 Hz, 1H), 7.43 (dd, J = 9.0, 2.7 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H); MS *m/z* 420 [M+H]$^+$.

[0382] 实施例4

5-氟-N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺(Cpd 43)



步骤1: 将2,4-二氯-5-氟嘧啶(1.00 g, 5.99 mmol), 4-甲苯胺(642 mg, 5.99 mmol)和K_2CO_3(1.66 g, 12.0 mmol)在EtOH(10 mL)中的混合物在50℃下搅拌18小时。将该混合物通过Celite过滤并通过柱层析法纯化以获得2-氯-5-氟-N-*对甲苯基*嘧啶-4-胺(1.19 g, 84%)。

[0383] 步骤2: 将2-氯-5-氟-N-对甲苯基嘧啶-4-胺(165 mg, 0.69 mmol), 3-(三丁基甲锡烷基)-2-(三氟甲基)咪唑并[1,2-a]吡啶(300 mg, 0.63 mmol), Q-Phos(13.5 mg, 0.019 mmol)和$PdCl_2$(烯丙基)(6.9 mg, 0.019 mmol)在二氧杂环己烷(1.5 mL)中的混合物在90℃下搅拌2小时。将该混合物通过柱层析法纯化以获得标题化合物(213 mg, 80%)。

^{1}H NMR (500 MHz, 氯仿-*d*) δ ppm 9.24 - 9.29 (1H, m) 8.29 (1H, d, *J*=2.84 Hz) 7.66 - 7.71 (1H, m) 7.46 (2H, d, *J*=8.51 Hz) 7.31 (1H, ddd, *J*=9.14, 6.62, 1.26 Hz) 7.14 (2H, d, *J*=8.20 Hz) 6.82 - 6.89 (2H, m) 2.30 (3H, s); MS *m/z* 388.2 [M+H]$^+$.

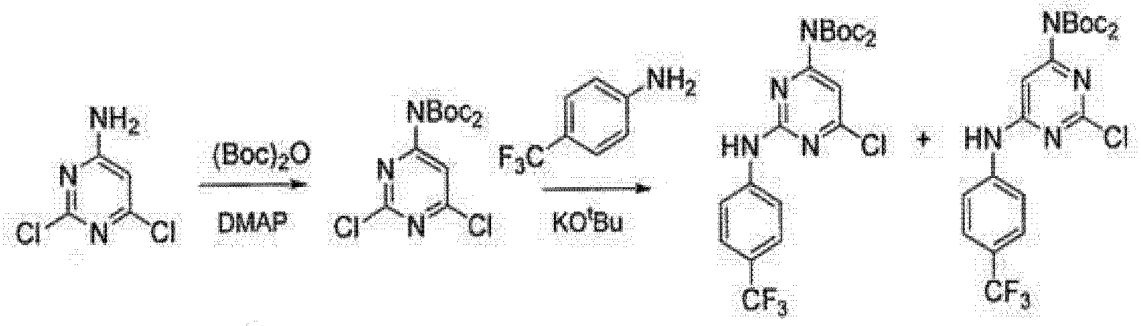
[0384] 可以根据实施例4的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式(I)化合物或其形式。

Cpd	名称 & 数据
44	**5-氯-N-(4-甲基苯基)-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4-胺** ^{1}H NMR (500 MHz, 氯仿-*d*) δ ppm 9.34 - 9.42 (1H, m) 8.51 (1H, s) 7.80 (1H, dd, *J*=9.14, 0.95 Hz) 7.49 (2H, d, *J*=8.51 Hz) 7.41 (1H, ddd, *J*=8.99, 6.78, 1.26 Hz) 7.20 - 7.27 (3H, m) 6.91 (1H, td, *J*=6.94, 1.26 Hz) 2.42 (3H, s); MS *m/z* 404.2 [M+H]$^+$

[0385] 实施例5

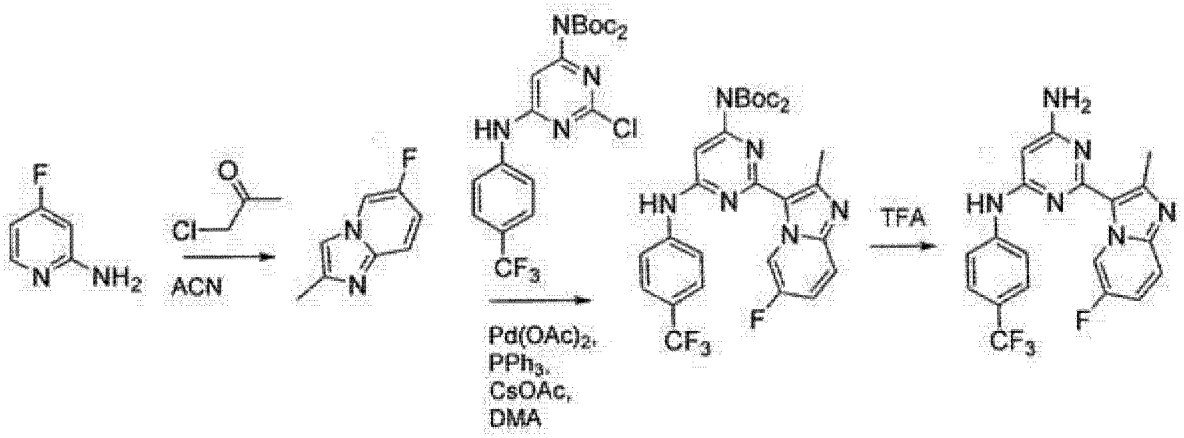
2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二

胺 (Cpd 68)



步骤 1. 将 2,6- 二氯嘧啶 -4- 胺 (3.78 g, 23.05 mmol) 和 DMAP (cat.) 在二氯甲烷 (20 mL) 中的混合物在 0℃下用二碳酸二叔丁酯 (11.05 g, 50.71 mmol) 处理。在添加之后,将所得混合物在环境温度下搅拌过夜。将该混合物倾倒在冰水 (120 mL) 中并用二氯甲烷 (150 mL) 萃取。分离有机相,用盐水 (100 mL) 洗涤,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶垫 (100 g) 过滤分离残余物质以获得油形式的 (2,6- 二氯嘧啶 -4- 基) 酰亚胺基二碳酸二叔丁酯 (7.55 g, 90%)。

[0386] 步骤 2. 在 -78℃下,用叔丁醇钾溶液 (1M 在 THF 中, 9.62 mL, 9.62 mmol) 处理 (2,6- 二氯嘧啶 -4- 基) 酰亚胺基二碳酸二叔丁酯 (1.75 g, 4.81 mmol) 和 4- 三氟甲基苯胺 (775.0 mg, 4.81 mmol) 在 THF (10 mL) 中的溶液。使该混合物搅拌并经 20 分钟温热至 0℃。然后将该混合物倾倒在冰水 (120 mL) 中并用二氯甲烷 (150 mL) 萃取。分离有机相,用盐水 (100 mL) 洗涤,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余物质 (通过用已烷然后用 2% 乙酸乙酯 - 已烷洗脱) 以获得 6- 氯 -2-(4-(三氟甲基) 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯酯 (750.0 mg, 32% 收率), 和 (通过使用 4% 乙酸乙酯 - 已烷洗脱) 2- 氯 -6-(4-(三氟甲基) 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (1.08 g, 46%)。



[0387] 步骤 3. 在 0℃下在 250 mL 圆底烧瓶中预混合并搅拌 4- 氟吡啶 -2- 胺 (8.57 g, 76.44 mmol) 和氯丙酮 (12.99 g, 71.67 mmol) 15 分钟。用乙腈 (50 mL) 稀释所得混合物并回流过夜。蒸馏乙腈,添加乙醚 (200 mL) 以生产沉淀物,其通过过滤收集。该固体在二氯甲烷 (300 mL) 和饱和 $NaHCO_3$溶液 (250 mL) 之间分配。分离有机层,经 $MgSO_4$干燥,然后过滤并在减压下浓缩。通过硅胶柱层析法 (1: 1 乙酸乙酯 - 已烷) 分离残余物质以获得玻璃状固体形式的 6- 氟 -2- 甲基咪唑并 [1,2-*a*] 吡啶 (5.20 g, 46%)。

^{1}H NMR (500 MHz, 氯仿 -d) δ ppm 7.95 - 7.99 (m, 1H), 7.46 (dd, J = 5.04, 9.77 Hz, 1H), 7.34 (s, 1H), 6.99 - 7.06 (m, 1H), 2.44 (d, J = 0.63 Hz, 3H); MS m/z 151.0 (100) $[M+H]^+$.

[0388] 步骤 4. 将 6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 (445.0 mg, 2.97 mmol), 2- 氯 -6-(4-(三氟甲基) 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (1.0 g, 5.78 mmol), 乙酸钯 (II) (33.4 mg, 0.149 mmol), 三苯基膦 (46.7 mg, 0.178 mmol), 乙酸铯 (1.14 g, 5.94 mmol) 和 DMA (5 mL) 的混合物通过三次真空泵抽和 N_2吹扫循环脱气,然后加热至 100℃,持续 1 小时。将该溶液冷却并倾倒在水 (50 mL) 中,用二氯甲烷萃取该混合物。经 $MgSO_4$干燥萃取物,然后过滤并在减压下浓缩。用乙醚磨碎残余物质以获得 2-(6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-6-(4-(三氟甲基) 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (706.0 mg, 83%)。

[0389] 步骤 5. 在 0℃下将 2-(6- 氟 -2- 甲基咪唑并 [1,2-a] 吡啶 -3- 基)-6-(4-(三氟甲基) 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (140 mg, 0.24 mmol) 在二氯甲烷 (2 mL) 中的溶液经 TFA (0.4 mL) 处理。在环境温度下搅拌所得混合物 4 小时。在减压下浓缩溶剂,残余物质在乙酸乙酯和饱和 $NaHCO_3$溶液之间分配。分离有机层,经 $MgSO_4$干燥,然后过滤并蒸发。用乙醚研磨残余物质以获得白色固体形式的标题化合物 (87.0 mg, 87%). m.p. 209-211 ℃。

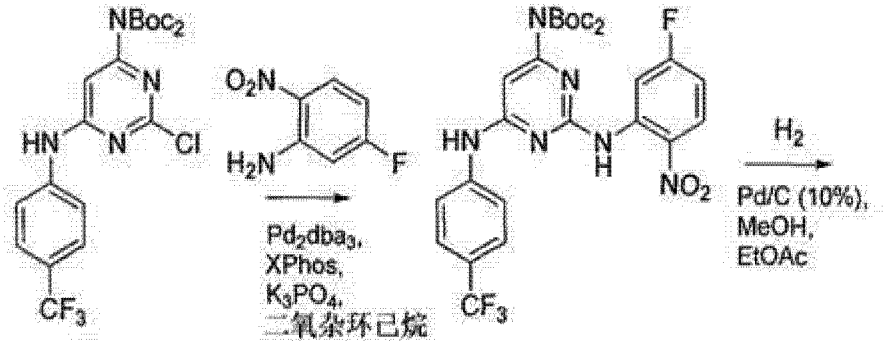
^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 10.40 (dd, J = 2.21, 5.36 Hz, 1H), 8.88 (s, 1H), 8.11 - 8.27 (m, 1H), 7.78 - 7.85 (m, 1H), 7.74 (d, J = 8.83 Hz, 2H), 7.69 (d, J = 8.83 Hz, 2H), 6.47 (br. s., 2H), 6.03 (s, 1H), 2.93 (s, 3H); MS m/z 403.5 (100) $[M+H]^+$, 404.4 (30).

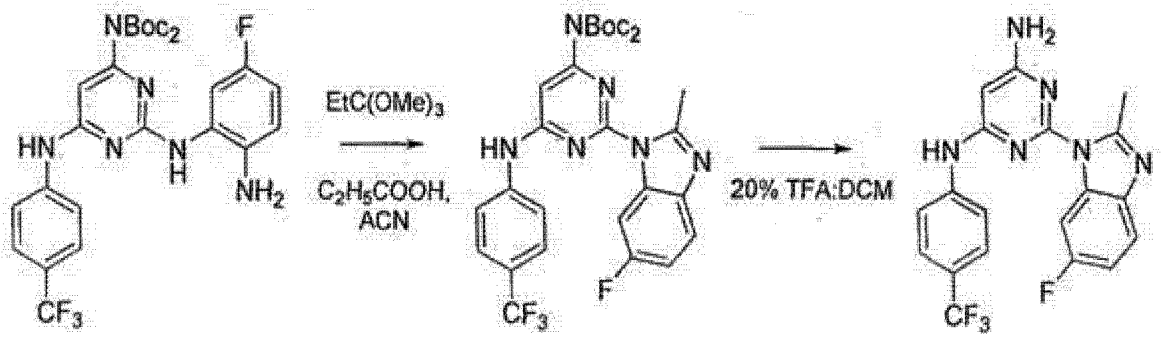
[0390] 可以根据实施例 5 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称&数据
65	**N-[4-(二氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.67 (ddd, *J* = 1.10, 1.26, 7.09 Hz, 1H), 8.40 (s, 1H), 7.73 (td, *J* = 1.10, 9.14 Hz, 1H), 7.59 - 7.66 (d, J = 9.1 Hz, 2H), 7.51 (ddd, *J* = 1.26, 6.94, 9.14 Hz, 1H), 7.15 - 7.23 (d, J = 9.1 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 7.05 - 7.12 (m, 1H), 6.11 (br. s., 2H), 5.96 (s, 1H); MS *m/z* 437.3 [M+H]$^+$
66	**2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** m.p. 203-205 °C; MS *m/z* 439.4 [M+H]$^+$
67	**N-[4-(三氟甲氧基)苯基]-2-[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]嘧啶-4,6-二胺** m.p. 199-202 °C; MS *m/z* 455.3 [M+H]$^+$
69	**N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 10.41 (dd, *J* = 2.21, 5.36 Hz, 1H), 8.57 (s, 1H), 8.19 (s, 1H), 7.71 - 7.89 (m, 1H), 7.53 (d, *J* = 9.77 Hz, 2H), 7.20 - 7.26 (d, *J* = 9.77 Hz, 2H), 6.81 – 7.11 (t, J = 75.00 Hz, 1H), 6.36 (br, s., 2H), 5.91 (s, 1H), 2.91 (s, 3H); m.p. 136-138 °C; MS *m/z* 401.5 [M+H]$^+$
75	**2-(2-环丙基-6-氟咪唑并[1,2-a]吡啶-3-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.06 (dd, *J* = 2.21, 5.99 Hz, 1H), 9.28 (s, 1H), 7.70 - 7.87 (m, 1H), 7.58 (dd, *J* = 5.52, 9.62 Hz, 1H), 7.41 (ddd, *J* = 2.68, 7.72, 9.77 Hz, 1H), 6.98 – 7.28 (t, J = 75.00 Hz, 1H), 7.24 - 7.32 (m, 1H), 7.18 - 7.24 (m, 1H), 6.73 (s, 2H), 5.72 (s, 1H), 3.42 - 3.56 (m, 1H), 0.89 - 1.11 (m, 4H); m.p. 198-200 °C; MS *m/z* 445.5 [M+H]$^+$
84	**[3-(4-氨基-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-6-氟咪唑并[1,2-a]吡啶-2-基]甲醇** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 9.36 - 9.77 (m, 1 H), 7.90 - 7.97 (m, 2 H), 7.59 - 7.69 (m, 1 H), 7.50 - 7.55 (m, 2 H), 7.- 7.45 (m, 1 H), 6.55 - 6.58 (m, 1 H), 4.86 (s, 2 H); MS *m/z* 419.1 [M+H]$^+$
100	**2-(6-氟-2-甲基咪唑并[1,2-a]嘧啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.45 (dd, *J* = 2.84, 5.67 Hz, 1H), 9.46 (s, 1H), 8.76 (d, *J* = 2.84 Hz, 1H), 7.72 (d, *J* = 8.51 Hz, 2H), 7.64 (d, *J* = 8.51 Hz, 2H), 6.82 (s, 2H), 5.79 (s, 1H), 2.84 (s, 3H); m.p. 256-258 °C; MS *m/z* 404.3 [M+H]$^+$

[0391] 实施例 6

2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺 (Cpd 71)





步骤 1：将 5- 氟 -2- 硝基苯胺（156.2 mg，1.00 mmol），），2- 氯 -6-(4-(三氟甲基）苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯（480.0 mg，0.98 mmol），2- 二环己基膦基 -2',4',6'- 三异丙基联苯（Xphos）（56.1 mg，0.1 mmol），三（二苄叉基丙酮）二钯 (0)（53.8 mg，0.05 mmol）和磷酸钾 (625.0 mg，2.95 mmol) 在二氧杂环己烷（2 mL）中的混合物通过三个真空泵抽和 N_2 吹扫脱气循环，然后加热至 100℃持续 2 小时。冷却该溶液并倾倒在水（10 mL）中，用乙酸乙酯（15 mL）萃取该混合物。经 $MgSO_4$ 干燥该萃取物，然后过滤并蒸发。通过柱层析法分离残余物质（用 1:1 二氯甲烷：己烷，然后用 1:2 乙酸乙酯：二氯甲烷洗脱）以获得 2-(5- 氟 -2- 硝基苯基氨基)-6-(4-(三氟甲基）苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯（483.0 mg，81%）。

[0392] 步骤 2：将用 2-(5- 氟 -2- 硝基苯基氨基)-6-(4-(三氟甲基）苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯（483.0 mg），Pd/C（10%，湿，48.0 mg）和 1:1 乙酸乙酯：甲醇（5 mL）装填的压力反应容器放置在 Parr 振动器上。通过三次真空泵抽和 N_2 吹扫将该混合物脱气。将该容器加压至 40 psi 氢气并振动 2 小时。通过过滤除去炭，并蒸发溶剂以提供 2-(2- 氨基 -5- 氟苯基氨基)-6-(4-(三氟甲基）苯基氨基)- 嘧啶 -4- 基亚氨基二碳酸二叔丁酯。在下一步骤中使用该残余物质而不经进一步纯化。MS *m/z* 579.6（100）$[M+H]^+$，580.6（40）。

[0393] 步骤 3：将 2-(2- 氨基 -5- 氟苯基氨基)-6-(4-(三氟甲基)- 苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯（365.0 mg，0.63 mmol），原乙酸三乙酯（306.0 mg，1.89 mmol），*对甲苯磺酸* (5.0 mg，0.025 mmol）和乙醇（2.0 mL）的混合物加热至回流持续 2 小时。在冷却之后，该混合物在二氯甲烷（20 mL）和饱和 $NaHCO_3$ 溶液 (10 mL) 之间分配。用盐水（10 mL）洗涤有机相，经 $MgSO_4$ 干燥，然后过滤并蒸发。用乙醚研磨残余油以获得 2-(6- 氟 -2- 甲基 -1*H*- 苯并 [*d*] 咪唑 -1- 基)-6-(4-(三氟甲基）苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯（316.0 mg，83%）。MS *m/z* 603.6（100）$[M+H]^+$，604.6（40）。

[0394] 步骤 4：将产物 (316.0 mg，0.52 mmol）在二氯甲烷（3 mL）中的溶液在 0℃下

用 TFA（1 mL）处理。在环境温度下搅拌该所得混合物 4 小时。蒸发溶剂，用乙醚研磨残余物质以获得白色固体形式的标题化合物（152.0 mg，73%）。m.p. 253 - 255℃。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.72 (s, 1H), 8.00 (d, J = 8.51 Hz, 2H), 7.52 - 7.69 (m, 3H), 7.45 (dd, J = 1.89, 9.14 Hz, 1H), 7.01 - 7.24 (m, 3H), 6.20 (s, 1H), 2.66 (s, 3H); MS m/z 403.3 (100) $[M+H]^+$.

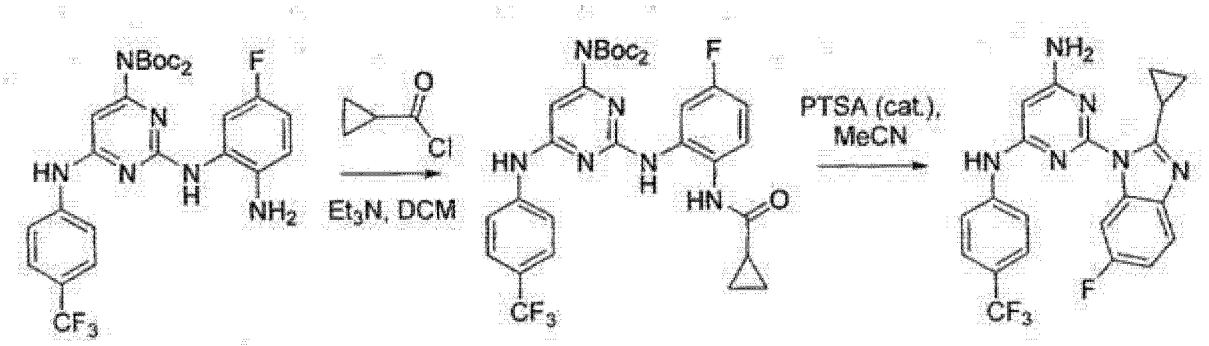
[0395] 可以根据实施例 6 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式（I）化合物或其形式。

Cpd	名称 & 数据
93	**2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.76 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 8.5, 1.9 Hz, 1H), 7.02 (br. s., 2H), 5.90 (s, 1H), 2.83 (s, 3H); MS m/z 419.8 $[M+H]^+$
72	**N-[4-(二氟甲氧基)苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.25 (s, 1H), 7.99 (dd, J = 2.21, 10.09 Hz, 1H), 7.56 (dd, J = 5.04, 8.83 Hz, 1H), 7.48 (d, J = 8.83 Hz, 2H), 7.00 – 7.30 (t, J = 75.00 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.07 (dt, J = 2.36, 9.06 Hz, 1H), 6.84 (br. s., 2H), 5.74 (s, 1H), 2.80 (s, 3H); m.p. 168-170 °C; MS m/z 401.5 $[M+H]^+$
76	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.47 (s, 1H), 7.96 (d, J = 9.14 Hz, 1H), 7.66 (d, J = 12.93 Hz, 1H), 7.57 (dd, J = 5.04, 8.20 Hz, 1H), 7.00 – 7.28 (t, J = 70.00 Hz, 1H), 7.27 - 7.39 (m, 1H), 7.23 (d, J = 8.51 Hz, 1H), 7.08 (t, J = 8.20 Hz, 1H), 6.94 (br. s., 2H), 5.80 (s, 1H), 2.50 (br. s., 3H); m.p. 182-183 °C; MS m/z 419.4 $[M+H]^+$
77	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.47 (br. s., 1H), 7.90 (d, J = 9.14 Hz, 1H), 7.50 - 7.74 (m, 2H), 7.29 (d, J = 5.04 Hz, 1H), 7.00 – 7.28 (t, J = 70.00 Hz, 1H), 7.22 (d, J = 8.20 Hz, 1H), 7.09 (d, J = 7.88 Hz, 1H), 6.93 (br. s., 2H), 5.80 (s, 1H), 3.27 (m,2H), 1.28 (t, J = 6.62 Hz, 3H); m.p. 156-158 °C; MS m/z 433.5 $[M+H]^+$
81	**2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.64 (s, 1H), 7.89 (dd, J = 2.52, 10.09 Hz, 1H), 7.70 (d, J = 8.20 Hz, 2H), 7.58 - 7.66 (m, 3H), 7.05 - 7.13 (m, 1H), 6.98 (br. s., 2H), 5.88 (s, 1H), 3.28 (q, J = 7.46 Hz, 2H), 1.28 (t, J = 7.57 Hz, 3H); m.p. 201-203 °C; MS m/z 417.2 $[M+H]^+$
96	**2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.11 (br. s, 1H), 8.27 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 13.9, 1.6 Hz, 1H), 7.65 (t, J = 8.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 8.5, 1.9 Hz, 1H), 6.57 (br. s., 2H), 6.07 (s, 1H), 2.87 (s, 3H); MS m/z 437.8 $[M+H]^+$

Cpd	名称 & 数据
97	**2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.56 (br. s, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 6.6, 2.2 Hz, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.23 (dd, J = 8.5, 2.2 Hz, 1H), 7.20 (dd, J = 6.6, 2.2 Hz, 2H), 6.94 (t, J = 74.7 Hz, 1H), 6.35 (br. s., 2H), 5.91 (s, 1H), 2.85 (s, 3H); MS *m/z* 418.0 [M+H]$^+$
98	**2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.94 (br. s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.82 (dd, J = 14.3, 1.4 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.42 (dd, J = 8.7, 1.1 Hz, 1H), 7.27 (dd, J = 8.7, 2.0 Hz, 1H), 7.10 (br. s, 2H), 5.93 (s, 1H), 2.83 (s, 3H); MS *m/z* 437.8 [M+H]$^+$
99	**2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (br. s, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 8.00 - 8.03 (m, 2H), 7.65 - 7.67 (m, 2H), 7.64 (dd, J = 8.8, 2.2 Hz, 1H), 7.42 (t, J = 75.0 Hz, 1H), 6.79 (br. s., 2H), 6.38 (s, 1H), 3.32 (s, 3H); MS *m/z* 417.8 [M+H]$^+$
144	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.25 (s, 1H), 7.84 - 8.12 (m, 1H), 7.60 (dd, *J* = 5.04, 8.51 Hz, 1H), 7.49 (d, *J* = 8.83 Hz, 2H), 7.01 – 7.31 (t, J = 75.00 Hz, 1H), 7.15 (d, *J* = 8.20 Hz, 2H), 7.04 - 7.13 (m, 1H), 6.84 (br. s., 2H), 5.76 (s, 1H), 3.28 (q, *J* = 7.25 Hz, 2H), 1.28 (t, *J* = 7.41 Hz, 3H); m.p. 166-168 °C; MS *m/z* 415.4 [M+H]$^+$

[0396] 实施例 7

2-(2- 环丙基 -6- 氟 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺 (Cpd 82)



步骤 1: 在 0℃下向 2-(2- 氨基 -5- 氟苯基氨基)-6-(4-(三氟甲基)- 苯基氨基) 嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (212.0 mg, 0.37 mmol), 三乙胺 (42.0 mg, 0.41 mmol) 在二氯甲烷 (2 mL) 中的溶液中加入环丙烷酰氯 (38.3 mg, 0.37 mmol)。在环境温度下搅拌该混合物 3 小时,然后在二氯甲烷和水之间分配。用盐水洗涤有机层,经 $MgSO_4$干燥,然后过滤并蒸发以提供 2-(2-(环丙烷甲酰胺基)-5- 氟苯基氨基)-6-(4-(三氟甲基) 苯基氨基)- 嘧啶 -4- 基亚氨基二碳酸二叔丁酯。在下一步骤中直接使用残余固体而不经进一步纯化。

[0397] 步骤 2: 在微波炉中在 180℃下将粗 2-(2-(环丙烷甲酰胺基)-5- 氟苯基氨基)-6-(4-(三氟甲基) 苯基氨基)- 嘧啶 -4- 基亚氨基二碳酸二叔丁酯, 对甲苯磺酸

(7.0 mg, 0.037 mmol) 和乙腈 (3 mL) 的混合物加热 30 分钟。该混合物在乙酸乙酯和饱和 $NaHCO_3$溶液之间分配。用盐水洗涤有机层,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余物质 (用 1:1 二氯甲烷:已烷, 然后用 1:5 MeOH: 二氯甲烷中 50% 乙酸乙酯洗脱) 以获得标题化合物 (103.0mg, 65% 对于两步)。m.p. 203 - 206℃。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.49 - 9.59 (m, 1H), 7.70 (td, J = 1.00, 13.24 Hz, 1H), 7.64 (d, J = 8.57 Hz, 2H), 7.49 (d, J = 8.57 Hz, 2H), 7.36 - 7.42 (m, 1H), 6.91 - 6.97 (m, 1H), 6.88 (br. s, 2H), 5.77 (s, 1H), 2.88 - 3.01 (m, 1H), 0.97 - 1.05 (m, 2H), 0.86 - 0.95 (m, 2H); MS m/z 429.2 (100) $[M+H]^+$, 430.2 (20).

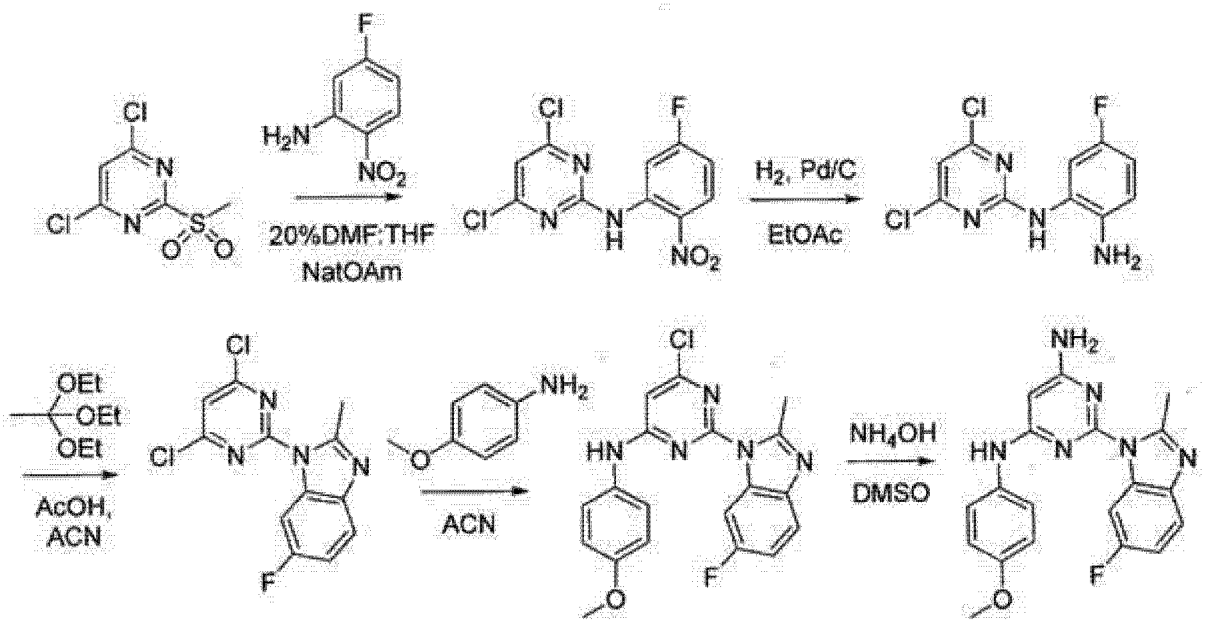
[0398] 可以根据实施例 7 的步骤通过替代合适的起始原料、试剂和反应条件制备本文中所述的另外的式 (I) 化合物或其形式。

Cpd	名称 & 数据
78	**2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 7.70 - 7.95 (m, 2H), 7.52 (dd, J = 5.04, 8.83 Hz, 1H), 7.28 (d, J = 2.52 Hz, 1H), 6.98 – 7.26 (t, J = 70.00 Hz, 1H), 7.22 (m, 1H), 7.03 - 7.09 (m, 1H), 6.98 (br. s, 2H), 5.82 (s, 1H), 3.07 (m, 1H), 1.10 - 1.15 (m, 2H), 1.01 - 1.08 (m, 2H); m.p. 186-188 °C; MS m/z 445.5 $[M+H]^+$
83	**2-(2-环丙基-5-氟-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (s, 1H), 7.96 (d, J = 5.04, 8.83 Hz, 1H), 7.79 (d, J = 8.51 Hz, 2H), 7.61 (d, J = 8.51 Hz, 2H), 7.34 (dd, J = 2.52, 9.46 Hz, 1H), 6.93 - 7.09 (m, 3H), 5.78 - 5.93 (m, 1H), 3.02 (s, 1H), 1.13 - 1.19 (m, 2H), 1.04 - 1.08 (m, 2H); MS m/z 429.2 $[M+H]^+$

Cpd	名称 & 数据
143	**2-(2-环丙基-6-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.30 (s, 1H), 7.83 - 7.90 (m, 1H), 7.54 (d, J = 8.83 Hz, 3H), 7.00 – 7.30 (t, J = 75.00 Hz, 1H), 7.11 - 7.18 (m, 2H), 7.02 - 7.10 (m, 1H), 6.83 - 6.92 (m, 2H), 5.78 (s, 1H), 3.08 - 3.20 (m, 1H), 1.09 - 1.14 (m, 2H), 0.99 - 1.07 (m, 2H); m.p. 175-177 °C; MS m/z 427.2 $[M+H]^+$
145	**N-[4-(二氟甲氧基)苯基]-2-[2-(二氟甲基)-6-氟-1H-苯并咪唑-1-基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.32 (s, 1H), 8.36 (dd, J = 1.89, 10.09 Hz, 1H), 7.95 – 8.16 (t, J = 52.5 Hz, 1H), 7.85 (dd, J = 5.04, 8.83 Hz, 1H), 7.44 (d, J = 8.83 Hz, 2H), 7.04 – 7.34 (t, J = 75.00 Hz, 1H), 7.27 (dt, J = 2.36, 9.06 Hz, 1H), 7.20 (d, J = 8.83 Hz, 2H), 6.98 (br. s., 2H), 5.76 (s, 1H); m.p. 114-115 °C; MS m/z 437.4 $[M+H]^+$
149	**2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.70 (s, 1H), 7.92 - 7.97 (m, 1H), 7.81 (d, J = 8.51 Hz, 2H), 7.60 (d, J = 8.51 Hz, 2H), 7.50 - 7.55 (m, 1H), 7.19 (ddd, J = 1.58, 5.04, 7.25 Hz, 2H), 7.00 (br. s., 2H), 5.90 (s, 1H), 2.94 - 3.03 (m, 1H), 1.15 (m, 2H), 1.05 (m, 2H); m.p. 199-201 °C; MS m/z 411.3 $[M+H]^+$
150	**2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.66 (s, 1H), 8.09 - 8.20 (m, 1H), 7.73 (d, J = 8.51 Hz, 2H), 7.67 - 7.71 (m, 1H), 7.63 (d, J = 8.51 Hz, 2H), 7.26 - 7.31 (m, 2H), 6.97 (br. s., 2H), 5.87 (s, 1H), 5.04 (s, 2H), 3.25 (s, 3H); m.p. 212-213 °C; MS m/z 415.4 $[M+H]^+$
151	**2-[2-(丙-2-基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (s, 1H), 7.85 - 7.91 (m, 1H), 7.74 (d, J = 8.83 Hz, 2H), 7.61 - 7.65 (m, 1H), 7.59 (d, J = 8.83 Hz, 2H), 7.17 - 7.25 (m, 2H), 6.95 (s, 2H), 5.90 (s, 1H), 3.96 - 4.08 (m, 1H), 1.29 (d, J = 6.94 Hz, 6H); m.p. 216-218 °C; MS m/z 413.4 $[M+H]^+$
152	**2-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.71 (s, 1H), 8.36 - 8.52 (m, 1H), 7.89 – 8.11 (t, J = 55.00 Hz, 1H), 7.80 - 7.87 (m, 1H), 7.68 (m. 4H), 7.35 - 7.48 (m, 2H), 6.92 - 7.20 (m, 2H), 5.91 (s, 1H); m.p. 187-188 °C; MS m/z 421.4 $[M+H]^+$

[0399] 实施例 8

2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基)-N-(4- 甲氧基苯基) 嘧啶 -4,6- 二胺 (Cpd 265)



步骤1：在-78℃下向5-氟-2-硝基苯胺（8.16 g，35.93 mmol），4,6-二氯-2-(甲基磺酰基)嘧啶（5.06 g，32.67 mmol），THF（50 mL）和DMF（12 mL）的混合物中逐滴添加叔戊醇钠（2.5 M 在THF中，28.6mL，71.5 mmol）。在-78℃下搅拌该混合物30分钟，然后添加冰/水（300 mL）以形成沉淀物。通过过滤收集固体，然后用水和己烷洗涤以获得4,6-二氯-N-(5-氟-2-硝基苯基)嘧啶-2-胺（9.32 g，95%）。

[0400] 步骤2：通过三次真空泵抽和N_2吹扫循环将用4,6-二氯-N-(5-氟-2-硝基苯基)嘧啶-2-胺（6.35 g，21.03 mmol），Pd/C（10%，湿，635.0 mg）和乙酸乙酯（50 mL）装填的250 mL烧瓶脱气，然后用氢气球中的氢气填充。在环境温度下搅拌该混合物16小时。通过过滤除去碳，蒸发溶剂。用己烷洗涤残余物质以获得白色固体形式的N^1-(4,6-二氯嘧啶-2-基)-5-氟苯-1,2-二胺（5.55 g，97%）。

[0401] 步骤3：将N^1-(4,6-二氯嘧啶-2-基)-5-氟苯-1,2-二胺（2.57 g，9.47 mmol），原乙酸三乙酯（6.06 g，37.87 mmol），乙酸（6 mL）和乙腈（30 mL）的混合物在环境温度下搅拌18小时。在0℃下按份将饱和$NaHCO_3$溶液添加至混合物中，所得混合物冒泡。将该溶液添加至混合物中直到冒泡停止。然后用乙酸乙酯萃取产物。用盐水洗涤有机相，经$MgSO_4$干燥，然后过滤并蒸发。用己烷洗涤残余物质以获得褐色固体形式的1-(4,6-二氯嘧啶-2-基)-6-氟-2-甲基-1H-苯并[d]咪唑（2.41 g，86%）。

[0402] 步骤4：将1-(4,6-二氯嘧啶-2-基)-6-氟-2-甲基-1H-苯并[d]咪唑（150.0 mg，0.51 mmol），4-甲氧基苯胺（125.0 mg，1.01 mmol）和乙腈（1 mL）的混合物在80℃下搅拌18小时。在冷却之后，将乙醚添加至该混合物以形成沉淀物形式的6-氯-2-(6-氟-2-甲基-1H-苯并[d]咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4-胺，其通过过滤分离。

[0403] 步骤5：向6-氯-2-(6-氟-2-甲基-1H-苯并[d]咪唑-1-基)-N-(4-甲氧基苯基)-嘧啶-4-胺中添加DMSO（2 mL）和NH_4OH（27%，0.1 mL）。密封反应混合物，置于微波炉中并在170℃下加热1小时。反应混合物在乙酸乙酯和水之间分配。用水（2 x 20 mL）和盐水洗涤有机层，然后经$MgSO_4$干燥并通过硅胶垫（10 g）过滤。蒸发溶剂，用二氯甲烷

研磨残余物质以获得白色固体形式的标题化合物（161.0 mg，88%）。m.p. 193 - 195℃。

^{1}H NMR (500 MHz, 丙酮 -d_6)□ δ ppm 8.74 (s, 1H), 8.11 (dd, J = 2.52, 10.40 Hz, 1H), 7.52 (dd, J = 5.20, 8.67 Hz, 1H), 7.34 - 7.43 (d, J = 9.14 Hz, 2H), 7.01 (d, J = 2.84 Hz, 1H), 6.94 (d, J = 9.14 Hz, 2H), 6.49 (br. s., 2H), 5.76 (s, 1H), 3.79 (s, 3H), 2.84 (s, 3H); MS *m/z* 365.0 (100) $[M+H]^+$.

[0404] 可以根据实施例 8 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式（I）化合物或其形式。

Cpd	名称 & 数据
52	**2-{[6-{[4-(二氟甲氧基)苯基]氨基}-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}乙醇** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.17 (1H, dd, J = 7.2, 1.5 Hz), 7.59 (1H, dd, J = 7.2, 1.5 Hz), 7.51 (2H, d, J = 9 Hz), 7.28 (1H, m), 7.13 (2H, d, J = 9 Hz), 6.78 (1H, t, J = 75 Hz), 5.81 (1H, s), 3.75 (2H, t, J = 6 Hz), 3.53 (2H, br), 2.89 (3H, s); MS *m/z* 427.1 $[M+H]^+$

Cpd	名称 & 数据
57	**2-{[2-(2-甲基-1H-苯并咪唑-1-基)-6-{[4-(三氟甲基)苯基]氨基}嘧啶-4-基]氨基}乙醇** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.13 (1H, d, J = 7.5 Hz), 7.71 (2H, d, J = 7.5 Hz), 7.6 (1H, dd, J = 9, 1 Hz), 7.56 (2H, d, J = 9 Hz), 7.27 (1H, m), 7.13 (2H, d, J = 9 Hz), 5.91 (1H, s), 3.76 (2H, t, J = 6 Hz), 3.55 (2H, br), 2.89 (3H, s); MS *m/z* 429.2 [M+H]$^+$
58	**N^4-(2-甲氧基乙基)-2-(2-甲基-1H-苯并咪唑-1-基)-N^6-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (甲醇 -d_4) δ ppm 8.15 (1H, d, J = 8 Hz), 7.67 (2H, d, J =8.5 Hz), 7.59 (1H, d, J = 8 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.26 (1H, m), 5.87 (1H, s), 3.58 (4H, br), 3.38 (3H, s).2.87 (3H, s); MS *m/z* 443.1 [M+H]$^+$
59	**N^4-[4-(二氟甲氧基)苯基]-N^6-(2-甲氧基乙基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.06 (1H, d, J = 7 Hz), 7.47 (1H, m), 7.38 (2H, d, J = 9 Hz), 7.15 (1H, m), 7.00 (2H, d, J = 9 Hz), 5.68 (1H, s), 3.28 (3H, s), 2.76 (3H, s); MS *m/z* 441.1 [M+H]$^+$
63	**2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.13 (1H, m), 7.73 (2H, d, J = 8.5 Hz), 7.61 (1H, m), 7.58 (2H, d, J = 8.5 Hz), 7.29 (2H, m), 5.95 (1H, s), 2.89 (3H, s); MS *m/z* 385.1 [M+H]$^+$
64	**2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.19 (1H, dd, J = 11, 7.5 Hz), 7.67 (2H, d, J = 8.5 Hz), 7.6 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 11, 7.5 Hz), 5.93 (1H, s), 2.9 (3H, s); MS *m/z* 421.1 [M+H]$^+$
73	**2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.61 (1H, dd, J = 8, 1.5 Hz), 8.39 (1H, d, J = 4 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.28 (1H, dd, J = 8, 4 Hz), 5.91 (1H, s), 2.97 (3H, s); MS *m/z* 386.2 [M+H]$^+$
74	**2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.04 (1H, dd, J = 11, 7.5 Hz), 7.54 (1H, dd, J = 13.5, 1.5 Hz), 7.44 (1H, t, J = 8.5 Hz), 7.32 (1H, dd, J = 11, 7.5 Hz), 7.24 (1H, dd, J = 13.5, 1.5 Hz), 5.81 (1H, s), 2.78 (3H, s); MS *m/z* 439.1 [M+H]$^+$
79	**N-[4-(三氟甲基)苯基]-2-(2,5,6-三甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (s, 1H), 7.91 (s, 1H), 7.77 (d(AB), J = 8.8 Hz, 2H), 7.63 (d(AB), J = 7.9 Hz, 2H), 7.34 (s, 1H), 6.92 (br. s., 2H), 5.85 (s, 1H), 2.79 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H); MS *m/z* 413.0 [M+H]$^+$

Cpd	名称 & 数据
80	**N-[3-氟-4-(三氟甲基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.90 (s, 1H), 8.05 - 8.10 (m, 1H), 7.89 (d, J = 14.2 Hz, 1H), 7.65 (t, J = 8.7 Hz, 1H), 7.57 - 7.62 (m, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.20 - 7.28 (m, 2H), 7.05 (br. s, 1H), 5.91 (s, 1H), 2.82 (s, 3H); MS *m/z* 403.1 $[M+H]^+$
85	**2-(6-溴-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.73 (d(AB), J = 8.2 Hz, 2H), 7.65 (d(AB), J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 6.97 - 7.07 (m, 2H), 5.87 (s, 1H), 2.83 (s, 3H); MS *m/z* 463.0 $[M+H]^+$
86	**2-(2,6-二甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.63 (s, 1H), 7.88 (s, 1H), 7.74 (d(AB), J = 8.5 Hz, 2H), 7.61 (d(AB), J = 8.5 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 8.2, 1.3 Hz, 1H), 6.93 (br. s., 2H), 5.84 (s, 1H), 2.77 (s, 3H), 2.34 (s, 3H); MS *m/z* 339.0 $[M+H]^+$
87	**2-(6-乙基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 7.89 (s, 1H), 7.77 (d(AB), J = 8.5 Hz, 2H), 7.61 (d(AB), J = 8.8 Hz, 2H), 7.52 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 8.2, 1.3 Hz, 1H), 6.95 (br. s., 2H), 5.86 (s, 1H), 2.81 (s, 3H), 2.64 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H); MS *m/z* 413.0 $[M+H]^+$
88	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 7.85 (dd, J = 9.6, 2.0 Hz, 1H), 7.68 - 7.73 (d(AB), J = 8.5 Hz, 2H), 7.61 - 7.68 (d(AB), J = 8.8 Hz, 2H), 7.14 (td, J = 10.4, 2.2 Hz, 1H), 7.04 (br. s., 2H), 5.89 (s, 1H), 2.83 (s, 3H); MS *m/z* 421 $[M+H]^+$
89	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-N-[3-氟-4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.92 (s, 1H), 7.80 - 7.84 (m, J = 9.5, 2.2 Hz, 1H), 7.80 (dd, J = 14.0, 1.1 Hz, 1H), 7.66 (t, J = 8.7 Hz, 1H), 7.38 (dd, J = 8.5, 1.3 Hz, 1H), 7.16 (dd, J = 10.4, 2.2 Hz, 1H), 7.11 - 7.16 (m, 2H), 5.91 (s, 1H); MS *m/z* 439 $[M+H]^+$
90	**2-{[2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-6-{[4-(三氟甲基)苯基]氨基}嘧啶-4-基]氨基}乙醇** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.69 (br. s., 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.70 (d(AB), J = 7.9 Hz, 2H), 7.64 (d(AB), J = 8.8 Hz, 2H), 7.15 (td, J = 10.3, 2.4 Hz, 1H), 5.96 (br. s, 1H), 4.83 (br. s, 1H), 3.59 (q, J = 5.7 Hz, 2H), 3.38 - 3.51 (m, 2H), 2.85 (s, 3H); MS *m/z* 465.0 $[M+H]^+$

Cpd	名称 & 数据
91	**2-(6-乙烯基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 8.4, 1.4 Hz, 1H), 6.98 (br. s., 1H), 6.75 (dd, J = 17.7, 11.0 Hz, 1H), 5.87 (s, 1H), 5.64 (dd, J = 17.7, 0.6 Hz, 1H), 5.13 (dd, J = 11.0, 0.9 Hz, 1H), 2.82 (s, 1H); MS *m/z* 399 [M+H]$^+$
92	**2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.37 (1H, dd, J = 9, 3 Hz), 8.3 (1H, m), 7.72 (2H, d, J = 8.5 Hz), 7.6 (2H, d, J = 8.5 Hz), 5.96 (1H, s), 1.33 (2H, m), 1.19 (2H, m); MS *m/z* 430.1 [M+H]$^+$
94	**2-(6-氟-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.52 (1H, dd, J = 9, 3 Hz), 8.33 (1H, dd, m), 7.65 (2H, d, J = 9 Hz), 7.60 (2H, d, J = 9 Hz), 5.95 (1H, s), 3.00 (3H, s); MS *m/z* 404.2 [M+H]$^+$
101	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.19 (1H, dd, J = 11, 7.5 Hz), 7.53 (1H, dd, J = 13, 2.5 Hz), 7.44 (1H, dd, J = 10, 7.5 Hz), 7.23 (2H, m), 5.86 (1H, s), 2.89 (3H, s); MS *m/z* 437.1 [M+H]$^+$
102	**N-[4-(二氟甲氧基)苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (甲醇 -d_4) δ ppm 8.18 (1H, dd, J = 11.5, 7.5 Hz), 7.44 (2H, d, J = 9 Hz), 7.40 (1H, dd, J = 11.5, 7.5 Hz), 7.14 (2H, d, 9 Hz), 6.77 (1H, t, J = 75 Hz), 5.79 (1H, s), 2.87 (1H, s); MS *m/z* 419.1 [M+H]$^+$
103	**2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.38 (1H, dd, J = 9, 3 Hz), 8.29 (1H, m), 7.5 (2H, d, J = 9 Hz), 7.14 (2H, d, J = 7 Hz), 6.78 (1H, t, J = 75 Hz), 3.4 (1H, m), 1.3 (2H, m), 1.17 (2H, m); MS *m/z* 428.1 [M+H]$^+$
104	**2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.77 (d, *J*=2.21 Hz, 1H), 8.43 (d, *J*=2.21 Hz, 1H), 7.60 (d, *J*=6.94 Hz, 4H), 5.91 (s, 1H) 3.05 (s, 3H); MS *m/z* 420.1 [M+H]$^+$
105	**2-(6-氯-2-乙基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.66 (d, *J*=2.52 Hz, 1H), 8.38 (d, *J*=2.21 Hz, 1H), 7.62 (dd, *J*=19.50, 9.50 Hz, 4H), 5.92 (s, 1H), 3.48 (q, *J*=7.60 Hz, 2H), 1.39 (t, *J*=7.41 Hz, 3H); MS *m/z* 434.1 [M+H]$^+$

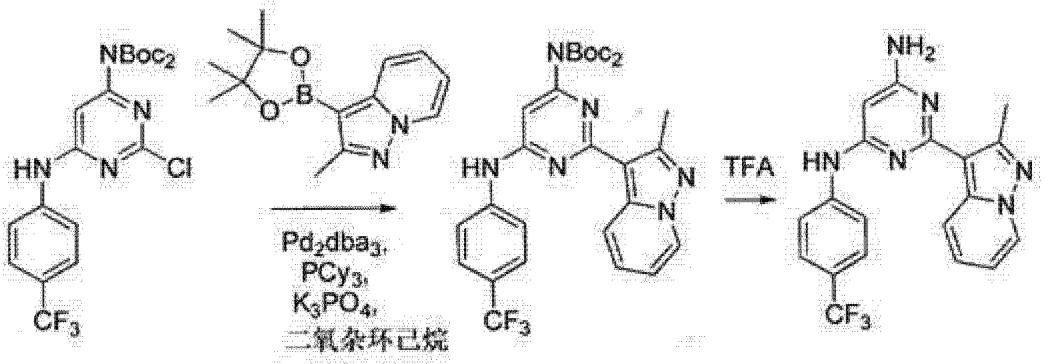
Cpd	名称 & 数据
146	**2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(甲基硫烷基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.45 - 8.50 (1H, s) 8.25 - 8.30 (1H, m) 7.55 - 7.59 (1H, m) 7.50 (2H, s) 7.32 (2H, s) 7.17 - 7.25 (2H, m) 6.24 - 6.33 (2H, m) 5.92 (1H, s) 2.51 (3H, s) 2.07 (3H, s); MS *m/z* 363.2 $[M+H]^+$
147	**2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.72 - 8.80 (1H, s) 7.66 - 7.76 (3H, m) 7.46 (3H, d, *J*=0.63 Hz) 7.08 (2 H, s) 6.18 - 6.28 (2H, m) 5.97 (1H,s) 1.30 (3H, s) 1.10 (2H, s) 0.61 (2H, d, *J*=2.21 Hz); MS *m/z* 425.2 $[M+H]^+$
148	**N-[4-(二氟甲氧基)苯基]-2-[2-(1-甲基环丙基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ □ppm 8.49 (1H, s) 8.16 - 8.20 (1H, m) 7.55 - 7.60 (3H, m) 7.15 - 7.23 (4H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.27 (2H, br. s.) 5.92 (1H, s) 3.32 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=6.90 Hz); MS *m/z* 423.3 $[M+H]^+$
153	**2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.66 (s, 1H), 7.96 - 8.10 (m, 1H), 7.73 (d, *J* = 8.83 Hz, 2H), 7.58 - 7.64 (m, 3H), 7.18 - 7.26 (m, 2H), 6.96 (br. s, 2H), 5.88 (s, 1H), 3.22 - 3.29 (m, 2H), 1.29 (t, *J* = 7.41 Hz, 3H); m.p. 183-185 ; MS *m/z* 415.4 (100) $[M+H]^+$, 416.4 (30)
156	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.49 (1H, s) 8.16 - 8.20 (1H, m) 7.55 - 7.60 (3H, m) 7.15 - 7.23 (4H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.27 (2H, br. s.) 5.92 (1H, s) 3.32 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=6.90 Hz); MS *m/z* 397.2 $[M+H]^+$
157	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.71 (1H, s) 8.13 - 8.18 (1H, m) 7.68 - 7.75 (1H, m) 7.57 - 7.62 (1H, m) 7.26 - 7.35 (2H, m) 7.16 - 7.25 (2H, m) 6.94 (1H, t, *J*=73.80 Hz) 6.36 (2H, s) 5.98 (1H, s) 3.33 (2H, q, *J*=7.60 Hz) 1.35 (3H, t, *J*=7.90 Hz); MS *m/z* 415.2 $[M+H]^+$
182	**2-[2-(甲基硫烷基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (br. s., 1H) 8.38 (d, *J*=7.88 Hz, 1H), 7.83 (d, *J*=8.51 Hz, 2H), 7.66 (d, *J*=8.51 Hz, 2H), 7.56 (d, *J*=7.57 Hz, 1H), 7.23 (td, *J*=7.57, 1.26 Hz, 1H), 7.13 - 7.19 (m, 1H), 6.41 (br. s., 2H), 6.02 (s, 1H), 2.63 (s, 3 H); MS *m/z* 418.3 $[M+H]^+$
196	**2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.13 (1H, m), 7.58 (1H, m), 7.3-7.25 (4H, m), 7.13 (1H, d, J = 8 Hz), 5.81 (1H, s), 2.86 (3H, s), 2.31 (3H, s); MS *m/z* 331.1 $[M+H]^+$
197	**N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.13 (1H, m), 7.58 (1H, m), 7.33 (2H, d, J = 9 Hz), 7.27 (2H, m), 6.94 (2H, d, J = 9 Hz), 5.72 (1H, s), 3.81 (3H, s), 2.86 (3H, s); MS *m/z* 347.1 $[M+H]^+$

Cpd	名称 & 数据
198	**N-[4-(二甲基氨基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.12 (1H, m), 7.58 (1H, m), 7.27 (2H, m), 7.22 (2H, d, J = 9 Hz), 6.81 (2H, d, J = 9 Hz), 5.67 (1H, s), 2.92 (6H, s), 2.86 (3H, s); MS *m/z* 360.4 $[M+H]^+$
205	**N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.04 (1H, s), 8.20-8.17 (1H, m), 7.61-7.58 (1H, m), 7.27-7.21 (2H, m), 7.15 (1H, d, J = 1.8 Hz), 6.91 (1H, d, J = 8.2 Hz), 6.86 (1H, dd, J = 8.2, 1.8 Hz), 6.76 (2H, br s), 6.03 (2H, s), 5.72 (1H, s), 2.84 (3H, s); m.p. 166-167; MS *m/z* 359.1 $[M+H]^+$
206	**N-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.40 (1H, s), 8.13 (1H, dd, J = 7.0, 1.2 Hz), 7.71 (1H, d, J = 2.1 Hz), 7.61 (1H, dd, J = 7.0, 1.2 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.28-7.20 (3H, m), 6.88 (2H, br s), 5.79 (1H, s), 2.83 (3H, s); m.p.: 141-142; MS *m/z* 397.1 $[M+H]^+$
207	**N-(3-氟-4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.19 (1H, s), 8.18-8.15 (1H, m), 7.62-7.59 (1H, m), 7.50 (1H, dd, J = 13.6, 2.2 Hz), 7.28-7.13 (4H, m), 6.82 (2H, br s), 5.76 (1H, s), 3.85 (3H, s), 2.84 (3H, s); m.p.: 233-234; MS *m/z* 365.2 $[M+H]^+$
208	**N-(6-甲氧基吡啶-3-基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.10 (1H, s), 8.24 (1H, d, J = 2.6 Hz), 8.14 (1H, dd, J = 8.4, 1.2 Hz), 7.84 (1H, dd, J = 8.8, 2.7 Hz), 7.59 (1H, dd, J = 8.4, 1.5 Hz), 7.27-7.20 (2H, m), 6.85 (1H, d, J = 8.8 Hz), 6.80 (2H, br s), 5.69 (1H, s), 3.87 (3H, s), 2.80 (3H, s); m.p.: 118-119; MS *m/z* 348.2 $[M+H]^+$
209	**N-(4-氯苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.11 (1H, m), 7.58 (1H, m), 7.45 (2H, d, J = 9 Hz), 7.28-7.23 (4H, m), 5.83 (1H, s), 2.85 (3H, s); MS *m/z* 351.6 $[M+H]^+$
210	**4-{[6-氨基-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.1 (1H, m), 7.75 (2H, d, J = 9 Hz), 7.61 (3H, m), 7.28 (2H, m), 5.95 (1H, s), 2.88 (3H, s); MS *m/z* 342.3 $[M+H]^+$
211	**2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-硝基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.16 (2H, m), 8.12 (1H, m), 7.79 (2H, m), 7.62 (1H, m), 7.29 (2H, m), 5.99 (1H, s), 2.90 (3H, s); MS *m/z* 362.3 $[M+H]^+$
212	**N-(4-溴苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.11 (1H, m), 7.59 (1H, m), 7.42 (4H, m), 7.27 (2H, m), 5.84 (1H, s), 2.86 (3H, s); MS *m/z* 397.0 $[M+H]^+$
221	**2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.11 (1H, m), 7.57 (1H, m), 7.54 (2H, d, 9 Hz), 7.24 (2H, m), 7.19 (2H, d, J = 9 Hz), 5.84 (1H, S), 2.85 (3H, s); MS *m/z* 401.0 $[M+H]^+$

Cpd	名称 & 数据
234	**N-[4-(二氟甲氧基)苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.11 (1H, m), 7.57 (1H, m), 7.45 (2H, d, 7 Hz), 7.25 (2H, m), 7.09 (2H, d, J = 9 Hz), 5.48 (1H, S), 2.85 (3H, s); MS *m/z* 383.1 [M+H]$^+$
235	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 甲醇 -d_4) δ ppm 8.10 (1H, m), 7.58-7.54 (2H, m), 7.27-7.14 (4H, m), 5.47 (1H, s), 2.85 (3H, s); MS *m/z* 401.0 [M+H]$^+$
263	**N-(4-氯苯基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.59 (s, 1H), 8.05 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.47 - 7.61 (m, 4H), 7.31 - 7.42 (m, 2H), 6.92 - 7.08 (m, 1H), 6.37 (br. s., 1H), 5.93 (s, 1H), 2.77 - 2.88 (m, 3H); m.p.: 183-185; MS *m/z* 369.0 [M+H]$^+$
264	**2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.37 (br. s., 1H), 8.10 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.52 (dd, *J* = 5.04, 8.83 Hz, 1H), 7.34 (d, *J* = 8.20 Hz, 2H), 7.18 (d, *J* = 8.20 Hz, 2H), 6.94 - 7.07 (m, 1H), 6.27 (br. s., 2H), 5.82 - 5.96 (m, 1H), 2.85 (s, 3H), 2.32 (s, 3H); m.p.: 210-212; MS *m/z* 349.0 [M+H]$^+$
266	**N-[4-(二甲基氨基)苯基]-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.11 - 8.16 (m, 1H), 8.07 - 8.10 (m, 1H), 7.47 - 7.56 (m, 1H), 7.23 (d, *J* = 9.77 Hz, 2H), 6.94 - 7.05 (m, 1H), 6.79 (d, *J* = 8.83 Hz, 2H), 6.09 - 6.25 (br, s, 2H), 5.67 (s, 1H), 2.94 (s, 6H), 2.85 (s, 3H); m.p.: 122-125; MS *m/z* 378.0 [M+H]$^+$
267	**N-(4-氯-3-氟苯基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.80 (s, 1H), 8.03 (dd, *J* = 2.52, 10.09 Hz, 1H), 7.67 (dd, *J* = 2.36, 11.82 Hz, 1H), 7.54 (dd, *J* = 5.04, 8.51 Hz, 1H), 7.44 (t, *J* = 8.67 Hz, 1H), 7.27 - 7.37 (m, 1H), 6.95 - 7.09 (m, 1H), 6.46 (br. s., 2H), 5.99 (s, 1H), 2.85 (s, 3H); m.p.: 225-227; MS *m/z* 387.0 [M+H]$^+$
268	**2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(3-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.37 - 8.52 (m, 1H), 8.14 (dd, *J* = 2.68, 10.25 Hz, 1H), 7.55 (dd, *J* = 5.20, 8.67 Hz, 1H), 7.40 (br. s., 1H), 7.22 - 7.30 (m, 2H), 7.00 - 7.11 (m, 1H), 6.94 (d, *J* = 6.62 Hz, 1H), 6.27 - 6.40 (s, 2H), 5.91 - 6.06 (s, 1H), 2.89 (s, 3H), 2.34 (s, 3H); m.p.: 203-205; MS *m/z* 349.0 [M+H]$^+$
269	**N-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.62 (s, 1H), 8.04 (dd, *J* = 2.52, 10.40 Hz, 1H), 7.56 (d, *J* = 1.89 Hz, 1H), 7.53 (dd, *J* = 5.04, 8.83 Hz, 1H), 7.21 - 7.29 (m, 2H), 6.97 - 7.05 (m, 1H), 6.38 (br. s., 2H), 5.91 (s, 1H), 2.83 (s, 3H); m.p.: 212-215; MS *m/z* 415.0 [M+H]$^+$

[0405] 实施例 9

2-(2- 甲基吡唑并 [1,5-a] 吡啶 -3- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺 (Cpd 154)



通过用氩气吹扫将 2- 甲基 -3-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼杂环戊烷 -2- 基）吡唑并 [1,5-a] 吡啶 (53 mg, 0.205 mmol), 2- 氯 -6-(4-(三氟甲基）苯基氨基）嘧啶 -4- 基亚氨基二碳酸二叔丁酯 (110 mg, 0.225 mmol), 三（二苄叉基丙酮） 二钯 (0) (18 mg, 0.02 mmol) 三环己基膦 (14 mg, 0.051 mmol), 和磷酸钾 (87.0 mg, 0.41 mmol) 在二氧杂环己烷 (3.5 mL) 和水 (0.1 mL) 中的混合物脱气，然后在 85℃下加热 3 小时。将该溶液冷却并通过 Celite 塞过滤。将滤液浓缩并通过硅胶柱层析法纯化，提供清澈油形式的 3,3- 二甲基丁酰基 (2-(2- 甲基吡唑并 [1,5-a] 吡啶 -3- 基）-6-(4-(三氟甲基）苯基氨基）- 嘧啶 -4- 基）氨基甲酸叔丁酯 (25mg, 21%)，其溶解在二氯甲烷 (1 mL) 中并在 0℃下用 TFA (0.1 mL) 处理。在室温下搅拌所得混合物 4 小时。浓缩溶剂，残余材料在乙酸乙酯和饱和 $NaHCO_3$溶液之间分配。分离有机层，经 Na_2SO_4干燥，然后过滤并蒸发。用乙醚研磨残余物质以获得黄色固体形式的标题化合物 (8 mg, 50%)。

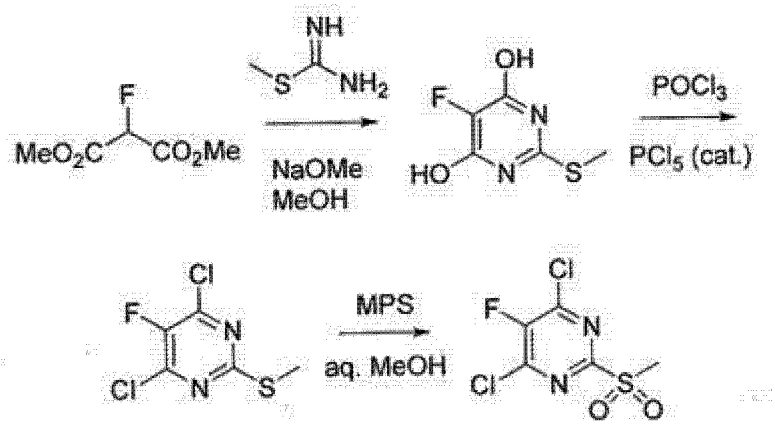
^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.55 (d, J = 8.8 Hz, 1H), 8.42 (br. s., 1H), 8.37 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.13 (ddd, J = 8.4, 7.3, 0.8 Hz, 1H), 6.77 (td, J = 6.6, 1.6 Hz, 1H), 5.82 (br. s., 2H), 5.77 (s, 1H), 2.66 (s, 3H); MS *m/z* 385.3 [M+H]$^+$.

[0406] 可以根据实施例 9 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 & 数据
70	N-[4-(三氟甲基)苯基]-2-(1,3,5-三甲基-1H-吡唑-4-基)嘧啶-4,6-二胺 ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.54 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz), 5.86 (1H, s), 5.60 (2H, v br), 3.73 (3H, s), 2.53 (3H, s), 2.50 (3H, s); m.p. 270-271 °C; MS *m/z* 363.0 [M+H]$^+$

[0407] 实施例 10

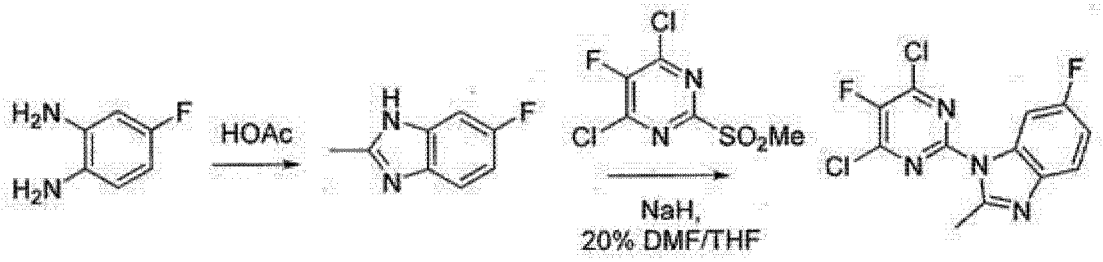
5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并咪唑 -1- 基）-N-(4- 甲氧基苯基）嘧啶 -4,6- 二胺 (Cpd 179)



步骤 1. 在 0℃下向甲基异硫脲 -$(H_2SO_4)_{1/2}$盐 (45.90 g, 0.33 mol) 和 2- 氟丙二酸二甲酯 (45.03 g, 0.30 mol) 在 MeOH (450 mL) 溶液中缓慢添加甲醇钠 (4.37 M 在 MeOH 中, 226 mL, 0.99 mol)。在室温下搅拌该混合物 16 小时。在减压下浓缩该溶液。用水 (50 mL) 稀释所得浆液并使用 6N HCl 溶液酸化至约 pH 2。收集所得沉淀物,用水洗涤并在真空下干燥以提供 5- 氟 -2-(甲硫基) 嘧啶 -4,6- 二醇 (46.85 g, 88%)。

[0408] 向 5- 氟 -2-(甲硫基) 嘧啶 -4,6- 二醇 (13.2 g, 74.9 mmol) 在 $POCl_3$ (60 mL) 中的溶液中添加催化剂量的 PCl_5 (60 mg)。在 100℃ 下加热该混合物 16 小时,然后在减压下浓缩。向该混合物中小心添加冰水 (150 mL)。通过过滤除去所得沉淀物,用水洗涤,然后在氮气下干燥以提供 4,6- 二氯 -5- 氟 -2-(甲硫基) 嘧啶 (13.5 g, 85%)。

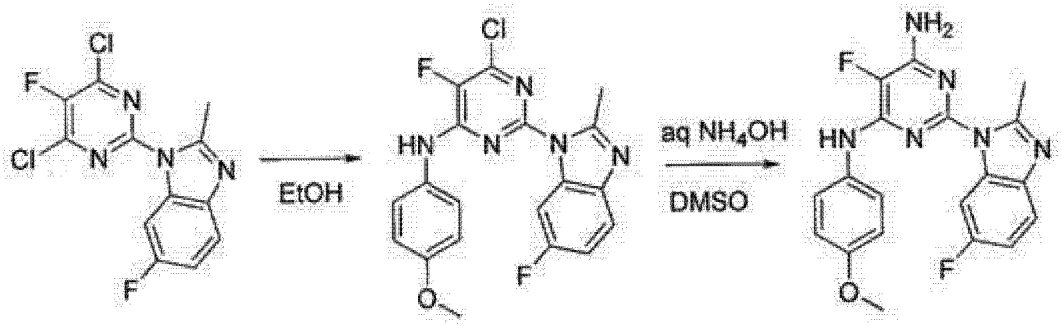
[0409] 向 4,6- 二氯 -5- 氟 -2-(甲硫基) 嘧啶 (12.4 g, 58.8 mmol) 在 MeOH (150 mL) 中的溶液中添加过一硫酸钾 ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (108.7 g, 176.4 mmol) 和水 (70 mL)。在室温下搅拌该混合物 6 小时。通过过滤除去盐,然后用 MeOH 洗涤直到没有观察到更多的产物。将合并的有机混合物浓缩,然后添加冰水至混合物中以提供沉淀物,其被过滤并用水洗涤。在氮气下干燥固体以获得白色固体形式的 4,6- 二氯 -5- 氟 -2-(甲基磺酰基) 嘧啶 (14.6 g, 99%)。



[0410] 步骤 2. 在 180℃下微波处理 4- 氟苯 -1,2- 二胺 (3.78 g, 30 mmol) 在乙酸 (10.0 mL) 中的溶液 1 小时。在减压下浓缩该混合物并用乙醚研磨以获得褐色固体形式的 6- 氟 -2- 甲基 -1H- 苯并 [d] 咪唑 (4.31 g, 88%)。

[0411] 在 -78℃下向 6- 氟 -2- 甲基 -1H- 苯并 [d] 咪唑 (2.31 g, 15.4 mmol) 在 THF (50 mL) 和 DMF (10 mL) 的溶液中添加 60% NaH (648 mg, 16.2 mmol)。在室温下搅拌该混合物约 10 分钟。在 -78℃下向混合物中一次性添加 4,6- 二氯 -5- 氟 -2-(甲基磺酰基) 嘧啶 (3.74 g, 15.3 mmol),然后在 -78℃ 下搅拌该混合物 15 分钟。用 1M HCl 溶液 (18 mL) 淬火该反应混合物并用 EtOAc (200 mL) 萃取粗混合物。在减压下浓缩有机层,并

通过柱层析法纯化（5~30% EtOAc/ 己烷）以提供白色固体形式的 1-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-6- 氟 -2- 甲基 -1H- 苯并 [d] 咪唑（1.83 g，38%）。



[0412] 步骤 3. 在 60℃ 下将 1-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-6- 氟 -2- 甲基 -1H- 苯并 [d]- 咪唑（63 mg，0.2 mmol）和 4- 甲氧基苯胺（49 mg，0.4 mmol）在 EtOH（1 mL）中的混合物搅拌 1 小时。通过添加水（10 mL）获得沉淀物。通过过滤除去产物 (6- 氯 -5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并 [d] 咪唑 -1- 基)-N-(4- 甲氧基苯基)- 嘧啶 -4- 胺) 并用水洗涤几次。在接下来步骤中使用所得粗 6- 氯 -5- 氟 -2-(6- 氟 -2- 甲基 -1H- 苯并 [d] 咪唑 -1- 基)-N-(4- 甲氧基苯基) 嘧啶 -4- 胺而不经进一步处理。

[0413] 向 DMSO 中的粗产物 (5 mL) 中添加 14 M NH_4OH 水溶液（3 mL）。在 100℃下加热悬浮混合物 18 小时直到消耗所有起始原料。在冷却至室温之后，添加水 (10 mL) 至混合物中形成沉淀物。通过过滤分离沉淀物并用水洗涤几次。在氮气下干燥所得产物以提供灰白色固体形式的标题化合物 (72 mg，94%)。

^{1}H NMR (500 MHz，丙酮 -d_6) δ ppm 8.30 (1H, br. s.) 7.94 (1H, dd, *J*=9.93, 2.36 Hz) 7.48 - 7.56 (3H, m) 6.93 - 7.05 (3H, m) 6.48 (2H, br. s.) 3.83 (3H, s) 2.75 (3H, s); MS *m/z* 383.2 $[M+H]^+$.

[0414] 可以根据实施例 10 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 & 数据
95	**5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.60 (1H, s) 8.02 (1H, dd, *J*=7.25, 2.21 Hz) 7.86 (2H, d, *J*=8.51 Hz) 7.65 (2H, d, *J*=8.51 Hz) 7.56 - 7.60 (1H, m) 7.29 (2 H, s) 7.17 - 7.26 (2H, m) 2.75 (3H, s); MS *m/z* 403.2 $[M+H]^+$

Cpd	名称 & 数据
106	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.39 (1H, s) 7.97 (1H, d, *J*=7.88 Hz) 7.59 - 7.64 (2H, m) 7.42 (1H, d, *J*=7.25 Hz) 7.01 - 7.11 (4H, m) 6.83 (1H, t, *J*=74.56 Hz) 6.40 (2H, br. s.) 2.63 (3H, s); MS *m/z* 401.1 $[M+H]^+$
107	**2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.69 (1H, br. s.) 7.91 (1H, d, *J*=7.88 Hz) 7.85 (2H, d, *J*=8.51 Hz) 7.53 (2H, d, *J*=8.51 Hz) 7.47 (1H, d, *J*=6.94 Hz) 7.02 - 7.13 (2H, m) 6.54 (2H, br. s.) 3.14 (2H, q, *J*=7.36 Hz) 1.20 (3H, t); MS *m/z* 417.1 $[M+H]^+$
108	**5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (1H, br. s.) 8.13 (1H, dd, *J*=9.46, 5.04 Hz) 7.98 (2H, d, *J*=8.51 Hz) 7.71 (2H, d, *J*=8.51 Hz) 7.31 (1H, dd, *J*=9.62, 2.36 Hz) 6.96 - 7.04 (1H, m) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 421.1 $[M+H]^+$
109	**5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (1H, br. s.) 7.89 - 8.00 (3H, m) 7.71 (2H, d, *J*=8.51 Hz) 7.56 (1H, dd, *J*=8.83, 5.04 Hz) 7.02 - 7.08 (1H, m) 6.76 (2H, br. s.) 2.82 (3H, s); MS *m/z* 421.1 $[M+H]^+$
110	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.01 (1H, dd, *J*=10.40, 2.21 Hz) 7.81 (1H, br. s.) 7.68 - 7.72 (2H, m) 7.65 (1H, dd, *J*=8.83, 5.04 Hz) 7.26 - 7.31 (2H, m) 7.12 - 7.18 (1H, m) 6.87 (1H, t, *J*=74.56 Hz) 5.87 (2H, br. s.) 2.87 (3H, s); MS *m/z* 419.1 $[M+H]^+$
111	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.73 (1H, s) 7.93 (1H, dd, *J*=9.93, 2.36 Hz) 7.80 (1H, dd, *J*=12.93, 2.52 Hz) 7.51 - 7.59 (2H, m) 7.36 (1 H, t, *J*=8.99 Hz) 7.01 - 7.08 (1H, m) 6.98 (1H, t, *J*=73.77 Hz) 6.71 (2H, br. s.) 2.81 (3H, s); MS *m/z* 437.1 $[M+H]^+$
112	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.19 (1H, dd, *J*=9.46, 5.04 Hz) 7.94 (1H, br. s.) 7.79 (1H, dd, *J*=12.93, 2.52 Hz) 7.35 - 7.50 (3H, m) 7.09 - 7.16 (1H, m) 6.87 (1H, t, *J*=73.77 Hz) 5.91 (2H, s) 2.90 (3H, s); MS *m/z* 437.2 $[M+H]^+$
113	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.19 (1H, dd, *J*=9.46, 5.04 Hz) 7.81 (1H, br. s.) 7.67 - 7.74 (2H, m) 7.42 (1H, dd, *J*=9.46, 2.84 Hz) 7.25 - 7.32 (2H, m) 7.07 - 7.16 (1H, m) 6.88 (1H, t, *J*=74.56 Hz) 5.84 (2H, s) 2.88 (3H, s); MS *m/z* 419.1 $[M+H]^+$

Cpd	名称 & 数据
114	**2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.91 (1H, s) 8.57 - 8.58 (1H, m) 8.39 (1H, d, *J*=2.21 Hz) 7.93 (2H, d, *J*=8.51 Hz) 7.75 (2H, d, *J*=8.51 Hz) 6.83 (2H, br. s.) 2.93 (3H, s); MS *m/z* 438.3 [M+H]$^+$
115	**2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.47 (1H, br. s.) 8.41 (1H, d, *J*=2.21 Hz) 8.23 (1H, d, *J*=2.52 Hz) 7.55 (2H, d, *J*=8.83 Hz) 7.11 (2H, d, *J*=9.14 Hz) 6.85 (1H, t, *J*=74.10 Hz) 6.55 (2H, br. s.) 2.74 (3H, s); MS *m/z* 436.2 [M+H]$^+$
116	**2-(6-氯-2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.77 (1H, s) 8.56 (1H, d, *J*=2.21 Hz) 7.73 (1H, dd, *J*=12.61, 2.52 Hz) 7.50 - 7.56 (1H, m) 7.39 (1H, t, *J*=8.99 Hz) 7.00 (1H, t, *J*=73.61 Hz) 6.79 (2H, br. s.) 2.91 (3H, s); MS *m/z* 454.1 [M+H]$^+$
117	**2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.90 (1H, s) 8.22 - 8.34 (2 H, m) 7.99 (2H, d, *J*=8.20 Hz) 7.71 (2H, d, *J*=8.20 Hz) 6.84 (2H, br. s.) 3.20 - 3.29 (1H, m) 1.26 - 1.34 (2H, m) 1.06 - 1.12 (2H, m); MS *m/z* 448.1 [M+H]$^+$
119	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.71 (1H, br. s.) 8.12 (1H, d, *J*=8.51 Hz) 7.87 (1H, dd, *J*=13.08, 2.68 Hz) 7.52 - 7.62 (2H, m) 7.34 (1H, t, *J*=8.99 Hz) 7.17 - 7.27 (2H, m) 6.98 (1H, t, *J*=73.93 Hz) 6.65 (2H, br. s.) 2.81 (3H, s); MS *m/z* 419.3 [M+H]$^+$
120	**2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (1H, br. s.) 8.06 (2H, d, *J*=8.51 Hz) 8.00 (1H, dd, *J*=7.25, 1.26 Hz) 7.67 (2H, d, *J*=8.51 Hz) 7.50 - 7.56 (1H, m) 7.14 - 7.25 (2H, m) 6.70 (2H, br. s.) 2.96 - 3.05 (1H, m) 1.20 - 1.26 (2H, m) 1.00 - 1.06 (2H, m); MS *m/z* 429.2 [M+H]$^+$
121	**2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.40 (1H, s) 7.86 (1H, dd, *J*=7.72, 1.73 Hz) 7.63 - 7.70 (2H, m) 7.36 (1H, d, *J*=9.14 Hz) 6.98 - 7.08 (4H, m) 6.64 - 6.97 (1H, m) 6.41 (2H, s) 2.83 - 2.91 (1H, m) 1.01 - 1.07 (2H, m) 0.80 - 0.87 (2H, m); MS *m/z* 427.2 [M+H]$^+$

Cpd	名称 & 数据
122	**2-(2-环丙基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.73 (1H, s) 7.96 - 8.03 (2H, m) 7.50 - 7.60 (2H, m) 7.32 (1H, t, *J*=8.83 Hz) 7.20 (2H, dtd, *J*=19.70, 7.33, 7.33, 1.26 Hz) 6.80 - 7.13 (2H, m) 6.66 (2H, s) 2.97 - 3.05 (1H, m) 1.23 (2H, dd, *J*=5.04, 2.84 Hz) 1.01 - 1.08 (2H, m); MS *m/z* 445.2 [M+H]$^+$
123	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.52 - 8.56 (1H, s) 8.04 - 8.09 (1H, m) 7.76 (2H, d, *J*=9.14 Hz) 7.57 - 7.61 (1H, m) 7.19 (4H, d, *J*=8.83 Hz) 6.97 (1H, m) 6.49 - 6.58 (2H, s) 3.25 (2H, d, *J*=7.57 Hz) 1.29 - 1.34 (3H, m); MS *m/z* 415.3 [M+H]$^+$
124	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.72 (1H, s) 8.05 - 8.09 (1H, m) 7.87 (1H, dd, *J*=12.93, 2.52 Hz) 7.59 - 7.63 (1H, m) 7.54 (1H, ddd, *J*=8.91, 2.60, 1.42 Hz) 7.33 (1H, t, *J*=8.83 Hz) 7.18 - 7.27 (2H, m) 6.98 (1H, t, *J*=74.70 Hz) 6.64 (2H, s) 3.28 (2H, q, *J*=7.36 Hz) 1.35 (3H, t, *J*=7.90 Hz); MS *m/z* 433.3 [M+H]$^+$
125	**2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.69 - 8.75 (1H, m) 7.97 - 8.04 (1H, m) 7.76 - 7.83 (2H, m) 7.55 - 7.61 (2H, m) 7.30 - 7.37 (1H, m) 6.59 - 6.69 (2H, m) 2.68 (3H, s); MS *m/z* 439.2 [M+H]$^+$
126	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.72 - 8.76 (1H, m) 8.12 - 8.18 (1H, m) 7.74 - 7.80 (1H, m) 7.45 - 7.55 (2H, m) 7.34 - 7.40 (1H, m) 6.90 - 7.05 (1H, m) 6.69 - 6.78 (2H, m) 2.82 (3H, s); MS *m/z* 455.2 [M+H]$^+$
127	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 - 8.90 (1H, m) 7.93 - 7.99 (2H, m) 7.77 - 7.82 (1H, m) 7.72 (2H, s) 6.90 - 6.97 (1H, m) 6.73 - 6.84 (2H, m) 2.83 (3H, s); MS *m/z* 439.2 [M+H]$^+$
128	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.71 - 8.79 (1H, m) 7.74 - 7.82 (2H, m) 7.48 - 7.55 (1H, m) 7.33 - 7.40 (1H, m) 6.83 - 7.15 (3H, m) 6.70 - 6.79 (2H, m) 2.82 (3H, s); MS *m/z* 455.2 [M+H]$^+$

Cpd	名称 & 数据
129	**2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.89 (1H, s) 7.95 (2H, d, *J*=8.51 Hz) 7.66 - 7.77 (3H, m) 6.90 - 6.98 (1H, m) 6.79 (2H, br. s.) 3.30 (2H, q, *J*=7.57 Hz) 1.34 (3H, t, *J*=7.41 Hz); MS *m/z* 453.2 $[M+H]^+$
130	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.75 (1H, s) 7.72 - 7.81 (2H, m) 7.51 (1H, ddd, *J*=8.91, 2.60, 1.42 Hz) 7.35 (1H, t, *J*=8.83 Hz) 6.81 - 7.14 (2H, m) 6.74 (2H, br. s.) 3.28 (2H, q, *J*=7.25 Hz) 1.34 (3H, t, *J*=7.41 Hz); MS *m/z* 469.2 $[M+H]^+$
131	**N-[4-(二氟甲氧基)苯基]-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.59 (1H, s) 7.79 (1H, ddd, *J*=9.85, 2.44, 0.95 Hz) 7.69 - 7.74 (2H, m) 7.20 - 7.24 (2H, m) 6.81 - 7.13 (2H, m) 6.65 (2H, br. s.) 2.78 (3H, s); MS *m/z* 437.2 $[M+H]^+$
132	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-4,6-二氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.59 (1H, s) 7.75 (1H, ddd, *J*=9.77, 2.21, 0.95 Hz) 7.68 - 7.72 (2H, m) 7.18 - 7.25 (2H, m) 6.81 - 7.13 (2H, m) 6.65 (2 H, s) 3.25 (2H, q, *J*=7.57 Hz) 1.28 - 1.33 (3H, m); MS *m/z* 451.2 $[M+H]^+$
133	**N-[4-(二氟甲氧基)苯基]-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, br. s.) 8.15 (1H, dd, *J*=11.82, 7.72 Hz) 7.68 - 7.74 (2H, m) 7.46 (1H, dd, *J*=10.72, 7.57 Hz) 7.21 - 7.26 (2H, m) 7.05 (2H, t, *J*=76.30 Hz) 6.65 (2H, s) 2.78 (3H, s); MS *m/z* 437.3 $[M+H]^+$
134	**5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.87 (1H, br. s.) 7.99 (2H, d, *J*=8.51 Hz) 7.92 (1H, d, *J*=8.20 Hz) 7.69 (2H, d, *J*=8.51 Hz) 7.19 (1H, td, *J*=8.20, 5.04 Hz) 7.01 (1H, dd, *J*=10.72, 7.25 Hz) 6.74 (2H, br. s.) 2.83 (3H, s); MS *m/z* 421.2 $[M+H]^+$
135	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, s) 7.92 (1H, d, *J*=9.14 Hz) 7.72 - 7.78 (2H, m) 6.80 - 7.24 (5H, m) 6.59 (2H, br. s.) 2.79 (3H, s); MS *m/z* 418.2 $[M+H]^+$
136	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(4-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.74 (1H, s) 7.93 (1H, d, *J*=7.57 Hz) 7.85 (1H, dd, *J*=12.93, 2.52 Hz) 7.51 - 7.57 (1H, m) 7.34 (1H, t, *J*=8.99 Hz) 6.82 - 7.23 (3H, m) 6.69 (2H, s) 2.86 (3H, s); MS *m/z* 437.2 $[M+H]^+$

Cpd	名称 & 数据
137	**5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.88 (1H, br. s.) 8.47 (1H, dd, *J*=8.04, 1.73 Hz) 8.40 - 8.44 (1H, m) 7.92 - 8.00 (2H, m) 7.72 (2H, d, *J*=8.51 Hz) 7.18 - 7.23 (1H, m) 6.70 - 6.80 (2H, m) 2.90 (3H, s); MS *m/z* 404.2 [M+H]$^+$
138	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.58 (1H, s) 8.46 (1H, dd, *J*=8.20, 1.58 Hz) 8.40 (1H, dd, *J*=4.73, 1.58 Hz) 7.70 - 7.76 (2H, m) 7.21 - 7.25 (2H, m) 7.15 - 7.19 (1H, m) 6.99 (2H, s) 6.56 - 6.66 (2H, m) 2.86 (3H, s); MS *m/z* 402.2 [M+H]$^+$
139	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基-1H-咪唑并[4,5-b]吡啶-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.75 (1H, br. s.) 8.45 - 8.50 (1H, m) 8.42 (1H, dd, *J*=4.73, 1.58 Hz) 7.80 (1H, dd, *J*=12.61, 2.52 Hz) 7.53 (1H, dt, *J*=9.06, 1.93 Hz) 7.37 (1H, t, *J*=8.83 Hz) 7.20 (1H, dd, *J*=8.20, 4.73 Hz) 6.83 - 7.16 (2H, m) 6.72 (2H, br. s.) 2.89 (3H, s); MS *m/z* 420.2 [M+H]$^+$
140	**2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.88 (1H, s) 8.05 (2H, d, *J*=8.51 Hz) 7.81 (1H, dd, *J*=8.20, 0.63 Hz) 7.67 (2H, d, *J*=8.51 Hz) 7.16 (1H, td, *J*=8.12, 4.89 Hz) 6.95 - 7.02 (1H, m) 6.74 (2H, s) 2.96 - 3.03 (1H, m) 1.24 - 1.29 (2H, m) 1.03 - 1.08 (2H, m); MS *m/z* 447.2 [M+H]$^+$
141	**2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.59 (1H, s) 7.77 - 7.84 (3H, m) 7.16 - 7.20 (2H, m) 7.12 - 7.16 (1H, m) 6.81 - 7.11 (2H, m) 6.61 (2H, s) 3.01 (1H, tt, *J*=8.28, 4.97 Hz) 1.20 - 1.24 (2H, m) 1.03 (2H, dq, *J*=8.32, 3.43 Hz); MS *m/z* 445.2 [M+H]$^+$
142	**2-(2-环丙基-4-氟-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)-3-氟苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.77 (1H, s) 7.99 (1H, dd, *J*=12.93, 2.52 Hz) 7.83 (1H, dd, *J*=8.20, 0.95 Hz) 7.57 (1H, ddd, *J*=9.06, 2.60, 1.58 Hz) 7.33 (1H, t, *J*=8.99 Hz) 7.18 (1H, td, *J*=8.12, 4.89 Hz) 6.83 - 7.13 (2H, m) 6.72 (2 H, s) 3.01 (1H, tt, *J*=8.28, 4.97 Hz) 1.23 - 1.30 (2H, m) 1.08 (2H, dq, *J*=8.32, 3.43 Hz); MS *m/z* 463.2 [M+H]$^+$
155	**2-(2-环丙基-6-氟-1H-咪唑并[4,5-b]吡啶-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.62 (1H, s) 8.23 - 8.32 (2H, m) 7.72 - 7.78 (2H, m) 7.18 - 7.24 (2H, m) 6.98 (1H, t, *J*=75.30 Hz) 6.71 (2H, br. s.) 3.27 (1H, tt, *J*=8.28, 4.97 Hz) 1.25 (2H, dd, *J*=4.89, 3.00 Hz) 1.05 (2H, dd, *J*=8.20, 3.15 Hz); MS *m/z* 446.2 [M+H]$^+$

Cpd	名称 & 数据
158	**2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.82 (1H, d, *J*=1.58 Hz) 8.11 (1H, d, *J*=8.20 Hz) 7.92 - 7.99 (2H, m) 7.69 (2H, d, *J*=8.51 Hz) 7.58 (1H, d, *J*=2.21 Hz) 7.19 (1H, dd, *J*=8.83, 2.21 Hz) 6.70 (2H, br. s.) 2.82 (3H, s); MS *m/z* 437.2 $[M+H]^+$
159	**2-(5-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.42 (1H, s) 7.95 - 8.00 (1H, m) 7.55 - 7.62 (2H, m) 7.43 (1H, d, *J*=1.58 Hz) 7.01 - 7.10 (3H, m) 6.84 (1H, t, *J*=75.30 Hz) 6.44 (2H, br. s.) 2.64 (3H, s); MS *m/z* 435.2 $[M+H]^+$
160	**2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.83 (1H, br. s.) 8.19 (1H, d, *J*=1.58 Hz) 7.94 (2H, d, *J*=8.20 Hz) 7.70 (3H, d, *J*=8.51 Hz) 7.55 (1H, d, *J*=8.51 Hz) 7.21 - 7.27 (1H, m) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 437.2 $[M+H]^+$
161	**2-(6-氯-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, s) 8.17 - 8.22 (1H, m) 7.70 - 7.77 (2H, m) 7.55 (1H, d, *J*=8.20 Hz) 7.20 - 7.26 (3H, m) 6.97 (1H, t, *J*=74.70 Hz) 6.62 (2H, br. s.) 2.80 (3H, s); MS *m/z* 435.2 $[M+H]^+$
162	**2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (1H, br. s.) 8.08 (1H, dd, *J*=8.67, 5.20 Hz) 7.97 (2H, d, *J*=8.20 Hz) 7.64 - 7.73 (2H, m) 7.33 (1H, d, *J*=6.62 Hz) 6.98 - 7.04 (1H, m) 6.72 (2H, br. s.) 3.29 (2H, q, *J*=7.36 Hz) 1.34 (3H, t, *J*=8.20 Hz); MS *m/z* 435.3 $[M+H]^+$
163	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-5-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.56 (1H, s) 8.09 (1H, dd, *J*=9.46, 5.04 Hz) 7.69 - 7.75 (2H, m) 7.31 (1H, dd, *J*=9.30, 2.68 Hz) 7.18 - 7.24 (2H, m) 6.81 - 7.14 (2H, m) 6.57 (2H, br. s.) 3.22 - 3.29 (2H, m) 1.27 - 1.34 (3H, m); MS *m/z* 433.3 $[M+H]^+$
164	**2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.85 (1H, s) 7.96 (2H, d, *J*=8.51 Hz) 7.89 (1H, dd, *J*=10.09, 2.52 Hz) 7.70 (2H, d, *J*=8.51 Hz) 7.59 (1H, dd, *J*=8.51, 5.04 Hz) 7.01 - 7.09 (1H, m) 6.75 (2H, br. s.) 3.29 (2H, q, *J*=7.46 Hz) 1.33 (3H, t, *J*=14.80 Hz); MS *m/z* 435.3 $[M+H]^+$
165	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-6-氟-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.56 (1H, s) 7.90 (1H, dd, *J*=10.40, 2.52 Hz) 7.68 - 7.75 (2H, m) 7.56 (1H, dd, *J*=8.83, 5.04 Hz) 7.18 - 7.26 (2H, m) 6.81 - 7.12 (2H, m) 6.61 (2H, br. s.) 3.25 (2H, q, *J*=7.46 Hz) 1.26 - 1.34 (3H, m); MS *m/z* 433.3 $[M+H]^+$

Cpd	名称 & 数据
172	**5-甲基-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.19 (1H, s) 8.14 (1H, dt, *J*=8.20, 0.95 Hz) 7.87 (2H, d, *J*=8.51 Hz) 7.64 (2H, d, *J*=8.51 Hz) 7.55 - 7.60 (1H, m) 7.22 (1H, ddd, *J*=8.04, 7.09, 1.26 Hz) 7.15 (1H, ddd, *J*=8.28, 7.17, 1.26 Hz) 6.31 (2H, br. s.) 2.80 (3H, s) 2.22 (3H, s); MS *m/z* 399.2 [M+H]$^+$
183	**5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[6-(三氟甲基)吡啶-3-基]嘧啶-4,6-二胺** ^{1}H NMR (甲醇 -d_4) δ ppm 8.92 (1H, d, J = 2.5 Hz), 8.34 (1H, dd, J = 8.5, 2.4 Hz), 7.81 (1H, dd, J = 9.8, 2.5 Hz), 7.75 (1H, d, J = 8.7 Hz), 7.54 (1H, dd, J = 8.7, 5 Hz), 7.06 (1H, td, J = 9.2, 2.5 Hz), 2.82 (3H, s); MS *m/z* 422.3 [M+H]$^+$
184	**5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.37 (br. s., 1H), 7.94 (dd, J = 10.4, 2.5 Hz, 1H), 7.50 - 7.58 (m, 3H), 7.20 (d, J = 8.2 Hz, 2H), 7.01 (ddd, J = 9.8, 8.8, 2.5 Hz, 1H), 6.52 (br. s., 2H), 2.78 (s, 3H), 2.34 (s, 3H); MS *m/z* 367.2 [M+H]$^+$
185	**N-(4-氯苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.58 (br. s., 7H), 7.93 (dd, J = 10.2, 2.7 Hz, 1H), 7.70 - 7.76 (m, 2H), 7.54 (dd, J = 8.7, 5.2 Hz, 1H), 7.37 - 7.42 (m, 2H), 7.03 (ddd, J = 9.8, 8.8, 2.5 Hz, 1H), 6.63 (br. s., 2H), 2.79 (s, 3H); MS *m/z* 387.2 [M+H]$^+$
189	**5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-(3-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.43 (br. s., 1H), 7.97 (dd, J = 10.1, 2.5 Hz, 1H), 7.54 (dd, J = 8.8, 5.0 Hz, 1H), 7.32 - 7.37 (m, 1H), 7.23 - 7.31 (m, 2H), 7.03 (ddd, J = 9.5, 8.7, 2.8 Hz, 1H), 6.68 - 6.75 (m, 1H), 6.57 (br. s., 2H), 3.77 (s, 3H), 2.81 (s, 3H); MS *m/z* 383.2 [M+H]$^+$
190	**N-(3-氯苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.63 (br. s., 1H), 7.96 (dd, J = 10.1, 2.5 Hz, 1H), 7.91 (t, J = 2.0 Hz, 1H), 7.62 (ddd, J = 8.3, 2.0, 0.8 Hz, 1H), 7.55 (dd, J = 8.8, 5.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.14 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.04 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 6.68 (br. s., 2H), 2.82 (s, 3H); MS *m/z* 387.2 [M+H]$^+$
191	**5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.21 (br. s., 1H), 8.49 (dd, J = 10.2, 2.7 Hz, 1H), 8.32 - 8.42 (m, 2H), 8.10 (dd, J = 8.7, 5.2 Hz, 1H), 7.91 (dd, J = 9.1, 0.9 Hz, 2H), 7.59 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 7.21 (br. s., 2H), 3.34 (s, 3H); MS *m/z* 437.2 [M+H]$^+$

Cpd	名称 & 数据
192	**4-{[6-氨基-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.79 (br. s., 1H), 7.80 - 7.86 (m, 2H), 7.78 (dd, J = 10.1, 2.5 Hz, 1H), 7.61 (dt, J = 8.8, 2.5 Hz, 2H), 7.42 (dd, J = 8.8, 5.0 Hz, 1H), 6.91 (ddd, J = 9.5, 8.5, 2.6 Hz, 1H), 6.65 (br. s., 2H), 2.67 (s, 3H); MS *m/z* 378.2 [M+H]$^+$
193	**4-{[6-氨基-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲酸甲酯** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.82 (br. s., 1H), 7.99 - 8.04 (m, 2H), 7.96 (dd, J = 10.1, 2.5 Hz, 1H), 7.85 - 7.90 (m, 2H), 7.56 (dd, J = 8.8, 5.0 Hz, 1H), 7.05 (ddd, J = 9.5, 8.5, 2.5 Hz, 1H), 6.73 (br. s., 2H), 3.88 (s, 3H), 2.83 (s, 3H); MS *m/z* 411.2 [M+H]$^+$
194	**5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-(3-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.36 (1H, br. s.) 8.19 (1H, d, *J*=8.51 Hz) 7.64 (1H, s) 7.57 (1H, d, *J*=7.57 Hz) 7.46 (1H, dd, *J*=8.20, 2.21 Hz) 7.16 - 7.26 (3H, m) 6.94 (1H, d, *J*=7.57 Hz) 6.49 (2H, br. s.) 2.81 (3H, s) 2.33 (3H, s); MS *m/z* 439.2 [M+H]$^+$
195	**5-氟-N-(3-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.42 (1H, br. s.) 8.13 - 8.18 (1H, m) 7.58 (1H, d, *J*=7.25 Hz) 7.40 (1H, t, *J*=2.21 Hz) 7.16 - 7.32 (4H, m) 6.67 - 6.71 (1H, m) 6.52 (2H, br. s.) 3.75 (3H, s) 2.82 (3H, s); MS *m/z* 365.2 [M+H]$^+$
199	**5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.35 (1H, br. s.) 8.13 (1H, d, *J*=8.20 Hz) 7.54 - 7.61 (3H, m) 7.12 - 7.24 (4H, m) 6.45 (2H, br. s.) 2.78 (3H, s) 2.33 (3H, s); MS *m/z* 349.2 [M+H]$^+$
200	**5-氟-N-(4-甲氧基苯基)-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.28 (1H, br. s.) 8.12 (1H, d, *J*=8.20 Hz) 7.52 - 7.60 (3H, m) 7.12 - 7.24 (2H, m) 6.93 - 6.98 (2H, m) 6.41 (2H, br. s.) 3.82 (3H, s) 2.76 (3H, s); MS *m/z* 365.2 [M+H]$^+$
201	**N-(4-氯苯基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, br. s.) 8.07 - 8.14 (1H, m) 7.73 - 7.80 (2H, m) 7.58 (1H, d, *J*=6.94 Hz) 7.35 - 7.42 (2H, m) 7.15 - 7.26 (2H, m) 6.56 (2H, br. s.) 2.79 (3H, s); MS *m/z* 369.2 [M+H]$^+$
202	**4-{[6-氨基-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4-基]氨基}苯甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.92 (1H, br. s.) 8.08 - 8.13 (1H, m) 7.97 - 8.03 (2H, m) 7.71 - 7.77 (2H, m) 7.56 - 7.62 (1H, m) 7.24 (2H, quind, *J*=7.33, 7.33, 7.33, 7.33, 1.58 Hz) 6.73 (2H, br. s.) 2.80 - 2.83 (3H, m); MS *m/z* 360.2 [M+H]$^+$

Cpd	名称 & 数据
203	**N-(1,3-苯并二氧杂环戊烯-5-基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.33 (1H, br. s.) 8.15 (1H, d, *J*=6.62 Hz) 7.56 (1H, d, *J*=7.25 Hz) 7.28 (1H, d, *J*=2.21 Hz) 7.16 - 7.25 (2H, m) 7.09 (1H, dd, *J*=8.51, 2.21 Hz) 6.85 (1H, d, *J*=8.51 Hz) 6.45 (2H, br. s.) 6.02 (2H, s) 2.79 (3H, s); MS *m/z* 379.2 [M+H]$^+$
204	**5-氟-2-(2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.63 (1H, br. s.) 8.11 (1H, d, *J*=7.57 Hz) 7.80 - 7.89 (2H, m) 7.57 (1H, d, *J*=7.88 Hz) 7.31 - 7.38 (2H, m) 7.15 - 7.26 (2H, m) 6.58 (2H, br. s.) 2.79 (3H, s); MS *m/z* 419.1 [M+H]$^+$
213	**2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.40 (1H, br. s.) 8.15 (1H, dd, *J*=11.98, 7.88 Hz) 7.49 - 7.55 (2H, m) 7.44 (1H, dd, *J*=10.72, 7.57 Hz) 7.21 (2H, d, *J*=8.20 Hz) 6.55 (2H, br. s.) 2.79 (3H, s) 2.35 (3H, s); MS *m/z* 385.2 [M+H]$^+$
214	**2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.30 (1H, br. s.) 8.12 (1H, dd, *J*=11.98, 7.88 Hz) 7.46 - 7.51 (2H, m) 7.41 (1H, dd, *J*=10.72, 7.57 Hz) 6.93 - 6.98 (2H, m) 6.48 (2H, br. s.) 3.81 (3H, s) 2.75 (3H, s); MS *m/z* 401.3 [M+H]$^+$
215	**N-(4-氯苯基)-2-(5,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.61 (1H, br. s.) 8.15 (1H, dd, *J*=11.82, 7.72 Hz) 7.68 - 7.73 (2H, m) 7.38 - 7.50 (3 H, m) 6.66 (2H, br. s.) 2.80 (3H, s); MS *m/z* 405.2 [M+H]$^+$
216	**N-[4-(二氟甲氧基)苯基]-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.53 (1H, s) 8.13 - 8.17 (1H, m) 7.73 - 7.79 (2H, m) 7.64 - 7.69 (1H, m) 7.19 - 7.30 (4H, m) 6.82 - 7.13 (1H, m) 6.54 (2H, br. s.) 5.02 (2H, s) 3.28 (3H, s); MS *m/z* 431.3 [M+H]$^+$
217	**5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.36 (1H, br. s.) 8.18 (1H, dd, *J*=6.78, 1.73 Hz) 7.66 (1H, dd, *J*=6.62, 1.89 Hz) 7.54 - 7.60 (2H, m) 7.17 - 7.30 (4H, m) 6.46 (2H, br. s.) 4.99 - 5.04 (2H, m) 3.28 (3H, s) 2.34 (3H, s); MS *m/z* 379.3 [M+H]$^+$

Cpd	名称 & 数据
218	**5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.31 (1H, br. s.) 8.14 - 8.19 (1H, m) 7.65 (1H, dd, *J*=6.78, 1.73 Hz) 7.53 - 7.59 (2H, m) 7.25 (2H, quind, *J*=7.41, 7.41, 7.41, 7.41, 1.58 Hz) 6.93 - 6.99 (2H, m) 6.43 (2H, br. s.) 4.97 - 5.02 (2H, m) 3.82 (3H, s); MS *m/z* 395.3 [M+H]$^+$
219	**N-(4-氯苯基)-5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.58 (1H, br. s.) 8.12 - 8.17 (1H, m) 7.73 - 7.79 (2H, m) 7.65 - 7.70 (1H, m) 7.37 - 7.41 (2H, m) 7.24 - 7.32 (2H, m) 6.58 (2H, br. s.) 5.03 (2H, s) 3.29 (3H, s); MS *m/z* 399.2 [M+H]$^+$
220	**5-氟-2-[2-(甲氧基甲基)-1H-苯并咪唑-1-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.83 (1H, br. s.) 8.11 - 8.18 (1H, m) 7.96 - 8.03 (2H, m) 7.66 - 7.73 (3H, m) 7.25 - 7.33 (2H, m) 6.68 (2H, br. s.) 5.05 (2H, s) 3.29 (3H, s); MS *m/z* 433.2 [M+H]$^+$
222	**1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.91 (1H, s) 8.63 (1H, d, *J*=1.58 Hz) 7.92 - 7.99 (2H, m) 7.74 (3H, t, *J*=8.51 Hz) 7.61 (1H, dd, *J*=8.20, 1.58 Hz) 6.84 (2H, br. s.) 2.90 (3H, s); MS *m/z* 428.3 [M+H]$^+$
223	**1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-6-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.58 - 8.63 (2H, m) 7.68 - 7.75 (3H, m) 7.57 - 7.62 (1H, m) 7.22 - 7.27 (2H, m) 6.84 - 7.16 (1H, m) 6.68 (2H, br. s.) 2.87 (3H, s); MS *m/z* 426.3 [M+H]$^+$
224	**1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.61 (1H, s) 8.42 (1H, br. s.) 7.71 (1H, d, *J*=8.20 Hz) 7.49 - 7.60 (3H, m) 7.24 (2H, d, *J*=7.88 Hz) 6.58 (2H, br. s.) 2.87 (3H, s) 2.36 (3H, s); MS *m/z* 374.3 [M+H]$^+$
225	**1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-6-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.62 (1H, s) 8.37 (1H, s) 7.71 (1H, d, *J*=8.20 Hz) 7.49 - 7.60 (3H, m) 6.98 - 7.03 (2H, m) 6.57 (2H, br. s.) 3.84 (3H, s) 2.84 (3H, s); MS *m/z* 390.3 [M+H]$^+$
226	**1-(4-氨基-6-{[4-(二氟甲氧基)苯基]氨基}-5-氟嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.60 (1H, s) 8.28 (1H, dd, *J*=8.51, 0.63 Hz) 8.00 (1H, dd, *J*=1.58, 0.63 Hz) 7.70 - 7.77 (2H, m) 7.55 (1H, dd, *J*=8.51, 1.58 Hz) 7.19 - 7.25 (2H, m) 6.98 (1H, t, *J*=75.00 Hz) 6.63 (2H, br. s.) 2.83 (3H, s); MS *m/z* 426.3 [M+H]$^+$

Cpd	名称 & 数据
227	**1-{4-氨基-5-氟-6-[(4-甲基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.42 (1H, br. s.) 8.31 (1H, s) 7.99 (1H, s) 7.50 - 7.57 (3H, m) 7.20 (2H, d, *J*=8.20 Hz) 6.55 (2H, br. s.) 2.83 (3H, s) 2.34 (3H, s); MS *m/z* 374.3 $[M+H]^+$
228	**1-{4-氨基-5-氟-6-[(4-甲氧基苯基)氨基]嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.33 - 8.39 (1H, m) 8.29 (1H, d, *J*=8.51 Hz) 7.98 (1H, s) 7.49 - 7.56 (3H, m) 6.95 - 7.00 (2H, m) 6.51 (2H, br. s.) 3.83 (3H, s) 2.81 (3H, s); MS *m/z* 390.4 $[M+H]^+$
229	**1-(4-氨基-5-氟-6-{[4-(三氟甲基)苯基]氨基}嘧啶-2-基)-2-甲基-1H-苯并咪唑-5-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.90 (1H, s) 8.28 (1H, d, *J*=8.51 Hz) 8.02 (1H, s) 7.97 (2H, d, *J*=8.51 Hz) 7.71 (2H, d, *J*=8.20 Hz) 7.58 (1H, dd, *J*=8.51, 1.58 Hz) 6.78 (2H, br. s.) 2.87 (3H, s); MS *m/z* 428.3 $[M+H]^+$
230	**1-{4-氨基-6-[(4-氯苯基)氨基]-5-氟嘧啶-2-基}-2-甲基-1H-苯并咪唑-5-甲腈** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.64 (1H, br. s.) 8.28 (1H, dd, *J*=8.51, 0.63 Hz) 8.01 (1H, d, *J*=1.58 Hz) 7.70 - 7.76 (2H, m) 7.57 (1H, dd, *J*=8.51, 1.58 Hz) 7.36 - 7.43 (2H, m) 6.67 (2H, br. s.) 2.84 (3H, s); MS *m/z* 394.2 $[M+H]^+$
231	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.02 (1H, d, *J*=2.84 Hz) 8.62 (1H, br. s.) 8.19 (1H, dd, *J*=8.83, 2.52 Hz) 7.71 - 7.77 (3H, m) 6.94 (1H, t, *J*=75.00 Hz) 6.68 (2H, s) 2.88 (3H, s); MS *m/z* 446.2 $[M+H]^+$
232	**5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.03 (1H, d, *J*=2.84 Hz) 8.45 (1H, br. s.) 8.18 (1H, dd, *J*=8.83, 2.21 Hz) 7.74 (1H, d, *J*=8.83 Hz) 7.53 - 7.59 (2H, m) 7.18 (2H, d, *J*=7.88 Hz) 6.61 (2H, br. s.) 2.87 (3H, s) 2.32 (3H, s); MS *m/z* 394.2 $[M+H]^+$
233	**5-氟-N-(4-甲氧基苯基)-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.03 (1H, d, *J*=1.89 Hz) 8.38 (1H, br. s.) 8.17 (1H, dd, *J*=8.83, 2.21 Hz) 7.73 (1H, d, *J*=8.83 Hz) 7.52 - 7.60 (2H, m) 6.92 - 6.99 (2H, m) 6.57 (2H, br. s.) 3.80 (3H, s) 2.54 (3H, s); MS *m/z* 410.2 $[M+H]^+$
236	**5-氟-2-(2-甲基-6-硝基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.04 (1H, d, *J*=2.52 Hz) 8.90 (1H, br. s.) 8.21 (1H, dt, *J*=8.83, 1.42 Hz) 7.99 (2H, dd, *J*=8.35, 3.31 Hz) 7.77 (1H, d, *J*=8.83 Hz) 7.70 (2H, d, *J*=8.51 Hz) 6.83 (2H, br. s.) 2.92 (3H, s); MS *m/z* 448.2 $[M+H]^+$

Cpd	名称 & 数据
237	**N-(4-氯苯基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.62 (1H, br. s.) 7.79 (1H, dd, *J*=10.25, 2.05 Hz) 7.69 - 7.74 (2H, m) 7.37 - 7.44 (2H, m) 6.92 (1H, td, *J*=10.25, 2.21 Hz) 6.67 (2H, br. s.) 2.79 - 2.80 (3H, m); MS *m/z* 405.2 $[M+H]^+$
238	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.69 (1H, s) 7.75 - 7.85 (3H, m) 7.36 (2H, d, *J*=8.20 Hz) 6.92 (1H, td, *J*=10.25, 2.52 Hz) 6.69 (2H, br. s.) 2.79 (3H, s); MS *m/z* 456.1 $[M+H]^+$
240	**N-(1,3-苯并二氧杂环戊烯-5-基)-2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.37 (1H, br. s.) 7.80 (1H, dd, *J*=9.46, 1.89 Hz) 7.20 (1H, d, *J*=2.21 Hz) 7.05 (1H, dd, *J*=8.35, 2.05 Hz) 6.84 - 6.92 (2H, m) 6.55 (2H, br. s.) 6.02 (2H, s) 2.79 (3H, s); MS *m/z* 416.2 $[M+H]^+$
241	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.41 (1H, br. s.) 7.80 (1H, dd, *J*=9.93, 2.36 Hz) 7.50 - 7.56 (2H, m) 7.20 (2H, d, *J*=8.20 Hz) 6.90 (1H, td, *J*=10.25, 2.52 Hz) 6.56 (2H, br. s.) 2.79 (3H, s) 2.34 (3H, s); MS *m/z* 386.2 $[M+H]^+$
242	**2-(4,6-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.34 (1H, br. s.) 7.76 - 7.83 (1H, m) 7.47 - 7.55 (2H, m) 6.94 - 7.00 (2H, m) 6.89 (1H, td, *J*=10.25, 2.21 Hz) 6.52 (2H, br. s.) 3.82 (3H, s) 2.76 (3H, s); MS *m/z* 402.2 $[M+H]^+$
243	**2-(5,7-二氟-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.86 (1H, br. s.) 8.15 (1H, dd, *J*=11.66, 7.88 Hz) 7.91 - 7.98 (2H, m) 7.72 (2H, d, *J*=8.51 Hz) 7.48 (1H, dd, *J*=10.72, 7.57 Hz) 6.78 (2H, br. s.) 2.83 (3H, s); MS *m/z* 439.3 $[M+H]^+$
244	**5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.82 (1H, br. s.) 8.00 (2H, d, *J*=8.51 Hz) 7.65 - 7.73 (3H, m) 7.45 (1H, d, *J*=8.51 Hz) 6.83 - 6.89 (1H, m) 6.67 (2H, br. s.) 3.64 - 3.69 (3H, m) 2.78 (3H, s); MS *m/z* 434.2 $[M+H]^+$
245	**N-(4-氯苯基)-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, br. s.) 7.74 - 7.79 (2H, m) 7.68 (1H, d, *J*=2.52 Hz) 7.44 (1H, d, *J*=8.51 Hz) 7.35 - 7.41 (2H, m) 6.85 (1H, dd, *J*=8.83, 2.52 Hz) 6.57 (2H, br. s.) 3.69 (3H, s) 2.75 (3H, s); MS *m/z* 399.2 $[M+H]^+$

Cpd	名称 & 数据
246	**5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.64 (1H, s) 7.84 - 7.89 (2H, m) 7.69 (1H, d, *J*=2.21 Hz) 7.44 (1H, d, *J*=8.83 Hz) 7.34 (2H, d, *J*=8.20 Hz) 6.85 (1H, dd, *J*=8.51, 2.52 Hz) 6.58 (2H, br. s.) 3.68 (3H, s) 2.75 (3H, s); MS *m/z* 449.2 $[M+H]^+$
247	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.52 (1H, s) 7.74 - 7.79 (2H, m) 7.69 (1H, d, *J*=2.52 Hz) 7.43 (1H, d, *J*=8.51 Hz) 7.17 - 7.23 (2H, m) 6.81 - 7.12 (2H, m) 6.53 (2H, br. s.) 3.69 (3H, s) 2.74 (3H, s); MS *m/z* 432.2 $[M+H]^+$
248	**5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.34 (1H, br, s) 7.70 (1H, d, *J*=2.52 Hz) 7.56 - 7.60 (2H, m) 7.42 (1H, d, *J*=8.83 Hz) 7.17 (2H, d, *J*=8.20 Hz) 6.83 (1H, dd, *J*=8.83, 2.52 Hz) 6.45 (2H, br. s.) 3.65 (3H, s) 2.75 (3H, s) 2.33 (3H, s); MS *m/z* 380.2 $[M+H]^+$
249	**5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.27 (1H, br. s.) 7.70 (1H, d, *J*=2.52 Hz) 7.54 - 7.60 (2H, m) 7.38 - 7.43 (1H, m) 6.92 - 6.97 (2H, m) 6.82 (1H, dd, *J*=8.51, 2.52 Hz) 6.41 (2H, br. s.) 3.82 (3H, s) 3.67 (3H, s) 2.72 (3H, s); MS *m/z* 396.2 $[M+H]^+$
250	**N-(1,3-苯并二氧杂环戊烯-5-基)-5-氟-2-(6-甲氧基-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.32 (1H, br. s.) 7.71 (1H, d, *J*=2.52 Hz) 7.42 (1H, d, *J*=8.51 Hz) 7.30 - 7.33 (1H, m) 7.09 (1H, dd, *J*=8.35, 2.05 Hz) 6.81 - 6.87 (2H, m) 6.44 (2H, br. s.) 6.01 (2H, s) 3.72 (3H, s) 2.74 (3H, s); MS *m/z* 409.2 $[M+H]^+$
254	**5-氟-2-(2-甲基-5-硝基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.45 - 8.49 (1H, m) 8.44 (1H, d, *J*=1.89 Hz) 8.31 (1H, d, *J*=9.14 Hz) 8.11 (1H, dd, *J*=8.98, 2.36 Hz) 7.54 - 7.57 (2H, m) 7.21 (2H, d, *J*=8.20 Hz) 6.59 (2H, br. s.) 2.85 (3H, s) 2.34 (3H, s); MS *m/z* 394.2 $[M+H]^+$
255	**5-氟-N-(4-甲氧基苯基)-2-(2-甲基-5-硝基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.43 (1H, d, *J*=1.89 Hz) 8.40 (1H, br. s.) 8.30 (1H, d, *J*=9.14 Hz) 8.10 (1H, dd, *J*=8.99, 2.36 Hz) 7.52 - 7.57 (2H, m) 6.96 - 7.01 (2H, m) 6.55 (2H, br. s.) 3.83 (3H, s) 2.83 (3H, s); MS *m/z* 410.2 $[M+H]^+$
256	**2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.25 (1H, s) 7.53 - 7.59 (2H, m) 7.42 (1H, d, *J*=1.58 Hz) 7.24 (1H, d, *J*=8.83 Hz) 6.93 - 6.99 (2H, m) 6.61 (1H, dd, *J*=8.20, 2.21 Hz) 6.33 (2H, s) 4.30 (2H, br. s.) 3.81 (3H, s) 2.67 (3H, s); MS *m/z* 380.3 $[M+H]^+$

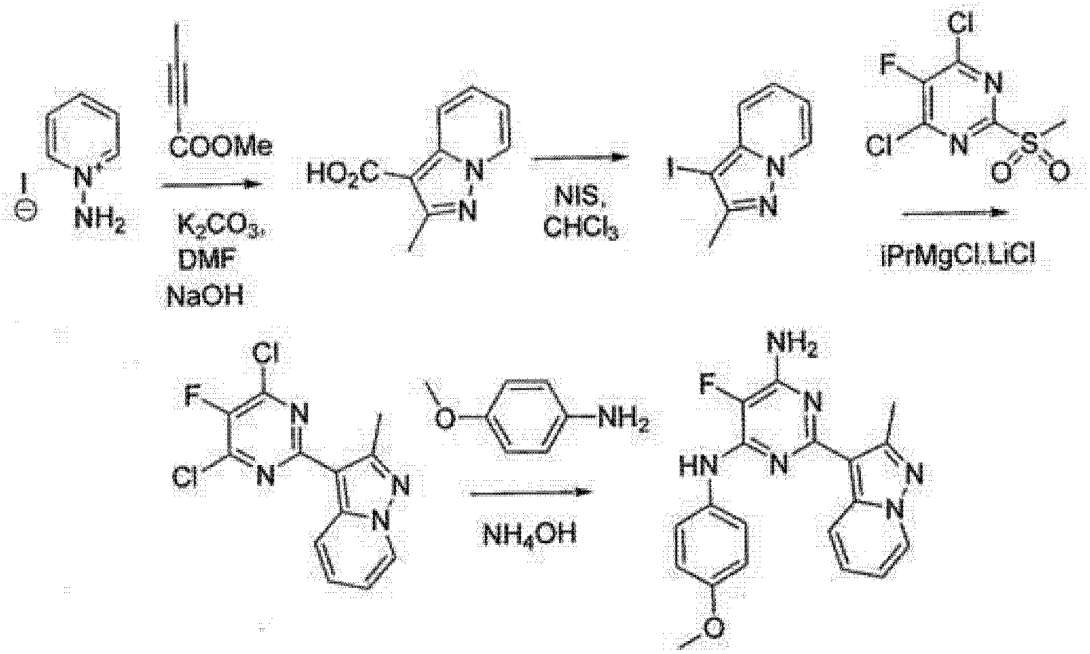
Cpd	名称 & 数据
257	**2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.48 (1H, br. s.) 7.75 - 7.82 (2H, m) 7.42 (1H, d, *J*=2.21 Hz) 7.25 (1H, d, *J*=8.20 Hz) 7.17 - 7.22 (2H, m) 6.96 (1H, t, *J*=75.00 Hz) 6.64 (1H, dd, *J*=8.51, 2.21 Hz) 6.44 (2H, br. s.) 4.36 (2H, s) 2.68 (3H, s); MS *m/z* 416.2 [M+H]$^+$
258	**2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.15 (1H, br. s.) 7.39 - 7.46 (2H, m) 7.28 (1H, d, *J*=2.21 Hz) 7.09 (1H, d, *J*=8.20 Hz) 7.04 (2H, d, *J*=8.20 Hz) 6.47 (1H, dd, *J*=8.51, 2.21 Hz) 6.22 (2H, br. s.) 4.16 (2H, s) 2.54 (3H, s) 2.18 (3H, s); MS *m/z* 364.3 [M+H]$^+$
259	**N-(4-氯苯基)-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.60 (1H, br. s.) 8.13 (1H, dd, *J*=9.46, 5.04 Hz) 7.71 - 7.78 (2H, m) 7.36 - 7.43 (2H, m) 7.29 (1H, dd, *J*=9.30, 2.36 Hz) 6.99 (1H, td, *J*=9.30, 2.52 Hz) 6.60 (2H, br. s.) 2.80 (3H, s); MS *m/z* 387.2 [M+H]$^+$
260	**N-(4-氯-3-氟苯基)-5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.76 (1H, br. s.) 8.13 (1H, dd, *J*=8.83, 5.04 Hz) 7.86 (1H, dd, *J*=11.98, 2.52 Hz) 7.54 - 7.59 (1H, m) 7.45 - 7.51 (1H, m) 7.30 (1H, dd, *J*=9.30, 2.36 Hz) 7.02 (1H, td, *J*=9.22, 2.68 Hz) 6.69 (2H, br. s.) 2.84 (3H, s); MS *m/z* 405.2 [M+H]$^+$
261	**N-(4-氯-3-氟苯基)-5-氟-2-(2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.74 (1H, br. s.) 8.11 (1H, dd, *J*=7.57, 1.89 Hz) 7.90 (1H, dd, *J*=11.98, 2.52 Hz) 7.58 (2H, td, *J*=7.88, 2.21 Hz) 7.47 (1H, t, *J*=8.67 Hz) 7.18 - 7.28 (2H, m) 6.65 (2H, br. s.) 2.82 (3H, s); MS *m/z* 387.2 [M+H]$^+$
262	**N-(4-氯-3-氟苯基)-5-氟-2-(6-氟-2-甲基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.77 (1H, br. s.) 7.93 (1H, dd, *J*=10.09, 2.21 Hz) 7.83 (1H, dd, *J*=11.82, 2.36 Hz) 7.53 - 7.59 (2H, m) 7.46 - 7.51 (1H, m) 7.05 (1H, td, *J*=9.14, 2.52 Hz) 6.72 (2H, br. s.) 2.82 (3H, s); MS *m/z* 405.2 [M+H]$^+$
270	**2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.36 (1H, br. s.) 8.07 - 8.11 (1H, m) 7.54 - 7.62 (3H, m) 7.15 - 7.24 (4H, m) 6.46 (2H, br. s.) 3.26 (2H, q, *J*=7.46 Hz) 2.33 (3H, s) 1.30 - 1.33 (3H, m); MS *m/z* 363.3 [M+H]$^+$
271	**2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.15 (1H, br. s.) 7.93 - 7.97 (1H, m) 7.39 - 7.46 (3H, m) 6.99 - 7.10 (2H, m) 6.78 - 6.83 (2H, m) 6.28 (2H, s) 3.68 (3H, s) 3.10 (2H, q, *J*=7.36 Hz) 1.14 - 1.17 (3H, m); MS *m/z* 379.3 [M+H]$^+$

Cpd	名称 & 数据
272	**2-(2-乙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.67 (1H, s) 8.04 - 8.10 (1H, m) 7.80 - 7.87 (2H, m) 7.58 - 7.64 (1H, m) 7.33 (2H, d, *J*=8.20 Hz) 7.14 - 7.26 (2H, m) 6.60 (2H, s) 3.26 (2H, q, *J*=7.36 Hz) 1.31 - 1.34 (3H, m); MS *m/z* 433.2 [M+H]$^+$
273	**N-(1,3-苯并二氧杂环戊烯-5-基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.32 (1H, br. s.) 8.08 - 8.13 (1H, m) 7.58 (1H, d, *J*=7.57 Hz) 7.28 (1H, d, *J*=1.89 Hz) 7.15 - 7.24 (2H, m) 7.07 (1H, dd, *J*=8.67, 2.05 Hz) 6.85 (1H, d, *J*=8.51 Hz) 6.40 - 6.48 (2H, m) 6.01 (2H, s) 3.25 (2H, q, *J*=7.57 Hz) 1.30 - 1.33 (3H, m); MS *m/z* 393.2 [M+H]$^+$
274	**N-(4-氯苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.57 (1H, br. s.) 8.03 - 8.09 (1H, m) 7.72 - 7.79 (2H, m) 7.60 (1H, d, *J*=7.57 Hz) 7.34 - 7.40 (2H, m) 7.16 - 7.26 (2H, m) 6.56 (2H, br. s.) 3.26 (2H, q, *J*=7.57 Hz) 1.33 (3H, t, *J*=7.57 Hz); MS *m/z* 383.4 [M+H]$^+$
275	**N-(4-氯-3-氟苯基)-2-(2-乙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.75 (1H, br. s.) 8.06 (1H, d, *J*=6.94 Hz) 7.90 (1H, dd, *J*=11.98, 2.52 Hz) 7.62 (1H, dd, *J*=6.94, 1.58 Hz) 7.54 - 7.58 (1H, m) 7.42 - 7.49 (1H, m) 7.18 - 7.29 (2H, m) 6.65 (2H, br. s.) 3.29 (2H, q, *J*=7.36 Hz) 1.36 (3H, t, *J*=7.41 Hz); MS *m/z* 401.4 [M+H]$^+$
276	**2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.36 (1H, br. s.) 8.02 - 8.06 (1H, m) 7.61 - 7.67 (2H, m) 7.46 - 7.53 (1H, m) 7.12 - 7.23 (4H, m) 6.47 (2H, br. s.) 3.01 - 3.10 (1H, m) 2.32 (3H, s) 1.16 - 1.21 (2H, m) 0.98 (2H, dq, *J*=8.47, 3.38 Hz); MS *m/z* 375.4 [M+H]$^+$
277	**2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.29 (1H, br. s.) 8.04 (1H, d, *J*=8.83 Hz) 7.58 - 7.65 (2H, m) 7.46 - 7.51 (1H, m) 7.10 - 7.21 (2H, m) 6.89 - 6.96 (2H, m) 6.43 (2H, br. s.) 3.81 (3H, s) 3.02 - 3.10 (1H, m) 1.13 - 1.18 (2H, m) 0.96 (2H, dq, *J*=8.35, 3.42 Hz); MS *m/z* 391.3 [M+H]$^+$
278	**2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.65 (1H, s) 7.98 - 8.03 (1H, m) 7.87 - 7.93 (2H, m) 7.49 - 7.54 (1H, m) 7.31 (2H, d, *J*=8.20 Hz) 7.12 - 7.24 (2H, m) 6.60 (2H, br. s.) 2.98 - 3.05 (1H, m) 1.17 - 1.23 (2H, m) 0.95 - 1.02 (2H, m); MS *m/z* 445.3 [M+H]$^+$

Cpd	名称 & 数据
279	**N-(4-氯苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.59 (1H, br. s.) 7.97 - 8.04 (1H, m) 7.80 - 7.86 (2H, m) 7.47 - 7.55 (1H, m) 7.32 - 7.38 (2H, m) 7.12 - 7.23 (2H, m) 6.58 (2H, br. s.) 2.96 - 3.05 (1H, m) 1.17 - 1.25 (2H, m) 0.97 - 1.04 (2H, m); MS *m/z* 395.3 $[M+H]^+$
280	**N-(4-氯-3-氟苯基)-2-(2-环丙基-1H-苯并咪唑-1-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.77 (1H, br. s.) 7.96 - 8.06 (2H, m) 7.60 (1H, dd, *J*=7.88, 2.52 Hz) 7.53 (1H, d, *J*=6.94 Hz) 7.45 (1H, t, *J*=8.67 Hz) 7.16 - 7.25 (2H, m) 6.68 (2H, br. s.) 2.96 - 3.03 (1H, m) 1.21 - 1.26 (2H, m) 1.02 - 1.07 (2H, m); MS *m/z* 413.3 $[M+H]^+$
281	**5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** 1H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.39 (1H, br. s.) 8.15 (1H, dd, J=8.51, 5.04 Hz) 7.53 - 7.58 (2H, m) 7.27 (1H, dd, J=9.62, 2.36 Hz) 7.19 (2H, d, J=8.20 Hz) 6.92 - 7.00 (1H, m) 6.51 (2H, br. s.) 2.79 (3H, s) 2.34 (3H, s); MS *m/z* 367.3 $[M+H]^+$
282	**5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.30 (1H, br. s.) 8.14 (1H, dd, *J*=9.30, 4.89 Hz) 7.51 - 7.58 (2H, m) 7.26 (1H, dd, *J*=9.46, 2.52 Hz) 6.91 - 7.00 (3H, m) 6.44 (2H, br. s.) 3.83 (3H, s) 2.76 (3H, s); MS *m/z* 383.3 $[M+H]^+$
283	**5-氟-2-(5-氟-2-甲基-1H-苯并咪唑-1-基)-N-[4-(三氟甲氧基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.66 (1H, s) 8.12 (1H, dd, *J*=8.67, 4.89 Hz) 7.80 - 7.86 (2H, m) 7.35 (2H, d, *J*=8.20 Hz) 7.29 (1H, dd, *J*=8.83, 2.52 Hz) 6.97 (1H, td, *J*=9.30, 2.52 Hz) 6.62 (2H, s) 2.79 (3H, s); MS *m/z* 437.3 $[M+H]^+$
284	**2-(6-氨基-2-甲基-1H-苯并咪唑-1-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 7.86 (2H, d, *J*=8.51 Hz) 7.53 (2H, d, *J*=8.51 Hz) 7.28 (1H, d, *J*=2.21 Hz) 7.13 (1H, d, *J*=8.51 Hz) 6.50 (1H, dd, *J*=8.51, 2.21 Hz) 6.42 (2H, br. s.) 4.26 (2H, s) 2.56 (3H, s) MS *m/z* 418.3 $[M+H]^+$

[0415] 实施例 11

5- 氟 -N-(4- 甲氧基苯基)-2-(2- 甲基吡唑并 [1,5-a] 吡啶 -3- 基) 嘧啶 -4,6- 二胺 (Cpd 239)



步骤 1. 在 0℃下向 1- 氨基吡啶鎓碘 (9.59 g, 43.2 mmol) 和丁 -2- 炔酸甲酯 (5.2mL, 51.83 mmol) 在 DMF (50 mL) 中的混合物中添加 K_2CO_3 (11.94g, 86.4 mmol)。将该反应混合物温热至室温并搅拌 3 天直到 UPLC 完全转化成产物。反应混合物在水和 EtOAc 之间分配。浓缩有机相,然后添加 MeOH (50 mL) 和 NaOH (6 mL, 50% 在 H_2O 中) 并在 70℃下加热该反应混合物 1 小时。蒸发 MeOH 并用 1N HCl 酸化残留混合物至约 pH 4。在过滤器上分离粗 2- 甲基吡唑并 [1,5-a] 吡啶 -3- 甲酸并在真空下干燥,然后溶解在 MeOH (50 mL) 和 $CHCl_3$ (100 mL) 中,并将 N- 碘代琥珀酰亚胺 (7.3g, 32.4 mmol) 一次性添加。将反应混合物在室温下搅拌 20 分钟。蒸发 MeOH 并用 $NaHCO_3$水溶液洗涤残留物三次。经 Na_2SO_4干燥有机层,在减压下除去溶剂,通过硅胶层析法纯化粗产物以提供灰白色固体形式的 3- 碘 -2- 甲基吡唑并 [1,5-a] 吡啶 (4.2 g, 38% 对于 3 步)。

^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.51 (dt, J = 6.8, 1.3 Hz, 1H), 7.41 (dt, J = 8.8, 1.3 Hz, 1H), 7.31 (ddd, J = 8.8, 6.8, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.3 Hz, 1H), 2.42 (s, 3H); MS *m/z* 298.1 $[M+H]^+$.

[0416] 步骤 2. 在 0℃下向 3- 碘 -2- 甲基吡唑并 [1,5-a] 吡啶 (340 mg, 1.32 mmol) 在干 THF (10 mL) 的溶液中添加异丙基氯化镁氯化锂复合物溶液 (iPrMgCl.LiCl) (1.5 mL, 1.97 mL)。在 0℃下搅拌该反应混合物 30 分钟并添加干 THF (20 mL) 中的 4,6- 二氯 -5- 氟 -2-(甲基磺酰基) 嘧啶 (484 mg, 1.97 mmol)。在 0℃下搅拌该反应混合物 1 小时,并用水淬火该反应。用 CH_2Cl_2萃取粗产物三次。用盐水洗涤合并的有机萃取物,然后经 Na_2SO_4干燥,浓缩,并在 CH_3CN (10 mL) 中研磨。过滤所得沉淀物并干燥,提供作为黄褐色固体分离的 3-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-2- 甲基吡唑并 [1,5-a] 吡啶 (270 mg, 68%)。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.79 (d, J = 6.9 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H), 7.61 (ddd, J = 8.8, 6.9, 0.9 Hz, 1H), 7.13 (td, J = 6.9, 1.1 Hz, 1H), 2.70 (s, 3H). MS *m/z* 298.1 $[M+H]^+$.

[0417] 步骤 3. 将 3-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-2- 甲基吡唑并 [1,5-a] 吡啶 (65 mg, 0.21 mmol) 和 4- 甲氧基苯胺 (52 mg, 0.42 mmol) 混合在 EtOH (1 mL) 中并在 100℃

下在密封管中加热直到 UPLC 示出完全转化 (3 小时)。在消耗起始原料之后,将该反应冷却至室温并用水 (5 mL) 稀释以使产物沉淀。通过过滤收集产物,用水洗涤并随后用己烷洗涤。在不经干燥的情况下,将粗产物溶解在 iPrOAc (2 mL) 中,然后添加饱和氨水 (150 μL)。在 100℃下在密封管中加热该反应混合物 24 小时直到 UPLC 示出起始原料完全消耗。通过添加水 (10 mL) 沉淀粗产物,然后过滤并通过在硅胶上用层析法纯化以提供标题化合物 (26 mg, 34 % 在两步中)。

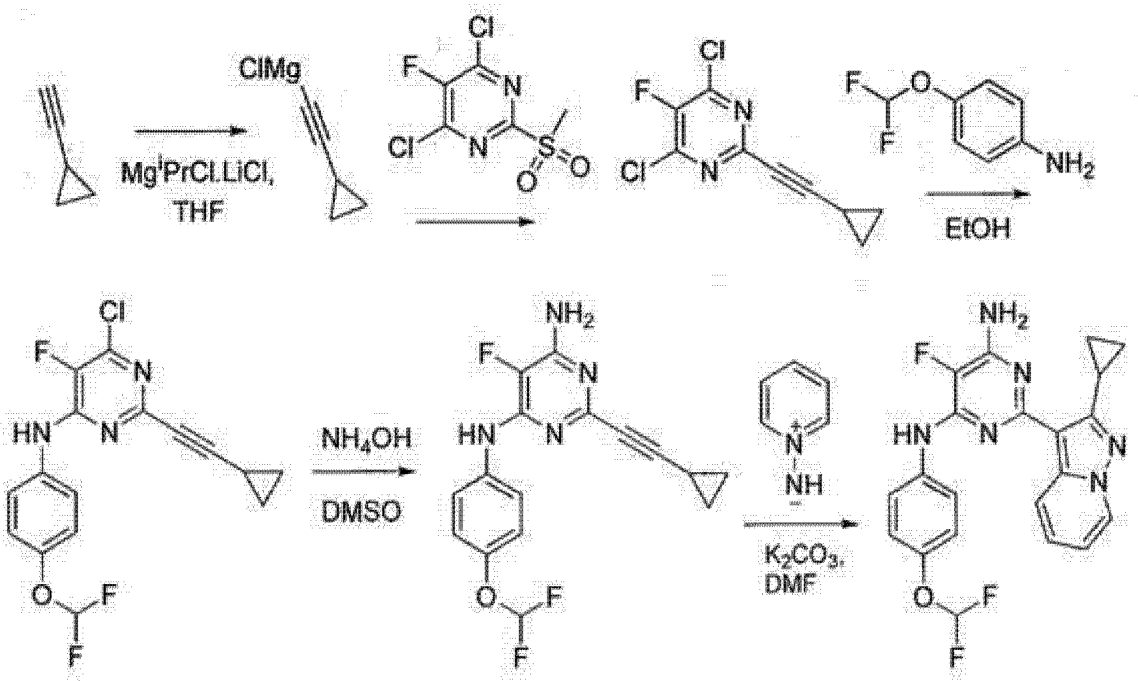
^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.54 (dt, J = 8.9, 1.2 Hz, 1H), 8.47 (dt, J = 6.9, 1.1 Hz, 1H), 7.93 (br. s., 1H), 7.59 (dd, J = 6.6, 2.2 Hz, 2H), 7.21 (ddd, J = 9.0, 6.8, 0.9 Hz, 1H), 6.98 (dd, J = 6.6, 2.2 Hz, 2H), 6.87 (td, J = 6.8, 1.3 Hz, 1H), 5.96 (br. s., 2H), 2.84 (s, 3H), 2.70 (s, 3H); MS *m/z* 383.2 $[M+H]^+$.

[0418] 可以根据实施例 11 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 & 数据
173	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.55 (dt, J = 8.9, 1.2 Hz, 1H), 8.49 (dt, J = 6.9, 1.0 Hz, 1H), 8.20 (br. s., 1H), 7.76 - 7.81 (m, 2H), 7.20 - 7.27 (m, 3H), 6.98 (t, J = 75 Hz, 1H) 6.89 (td, J = 6.9, 1.4 Hz, 1H), 6.08 (br. s, 2H), 2.72 (s, 3H); MS *m/z* 401.2 $[M+H]^+$
177	**5-氟-2-(2-甲基吡唑并[1,5-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.44 (dt, J = 9.1, 1.1 Hz, 1H), 8.37 (dt, J = 6.9, 0.9 Hz, 1H), 8.39 (br. s., 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.13 (ddd, J = 9.1, 6.7, 1.3 Hz, 1H), 6.77 (td, J = 6.8, 1.6 Hz, 1H), 6.09 (br. s., 2H), 2.62 (s, 3H); MS *m/z* 403.4 $[M+H]^+$
178	**5-氟-2-[6-氟-2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.76 - 8.81 (m, 1H), 8.70 (br. s., 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.68 (dd, J = 10.1, 4.7 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.45 (t, J = 9.8 Hz, 1H), 6.52 (br. s., 2H); MS *m/z* 475.3 $[M+H]^+$

[0419] 实施例 12

2-(2-环丙基吡唑并[1,5-a]吡啶-3-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺 (Cpd 180)



步骤1. 在-78℃下向环丙基乙炔(777.0 mg, 9.82 mmol)在THF (5 mL)中的溶液中逐滴添加异丙基氯化镁氯化锂复合物溶液(9.0 mL, 1.3 M 在THF中)。将该混合物温热至0℃并搅拌30分钟。在-78℃下向该混合物中添加4,6-二氯-5-氟-2-(甲基磺酰基)嘧啶 (4.80 g, 19.6 mmol),然后将该混合物温热至0℃并搅拌1小时。该混合物在乙酸乙酯和水之间分配。用盐水洗涤有机相,经$MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余材料(用1:9 乙酸乙酯-己烷洗脱)以提供4,6-二氯-2-(环丙基乙炔基)-5-氟嘧啶 (1.17 g, 45%)。

^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 1.53 - 1.67 (m, 1H), 0.98 - 1.10 (m, 2H), 0.83 - 0.94 (m, 2H); MS *m/z* 231.1 (100) [M+H]$^+$.

[0420] 步骤2. 将4,6-二氯-2-(环丙基乙炔基)-5-氟嘧啶 (241.0 mg, 1.04 mmol)和4-二氟甲氧基苯胺 (707.0 mg, 4.45 mmol)在EtOH (2 mL)中的混合物在回流下搅拌1小时。在冷却之后,该混合物在乙酸乙酯和水之间分配。用盐水洗涤有机层,经$MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余物质 (用1:20和1:10 乙酸乙酯-己烷洗脱)以获得6-氯-2-(环丙基乙炔基)-N-(4-(二氟甲氧基)苯基)-5-氟嘧啶-4-胺 (258.0 mg, 70%); MS *m/z* 354.2 (100) [M+H]$^+$, 356.2 (40)。

[0421] 步骤3. 向6-氯-2-(环丙基乙炔基)-*N*-(4(二氟甲氧基)苯基)-5-氟嘧啶-4-胺中添加DMSO (2 mL)和NH_4OH (27%, 0.1 mL)。密封该反应混合物并在100℃下搅拌2天。该反应混合物在乙酸乙酯和水之间分配。用水 (2 x 20 mL)和盐水洗涤有机相,经$MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余物质 (用1:4 乙酸乙酯-己烷洗脱)以提供2-(2-环丙基吡唑并[1,5-a]吡啶-3-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺 (149.0 mg, 64%)。MS *m/z* 335.5 (80) [M+H]$^+$, 336.2 (100)。

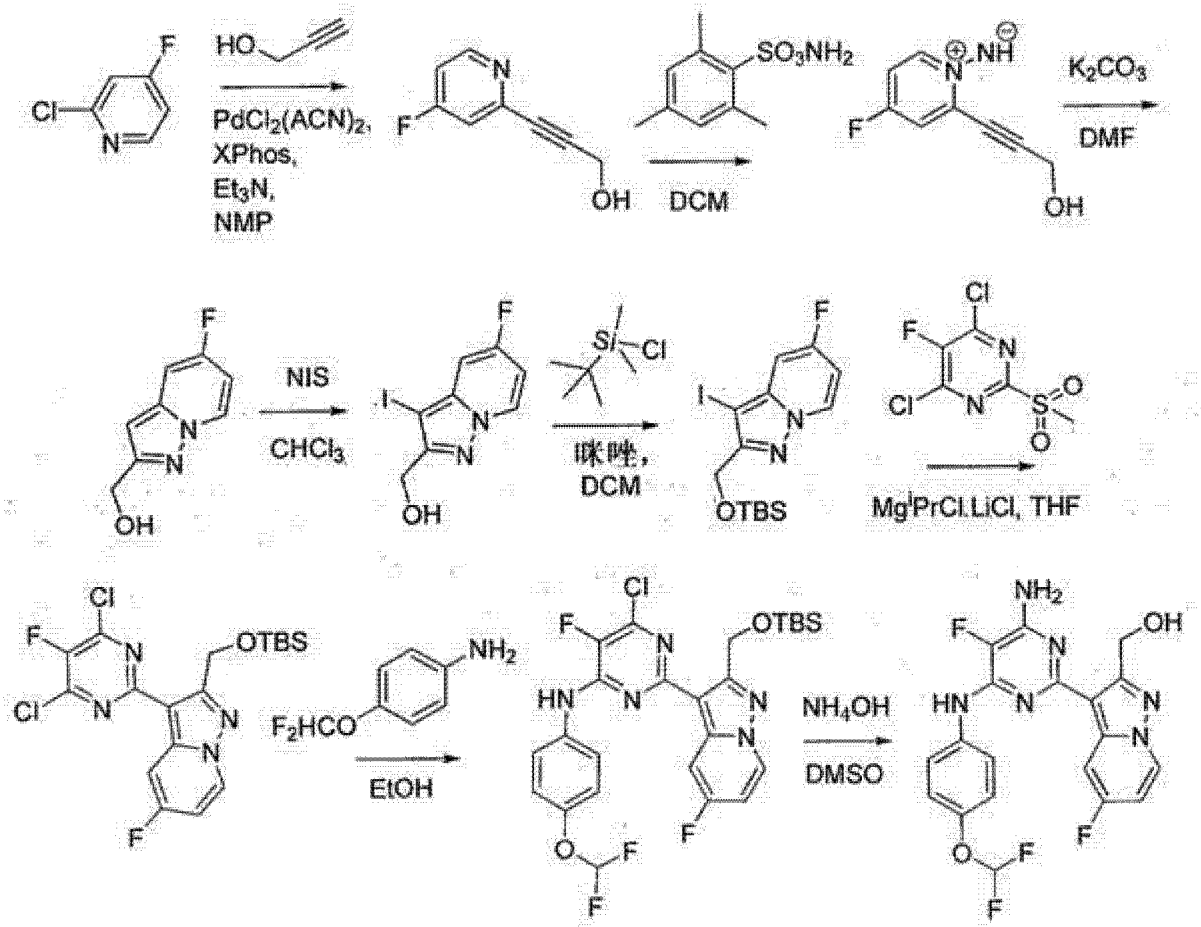
[0422] 步骤4. 在室温下搅拌2-(2-环丙基吡唑并[1,5-a]吡啶-3-基)-N-[4-(二氟甲氧基)苯基]-5-氟嘧啶-4,6-二胺 (100.0 mg, 0.30 mmol), 吡啶嗡-1-基氨基盐(pyridinium-1-ylazanide) (74.0 mg, 0.30 mmol), K_2CO_3 (43.0 mg, 0.31 mmol)和DMF

(2 mL) 的混合物 1 天，然后在 80℃下搅拌 1 天。该反应混合物在乙酸乙酯和水之间分配。用水和盐水洗涤有机相，经 $MgSO_4$干燥，然后过滤并蒸发。通过硅胶柱层析法分离残余物质（用 1:1 二氯甲烷：己烷， 然后用 1:3 乙酸乙酯：二氯甲烷洗脱） 以获得标题化合物 (32.0 mg, 28% 收率)：m.p. 53 - 55℃。

^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.55 (d, J = 8.83 Hz, 1H), 8.41 (d, J = 6.94 Hz, 1H), 8.20 (br. s., 1H), 7.63 - 7.91 (m, 2H), 7.21 (ddd, J = 0.95, 6.78, 8.98 Hz, 1H), 7.17 (d, J = 8.83 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.86 (dt, J = 1.26, 6.78 Hz, 1H), 6.10 (br. s., 2H), 3.44 (m, 1H), 0.53 - 1.13 (m, 4H); MS m/z 427.3 (100) $[M+H]^+$, 428.3 (50).

[0423] 实施例 13

[3-(4- 氨基 -6-{[4-(二氟甲氧基) 苯基] 氨基 }-5- 氟嘧啶 -2- 基)-5- 氟吡唑并 [1,5-a] 吡啶 -2- 基] 甲醇 (Cpd 181)



步骤 1. 通过三次泵抽和 N_2吹扫循环将 2- 氯 -4- 氟吡啶 (2.19 g, 16.65 mmol), 丙 -2- 炔 -1- 醇 (1.86 g, 33.29 mmol), 双 (乙腈) 二氯化钯 (II) (215.6 mg, 0.83 mmol) 和 2- 二环己基膦基 -2',4',6'- 三异丙基联苯 (Xphos) (794.3 mg, 0.17 mmol) 在 NMP (15 mL) 中的混合物脱气，然后添加三乙胺 (4.7 mL, 33.3 mmol)。将该混合物脱气并用 N_2吹扫，然后在 60℃下加热过夜。将溶液冷却并倾倒在水 (100 mL) 中，并用乙酸乙酯 (150 mL) 萃取产物。经 $MgSO_4$干燥萃取物，然后过滤并在减压下浓缩。通过柱层析法分离残余物质 (用 0 至 10% 二氯甲烷 - 己烷洗脱) 以获得油形式的 3-(4- 氟吡啶 -2- 基) 丙 -2- 炔 -1- 醇 (2.40 g, 96%)。

[0424] 步骤 2-4. 在 0℃下按份向 3-(4- 氟吡啶 -2- 基) 丙 -2- 炔 -1- 醇 (820.0 mg, 5.43 mmol) 在二氯甲烷 (10 mL) 中的溶液中添加 2-[(氨基氧基) 磺酰基]-1,3,5- 三甲基苯 (1.5 g, 6.98 mmol)。在环境温度下搅拌所得混合物 2 天。在吹 N_2流下除去溶剂以提供粗混合物。在 0℃下向 DMF 中的粗混合物 (3 mL) 中添加 K_2CO_3 (825.0 mg, 5.97 mmol)。在室温下搅拌所得混合物 24 小时,然后在乙酸乙酯和水之间分配。用水和盐水洗涤有机相,经 $MgSO_4$干燥,然后过滤并蒸发。在接下来的步骤中使用残余材料而不经进一步纯化。

[0425] 在环境温度下搅拌粗物质 *N*- 碘代琥珀酰亚胺 (1.2 g, 5.33 mmol) 在氯仿 (10 mL) 中的混合物 2 小时,然后在乙酸乙酯和水之间分配。用水和盐水洗涤有机相,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法 (用 1:1 二氯甲烷 : 己烷 , 然后用 1% 甲醇 /1:4 乙酸乙酯 : 二氯甲烷洗脱) 分离残余物质以获得油形式的 (5- 氟 -3- 碘代吡唑并 [1,5-a] 吡啶 -2- 基) 甲醇 (1.4 g, 50%)。

[0426] 步骤 5. 向 (5- 氟 -3- 碘代吡唑并 [1,5-a] 吡啶 -2- 基) 甲醇 (500.0 mg, 1.71 mmol) 在二氯甲烷 (3 mL) 中的溶液中添加咪唑 (139.5 mg, 2.05 mmol),然后在 0℃下逐滴添加二氯甲烷 (5 mL) 中的叔丁基二甲基甲硅烷基氯 (384.0 mg, 2.55 mmol)。在环境温度下搅拌该所得混合物 30 分钟,然后通过硅胶 /Celite 垫过滤,用二氯甲烷洗涤以提供 2-[(*叔丁基*二甲基甲硅烷基氧基) 甲基]-5- 氟 -3- 碘代吡唑并 [1,5-*a*] 吡啶 (470.0 mg, 72%)。

[0427] 步骤 6. 在 -78℃下向 2-[(*叔丁基*二甲基甲硅烷基氧基) 甲基]-5- 氟 -3- 碘代吡唑并 [1,5-*a*] 吡啶 (470.0 mg, 1.15 mmol) 在 THF (5 mL) 中的溶液中逐滴添加异丙基氯化镁氯化锂复合物溶液 (1.07 mL, 1.3 M 在 THF 中)。将该混合物温热至 0℃并搅拌 30 分钟,然后在 -78℃下一次性添加 4,6- 二氯 -5- 氟 -2-(甲基磺酰基) 嘧啶 (4.80 g, 19.6 mmol)。在 0℃下搅拌该混合物 1 小时,然后在乙酸乙酯和水之间分配。用盐水洗涤有机相,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余材料 (用 1:9 乙酸乙酯 : 己烷洗脱) 以提供 2-[(*叔丁基*二甲基甲硅烷基氧基) 甲基]-3-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-5- 氟吡唑并 [1,5-*a*] 吡啶 (205.0 mg, 40%)。

[0428] 步骤 7-8. 在 90℃下将 2-[(*叔丁基*二甲基甲硅烷基氧基) 甲基]-3-(4,6- 二氯 -5- 氟嘧啶 -2- 基)-5- 氟吡唑并 [1,5-*a*] 吡啶 (102.0 mg, 0.23 mmol), 4- 二氟甲氧基苯胺 (145.0 mg, 0.92 mmol) 和乙醇 (1 mL) 的混合物加热过夜。在冷却之后,将该混合物倾倒在冰水中以获得固体。通过过滤收集固体,然后用水和已烷洗涤。在真空下干燥固体以提供 2-[2-[(*叔丁基*二甲基甲硅烷基氧基) 甲基]-5- 氟吡唑并 [1,5-*a*] 吡啶 -3- 基]-6- 氯 -*N*-(4- 二氟甲氧基) 苯基]-*5*- 氟嘧啶 -4- 胺 (TBS 保护和未保护的产物混合物)。

[0429] 向干燥固体中添加 DMSO (3 mL) 和 NH_4OH (0.3 mL)。密封该反应混合物并在 100℃下搅拌 2 天。该混合物在乙酸乙酯和水之间分配,用水 (2 x 10 mL) 和盐水洗涤有机相,经 $MgSO_4$干燥,然后过滤并蒸发。通过硅胶柱层析法分离残余物质 (用 1-5 % 甲醇 / 二氯甲烷洗脱) 以提供白色固体形式的标题化合物 (25.0 mg, 25 % 对于两步); m.p. 198 - 200℃。

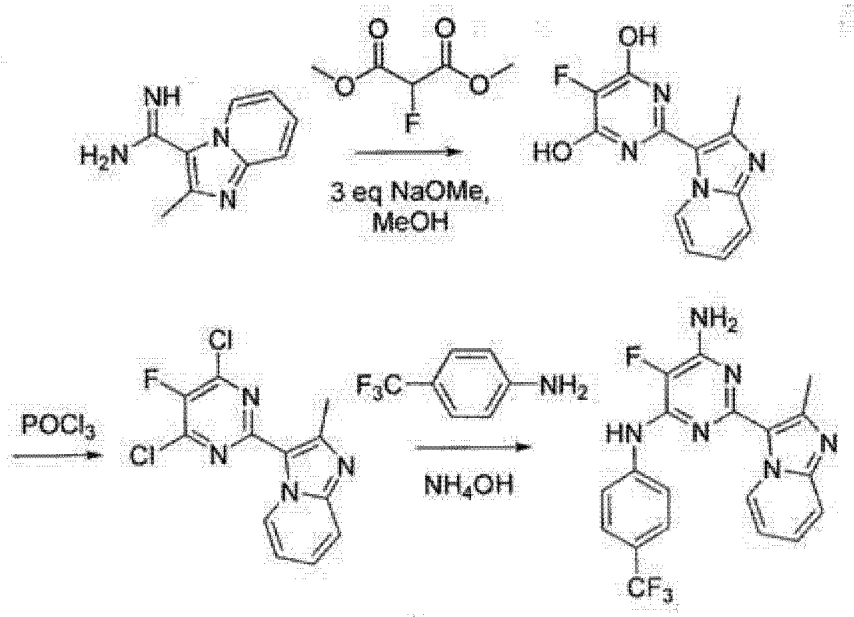
^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.50 - 8.64 (m, 1H), 8.35 (s, 1H), 8.06 - 8.21 (m, 1H), 7.64 (d, J = 8.83 Hz, 2H), 7.24 (d, J = 8.83 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.86 - 6.93 (m, 1H), 6.23 - 6.41 (m, 2H), 5.46 - 5.66 (m, 1H), 4.68 - 4.83 (m, 2H); MS m/z 435.2 (100) $[M+H]^+$, 436.2 (20).

[0430] 可以根据实施例 13 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 & 数据
186	**N-[4-(二氟甲氧基)苯基]-2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.54 (dd, J = 5.20, 7.41 Hz, 1H), 8.25 (dd, J = 2.68, 10.88 Hz, 1H), 8.18 (br. s., 1H), 7.71 (d, J = 9.14 Hz, 2H), 7.21 (d, J = 9.14 Hz, 2H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.76 - 6.88 (m, 1H), 6.14 (br. s., 2H), 3.24 (q, J = 7.57 Hz, 2H), 1.20 - 1.35 (m, 3H); m.p. 103-105 °C; MS m/z 433.6 $[M+H]^+$
187	**2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.53 - 8.59 (m, 1H), 8.50 (br. s., 1H), 8.28 (dd, J = 2.68, 10.25 Hz, 1H), 7.93 (d, J = 8.51 Hz, 2H), 7.69 (d, J = 8.51 Hz, 2H), 6.83 (dt, J = 2.99, 7.33 Hz, 1H), 6.28 (br. s., 2H), 3.28 (q, J = 7.46 Hz, 2H), 1.28 (t, J = 7.57 Hz, 3H); m.p. 164-166 °C; MS m/z 435.2 $[M+H]^+$
188	**N-[4-(二氟甲氧基)-3-氟苯基]-2-(2-乙基-5-氟吡唑并[1,5-a]吡啶-3-基)-5-氟嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.49 - 8.64 (m, 1H), 8.33 - 8.40 (m, 1H), 8.24 - 8.32 (m, 1H), 7.77 - 7.85 (m, 1H), 7.44 - 7.50 (m, 1H), 7.29 - 7.38 (m, 1H), 6.80 – 7.10 (t, J = 75.00 Hz, 1H), 6.81 - 6.87 (m, 1H), 6.17 - 6.34 (m, 2H), 3.27 (d, J = 7.57 Hz, 2H), 1.28 (t, J = 7.57 Hz, 3H); m.p. 150-152 °C; MS m/z 452. $[M+H]^+$

[0431] 实施例 14

5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺 (Cpd 169)



步骤 1. 向 2-甲基咪唑并[1,2-a]吡啶-3-甲脒三甲基乙酸盐 (250 mg, 0.905 mmol)

和2-氟丙二酸二甲酯（272 mg，1.81 mmol）在MeOH（5 mL）中的溶液中添加30% NaOMe / MeOH（0.2 mL）。在密封管中在85℃下加热该混合物72小时直到UPLC示出起始原料的完全消耗。在减压下浓缩反应混合物，然后用水（5 mL）稀释，并用1N HCl酸化至约pH 7。通过过滤收集黄褐色沉淀物，提供5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基）嘧啶-4,6-二醇。5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基）嘧啶-4,6-二醇（180 mg，76%）。将产物（180 mg，0.69 mmol）与三氯氧磷（3 mL）在微波小瓶中混合，然后密封该小瓶并在150℃下微波处理15分钟。将反应混合物转移至25 mL圆底烧瓶中，并在减压下浓缩。将残留物再次溶解在EtOAc（10 mL）中并用$NaHCO_3$水溶液洗涤三次。经Na_2SO_4干燥有机相，然后过滤并蒸发以提供黄色固体形式的3-(4,6-二氯-5-氟嘧啶-2-基）-2-甲基咪唑并[1,2-a]吡啶（164 mg，80%）。

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.59 (dt, J = 6.9, 0.9 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 6.9 Hz, 1H), 2.77 (s, 3H); MS *m/z* 298.1 $[M+H]^+$.

[0432] 步骤2. 将3-(4,6-二氯-5-氟嘧啶-2-基）-2-甲基咪唑并[1,2-a]吡啶（50 mg，0.168 mmol）和4-三氟甲基苯胺（54 mg，0.336 mmol）在EtOH（2 mL）中混合并在100℃下在密封管中加热直到UPLC示出起始原料完全消耗（48小时）。将该反应混合物冷却至室温并用水（5 mL）稀释以形成沉淀物。通过过滤收集产物，然后用己烷洗涤。在不经干燥的情况下，将粗产物溶解在CH_3CN（2 mL）中，然后添加饱和氨水（4 mL）。在100℃下在密封管中加热该反应混合物16小时直到UPLC示出起始原料完全消耗。通过添加水（10 mL）使粗产物沉淀。过滤该沉淀物，然后用己烷洗涤并干燥以获得浅褐色固体形式的标题化合物（32 mg，47 % 经两步）。

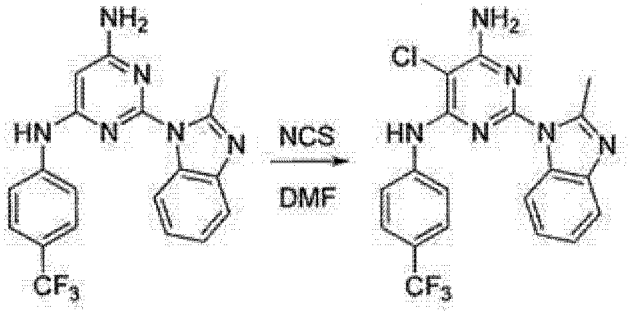
^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.76 (dt, J = 7.1, 1.0 Hz, 1H), 8.50 (br. s., 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.19 (ddd, J = 8.5, 6.5, 1.8 Hz, 1H), 6.74 (td, J = 6.9, 1.3 Hz, 1H), 6.27 (br. s., 2H), 2.64 (s, 3H); MS *m/z* 403.3 $[M+H]^+$.

[0433] 可以根据实施例14的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式（I）化合物或其形式。

Cpd	名称 & 数据
170	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺** MS *m/z* 401.3 [M+H]$^+$
171	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.83 (d, J = 6.9 Hz, 1H), 9.25 (br. s, 1H), 7.80 (dd, J = 13.4, 2.0 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.31 - 7.39 (m, 2H), 7.18 (t, J = 73.1 Hz, 1H), 6.88 - 6.97 (m, 3H), 3.31 (s, 3H); MS *m/z* 419.3 [M+H]$^+$
174	**5-氟-N-[4-(三氟甲基)苯基]-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 9.39 (s, 1H), 7.83 (d, *J* = 8.51 Hz, 2H), 7.68 (d, *J* = 8.83 Hz, 2H), 7.11 (s, 2H), 2.75 (s, 3H), 2.72 (s, 3H), 2.55 (s, 3H); m.p. 166-168 °C; MS *m/z* 432.3 [M+H]$^+$
175	**N-[4-(二氟甲氧基)苯基]-5-氟-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺** m.p. 141-143 °C; MS *m/z* 430.4 [M+H]$^+$
176	**N-[4-(二氟甲氧基)-3-氟苯基]-5-氟-2-(2,6,8-三甲基咪唑并[1,2-a]吡嗪-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.40 (s, 1H), 9.32 (s, 1H), 7.71 - 7.83 (m, 1H), 7.40 - 7.45 (m, 1H), 7.31 - 7.37 (m, 1H), 7.04- 7.32 (t, J = 70.00 Hz, 1H), 7.07 (s, 2H), 2.74 (s, 3H), 2.72 (s, 3H), 2.38 (s, 3H); m.p. 140-141 °C; MS *m/z* 448.4 [M+H]$^+$
251	**N-(4-氯苯基)-5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ □ ppm 9.88 - 10.04 (m, 1H), 8.33 - 8.46 (m, 1H), 7.72 (d, *J* = 8.83 Hz, 2H), 7.48 - 7.59 (m, 1H), 7.39 (d, *J* = 8.83 Hz, 2H), 7.27 - 7.34 (m, 1H), 6.34 - 6.45 (br., s, 2H), 2.73 (s, 3H); m.p. 226-229 °C; MS *m/z* 388.2 [M+H]$^+$
252	**5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲氧基苯基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 9.91 (dd, *J* = 2.52, 5.99 Hz, 1H), 8.10 (br. s., 1H), 7.45 - 7.58 (d, *J* = 8.83 Hz, 2H), 7.26 (d, *J* = 1.89 Hz, 1H), 6.96 (d, *J* = 8.83 Hz, 2H), 6.23 (br. s., 2H), 3.81 (s, 3H), 2.70 (s, 3H); m.p. 204-206 °C; MS *m/z* 384.2 [M+H]$^+$
253	**5-氟-2-(6-氟-2-甲基咪唑并[1,2-a]吡啶-3-基)-N-(4-甲基苯基)嘧啶-4,6-二胺** m.p. 210-212 °C; MS *m/z* 368.2 [M+H]$^+$

[0434] 实施例 15

5- 氯 -2-(2- 甲基 -1H- 苯并咪唑 -1- 基)-N-[4-(三氟甲基) 苯基] 嘧啶 -4,6- 二胺 (Cpd 166)



向 2-(2-甲基-1H-苯并[d]咪唑-1-基)-N4-(4-(三氟甲基)-苯基)嘧啶-4,6-二胺(76 mg, 0.20 mmol)在 DMF (1.5 mL)中的溶液中添加 N-氯代琥珀酰亚胺 (29 mg, 0.22 mmol)。在室温下搅拌该混合物 2 小时。将冰水 (5 mL)和饱和 $NaHCO_3$溶液 (2 mL)添加至该混合物中。过滤所得沉淀物,用水洗涤,在氮气下干燥以获得灰白色固体形式的标题化合物 (77 mg, 92%)。

^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.40 (1H, s) 7.95 - 8.00 (1H, m) 7.76 - 7.83 (2H, m) 7.57 (2H, d, *J*=8.51 Hz) 7.40 - 7.45 (1H, m) 7.06 - 7.11 (1H, m) 6.98 - 7.04 (1H, m) 6.52 - 6.75 (2H, m) 2.68 (3H, s); MS *m/z* 419.1 [M+H]$^+$.

[0435] 可以根据实施例 15 的步骤通过替代合适的起始原料、试剂和反应条件制备另外的本文中所述的式 (I) 化合物或其形式。

Cpd	名称 & 数据
167	**5-氯-2-(2-乙基-1H-苯并咪唑-1-基)-N-[4-(三氟甲基)苯基]嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.55 (1H, s) 8.07 - 8.12 (1H, m) 7.91 - 7.96 (2H, m) 7.71 (2H, d, *J*=8.51 Hz) 7.58 - 7.63 (1H, m) 7.13 - 7.26 (2H, m) 6.80 (2H, br. s.) 3.23 - 3.30 (2H, m) 1.31 (3H, t, *J*=7.41 Hz); MS *m/z* 433.2 [M+H]$^+$
168	**5-氯-N-[4-(二氟甲氧基)苯基]-2-(2-乙基-1H-苯并咪唑-1-基)嘧啶-4,6-二胺** ^{1}H NMR (500 MHz, 丙酮 -d_6) δ ppm 8.31 (1H, s) 8.09 - 8.13 (1H, m) 7.65 - 7.71 (2H, m) 7.55 - 7.60 (1H, m) 7.13 - 7.25 (4H, m) 6.99 (1H, t, *J*=74.40 Hz) 6.68 (2H, br. s.) 3.19 - 3.25 (2H, m) 1.28 (3H, t, *J*=7.41 Hz); MS *m/z* 431.2 [M+H]$^+$

[0436] 生物实施例

以下生物实施例示范了本文中所述的化合物抑制 Bmi-1 功能和降低 Bmi-1 蛋白含量的有用性。

[0437] 实施例 1

夹心 ELISA分析

细胞接种和化合物处理 (第 1天):

将 HT-1080 细胞以 8000 个细胞 / 孔 (50 μL) 接种在 96-孔组织培养板中。在细胞变粘着之后 (3-4 小时),添加在 50 μL 含有 1% DMSO 的 DMEM 中的测试化合物的 2x 稀释的储液 (最终 DMSO 浓度为 0.5%) 并在 37℃下在 5% CO_2下孵育该板 40-48 小时。

[0438] *ELISA板第一抗体制备 (第 2天):*

将在 PBS 中稀释成 2 μg/mL 的第一抗体 (Millipore Mouse, 对小鼠 *Bmi-1*单克隆, clone F6, catalog #05-637) 添加 (100 μL) 至 Nunc MaxiSorp 96-孔 ELISA 板的每孔中。用板密封物覆盖该板并使其静置过夜。

[0439] *细胞裂解物制备 (第 3天):*

在分析当天如下制备新鲜 1x Lysis 缓冲剂:1 mM EDTA, 150 mM NaCl, 0.5% Triton-X 100, 10 mM NaF, 20 mM B-甘油磷酸酯, 1 mM DTT (在 PBS 中, pH 7.2-7.4) 和 1x HALT 蛋白酶抑制剂混合物 (Pierce #78410)。

[0440] 将 1x Lysis 缓冲剂 (40 μL) 添加至每孔,并在定轨振荡器上振荡该板 5-10 分钟以获得细胞裂解物,然后将稀释物 (1% BSA 在 PBS 中在 0.5% NP40 中) (100 μL) 添加至

每孔。

[0441] 以下述 Bmi-1 浓度制备标准曲线 :8000, 4000, 2000, 1000, 500, 250, 125, 0 pg/mL。将用于制备标准曲线的 Bmi-1 重组蛋白标准 (Novus Biologicals PCGF4 重组蛋白 (P01), catalog # H00000648-P01) 储存在 -80℃下。在第一次解冻时,将 Bmi-1 重组蛋白标准在 Blocking Buffer (1% BSA 在 PBS 中 ; BSA: Fisher Scientific Catalog #1600-100) 中稀释成 10 μg/μL。分成小份并在 -80℃下再次冻结。可以将所述小份保持在 4℃下并在第一次解冻之后重新使用,但仅在 1-2 周之内。所述 Bmi-1 重组蛋白标准含有在 Western Blot 上在约 70 Kda 出现的 GST- 融合标签。

[0442] *ELISA分析 (第 3天):*

用 Wash Buffer (0.05% Tween-20 在 PBS 中) 洗涤制备的 ELISA 板 3x。从该板去除最终洗液并将该板剥离干。将 Blocking Buffer (300 μL) (1% BSA 在 PBS 中) 添加至各孔。用板密封物覆盖该板并在室温下孵育 1 小时。用 Wash Buffer 洗涤封阻的板 3x,然后去除最终洗液并将该板剥离干。添加之前制备的样品和标准 (100 μL/ 孔) 并用板密封物覆盖该板并在 4℃下孵育过夜。

[0443] *ELISA分析 (第 4天):*

从 4℃去除制备的 ELISA 板,在室温下孵育 30 分钟,然后如之前对第 3 天所述洗涤和剥离干。将在 Blocking Buffer 中稀释成 1:600 的第二抗体 (细胞信号传导兔抗 -Bmi-1, Cat# 2830) 添加 (100 μL) 至各孔,除了对于背景对照孔按需要进行。用板密封物覆盖该板并在室温下孵育 1.5 h。

[0444] 如上所述洗涤和剥离干所述 ELISA 板。将在 Blocking Buffer 中稀释成 1:300 的第三抗体 (细胞信号传导 HRP 缀合的抗 - 兔 IgG (CellSignaling, Cat#:7074) 添加 (100 μL) 至各孔,除了对于背景对照孔按需要进行。在室温下孵育该板 1 小时。

[0445] 如上所述洗涤并剥离干该板,然后在每个孔中添加制备的 TMB 底物 (TMB 底物套装, Pierce catalog #34021) (通过混合套装试剂 1:1 制备) (100 μL)。在室温下在黑暗下孵育该板 20-30 分钟,然后在每个孔中添加 Stop Solution (2 M 硫酸在水中) (50 μL)。在 OD450 (实验) 和 OD570 (参考) 下读板。

[0446] 如表 1 中所示,本文中所述的测试化合物的 Bmi-1 ELISA EC_{50}值为 > 0.1 μM 至 ≤ 3 μM (一颗星),EC_{50}值为 > 0.01 μM 至 ≤ 0.1 μM (两颗星),和 EC_{50}值为 > 0.001 μM 至 ≤ 0.01 μM (三颗星) 或 EC_{50}值为 ≤ 0.001 μM (四颗星)。

表1

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
1	**	72	**	143	***	214	**
2	*	73	**	144	**	215	*
3	**	74	*	145	***	216	**

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
4	**	75	*	146	**	217	**
5	*	76	**	147	*	218	***
6	**	77	**	148	*	219	*
7	*	78	**	149	**	220	**
8	*	79	*	150	**	221	*
9	***	80	**	151	**	222	*
10	**	81	**	152	**	223	*
11	*	82	**	153	**	224	**
12	**	83	**	154	*	225	**
13	*	84	*	155	**	226	*
14	*	85	*	156	***	227	**
15	**	86	**	157	**	228	**
16	**	87	*	158	*	229	*
17	*	88	**	159	*	230	*
18	*	89	*	160	**	231	*
19	*	90	*	161	**	232	**
20	*	91	*	162	**	233	**
21	***	92	**	163	**	234	**
22	**	93	**	164	**	235	**
23	*	94	**	165	***	236	*
24	*	95	**	166	*	237	**
25	*	96	*	167	**	238	*
26	*	97	**	168	*	239	**
27	*	98	*	169	*	240	***
28	*	99	*	170	*	241	**
29	**	100	*	171	*	242	***
30	*	101	**	172	*	243	**
31	**	102	**	173	*	244	**
32	*	103	**	174	*	245	**
33	**	104	**	175	*	246	**
34	***	105	**	176	*	247	**
35	*	106	**	177	*	248	**
36	**	107	**	178	*	249	**
37	**	108	*	179	***	250	**
38	*	109	**	180	*	251	*
39	*	110	**	181	**	252	**

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
40	*	111	**	182	*	253	***
41	*	112	**	183	**	254	**
42	**	113	**	184	***	255	*
43	**	114	**	185	**	256	**
44	*	115	**	186	*	257	**
45	*	116	**	187	*	258	***
46	*	117	**	188	*	259	*
47	*	118	*	189	*	260	*
48	*	119	**	190	*	261	**
49	*	120	**	191	**	262	**
50	**	121	***	192	*	263	**
51	*	122	**	193	**	264	***
52	*	123	***	194	*	265	***
53	*	124	**	195	*	266	**
54	*	125	*	196	***	267	*
55	*	126	**	197	***	268	*
56	*	127	**	198	***	269	*
57	*	128	**	199	***	270	***
58	*	129	**	200	***	271	***
59	*	130	**	201	**	272	**
60	**	131	**	202	*	273	***
61	*	132	**	203	***	274	**
62	**	133	**	204	**	275	**
63	**	134	**	205	***	276	***
64	**	135	**	206	**	277	****
65	**	136	**	207	***	278	*
66	**	137	**	208	***	279	**
67	*	138	**	209	**	280	**
68	**	139	*	210	*	281	***
69	**	140	**	211	*	282	***
70	*	141	**	212	**	283	*
71	**	142	**	213	***	284	**

[0447] 实施例 2

体外癌症干细胞分析

在体外小儿(pediatric)Baylor Xenograft Derived (BXD)脑肿瘤模型中和来自原发性患者培养物(PPC)的细胞中测试式(I)化合物或其形式对 Bmi-1 功能抑制和 Bmi-1 蛋白含量降低的效果。

[0448] 细胞在测试一般细胞生长的条件(例如在常规组织培养板中在含胎牛血清 (FBS) 的介质中) 下或在特定用于癌症干细胞 (CSC) 生长的条件(低血清、无粘连板) 中生长以评价在这些群体中式 (I) 化合物对 Bmi-1 抑制和 Bmi-1 蛋白含量降低的效果。用预定剂量范围的化合物 109 在固定时间点经 24 小时至 13 天的时间段处理细胞。使用细胞计数套件 (CCK) (由 Dojindo Molecular Technologies, Inc. 供应)使用常规 2D 生长和神经球生长定量对细胞生长活力的抑制效果。

[0449] 图 1 示范了化合物 109 在 BXD GBM 模型中的效果,其中 CSC 群体(如神经球数测量的) 在所述浓度的化合物 109 存在下经 13 天时间剂量依赖性降低。

[0450] 图 2 示范了化合物 109 在 BXD GBM 模型中的效果,其中 CSC 群体(如神经球数测量的) 在所述浓度的化合物 109 存在下经 13 天时间普遍性降低。

[0451] 图 3 示范了化合物 109 在肿瘤球分析中的效果,其中在标准 2D 组织培养物条件 (含有 FBS) 下或选择用于 CSC 生长(无粘连、无血清)的条件下在所述浓度的化合物 109 存在下培养每孔中的 2000 PPC CSC 达 13 天。分别在 62.5 nm 和 15.6 nm 的浓度下,单层和神经球 CSC 群体都由于 PPC CSC 接触化合物 109 (式 (I) 化合物或其形式的代表) 而减少。

[0452] 加在一起,图 1-3 的数据示范了由于经由式 (I) 化合物或其形式导致的 Bmi-1 功能抑制和 Bmi-1 蛋白含量降低导致的癌症干细胞群体相比于一般细胞群体的优先降低。

[0453] <u>实施例 3</u>

体内存活分析

构建恶性胶质瘤动物模型,其中将 U87-MG 肿瘤细胞颅内注射到 nu/nu 小鼠中,使肿瘤能够在 10 天时间内形成。采用媒介物、化合物 109 和替莫唑胺(护理标准试剂)如所指定的每日给药小鼠。在图 4 中示出给药媒介物、化合物 109 和替莫唑胺的每个处理组 (n = 10) 的存活的对比结果。

[0454] 图 4 示范了经 40 天时间在恶性胶质瘤的原位模型中针对存活,化合物 109 相比于替莫唑胺以指定剂量水平的每日给药效果。将细胞颅内植入裸小鼠中并在 10 天后采用媒介物、化合物 109 或替莫唑胺开始给药。化合物 109 示范了这些承载肿瘤的小鼠相比于媒介物和替莫唑胺的延长的存活 ($p<0.0001$)。

[0455] 出于任何和全部目的,以下公开以与各单独公开全部在本文中述及相同的程度并入本申请中作为参考:

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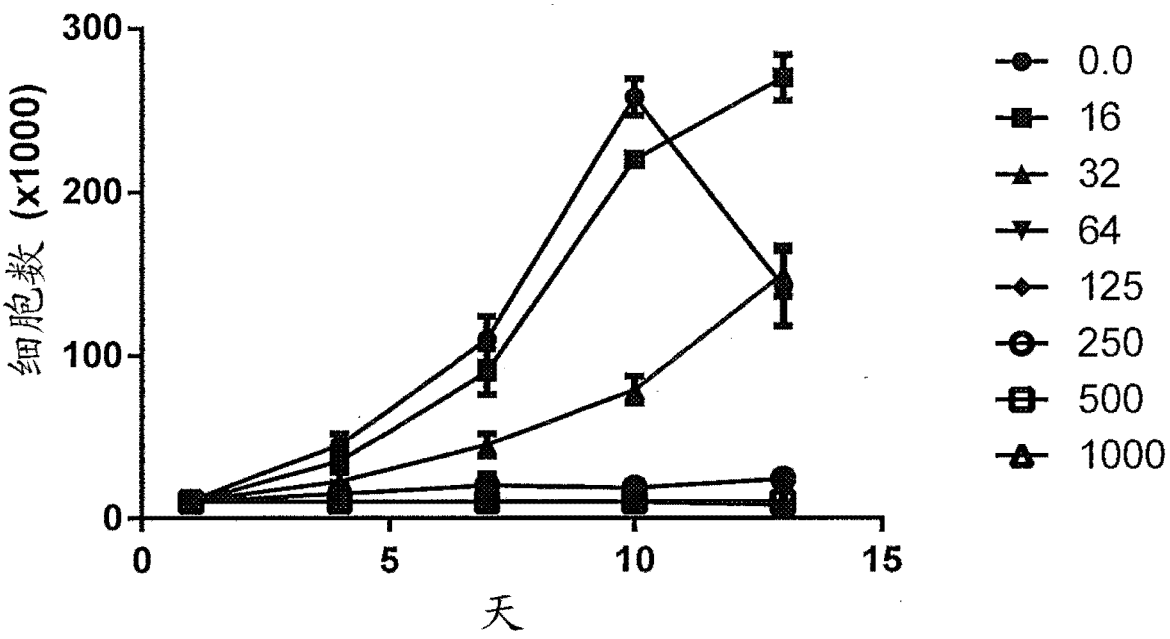
[0456] 不考虑本文中所述的文件是否具体和单个视为被并入作为参考，本文中涉及的全部文件都出于任何和全部目的如同本文中全部述及各单个文献一样的程度并入本申请中作为参考。

[0457] 尽管已经在上文中详细描述了某些实施方案，但本领域中普通技术人员清楚地理解为在实施方案中可以在不脱离其教导的情况下进行很多改变。全部此类改变都意在包括

在本文中所示的权利要求的范围内。


300
200
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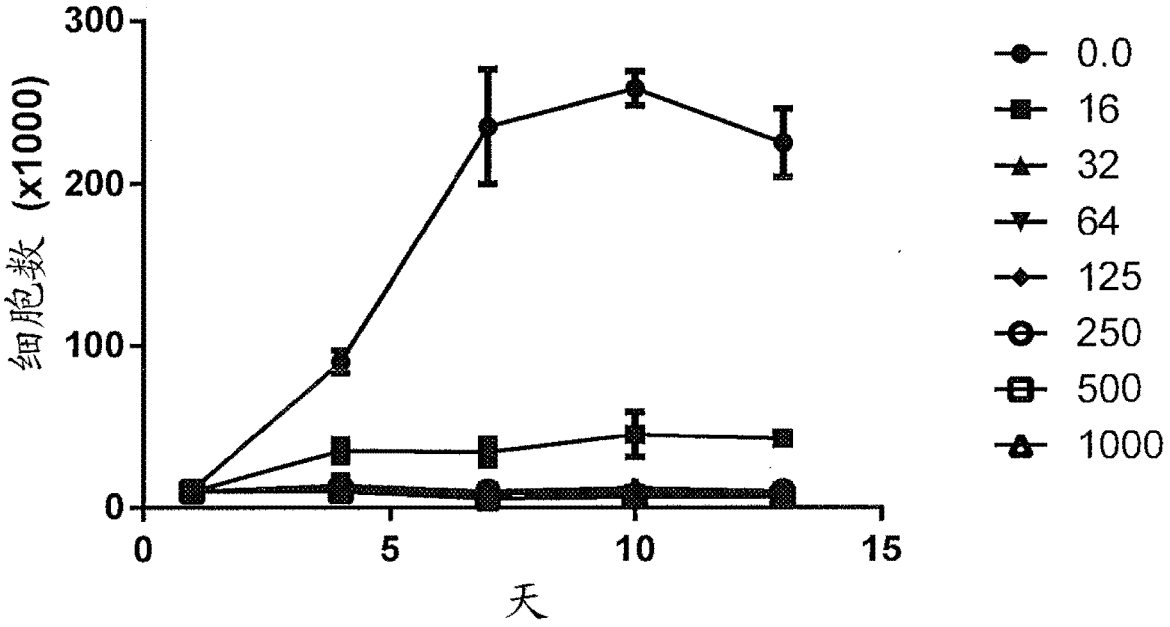
0
5
10
15
天
0.0
16
32
64
125
250
500
1000

图 1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1000

图 2

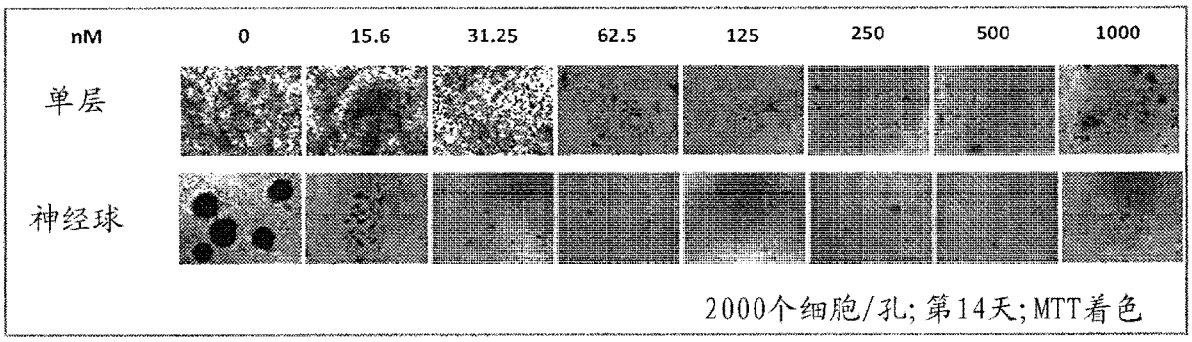
nM
0
15.6
31.25
62.5
125
250
500
1000
单层
神经球
2000个细胞/孔;第14天;MTT着色

图 3

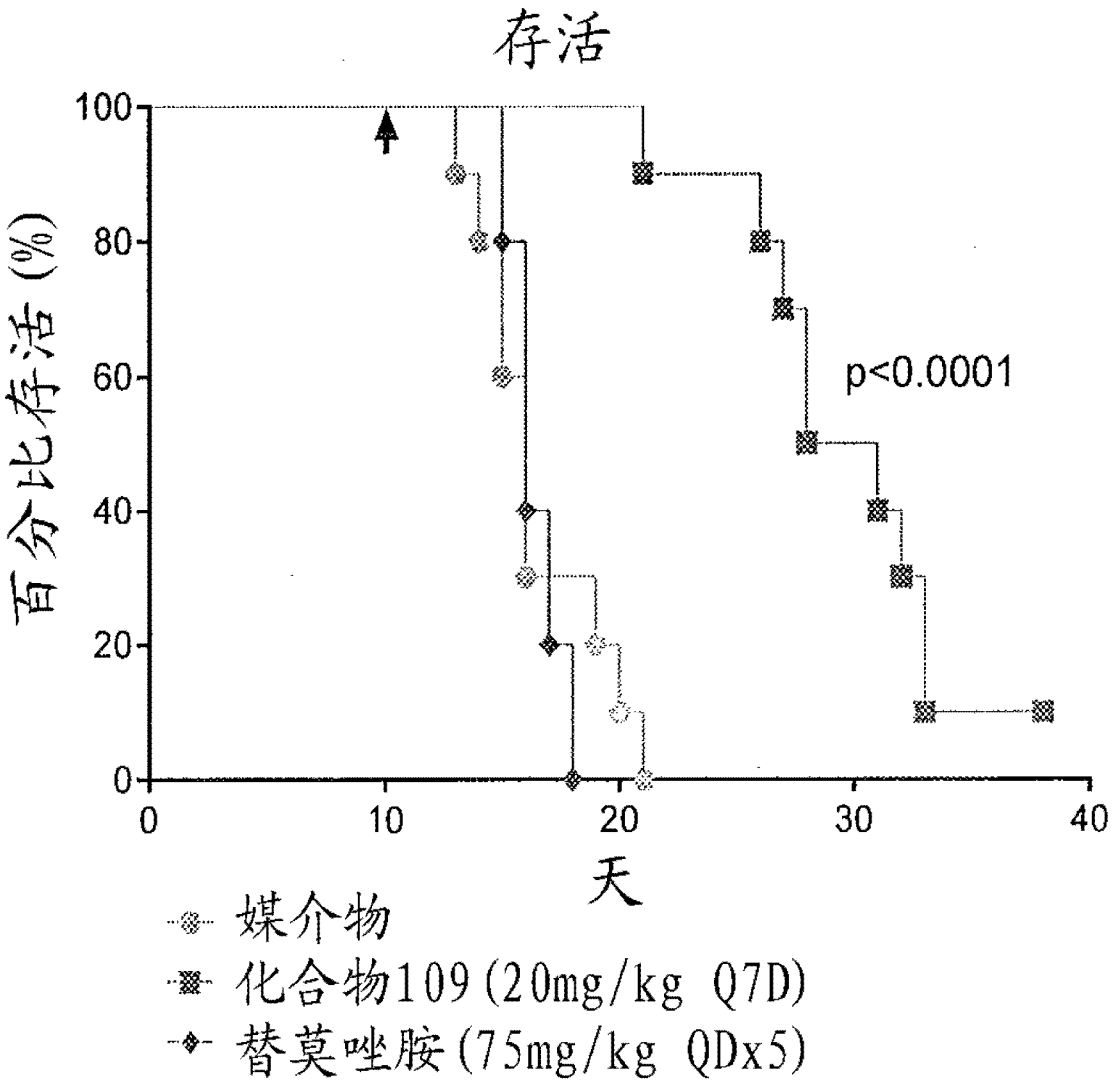
存活
百分比存活(%)
100
80
60
40
20
0
0
10
20
30
40
天
p<0.0001
媒介物
化合物109(20mg/kg Q7D)
替莫唑胺(75mg/kg QDx5)

图 4